**Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL**

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**ABSTRACT**

ADMIRE was a multi-center, randomized-controlled, open, phase IIB superiority trial in previously untreated Chronic Lymphocytic Leukemia (CLL). Conventional frontline therapy in fit patients is fludarabine, cyclophosphamide and rituximab (FCR). Initial evidence from non-randomized Phase II trials suggested that the addition of mitoxantrone to FCR (FCM-R) improved remission rates. 215 patients were recruited to assess the primary endpoint of complete remission (CR) rates according to IWCLL criteria. Secondary endpoints were progression-free survival (PFS), overall survival (OS), overall response rate, minimal residual disease (MRD) negativity and safety. At final analysis, CR rates were 69.8% FCR vs. 69.3% FCM-R [adjusted odds ratio (OR): 0.97; 95%CI: (0.53-1.79), *p*=0.932]. MRD-negativity rates were 59.3% FCR vs. 50.5% FCM-R [adjusted OR: 0.70; 95% CI: (0.39-1.26), *p*=0.231]. During treatment, 60.0% (n=129) of participants received G-CSF as secondary prophylaxis for neutropenia, a lower proportion on FCR compared with FCM-R (56.1% vs 63.9%). The toxicity of both regimens was acceptable. There are no significant differences between the treatment groups for PFS and OS. The trial demonstrated that the addition of mitoxantrone to FCR did not increase the depth of response. Oral FCR was well tolerated and resulted in impressive responses in terms of CR rates and MRD negativity compared to historical series with intravenous chemotherapy.

**INTRODUCTION**

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder accounting for 30% of adult leukaemia and 25% of Non-Hodgkin Lymphoma. CLL is the commonest form of leukaemia above the age of 50 years with a median age of diagnosis of 70 years. The treatment of CLL is tailored around the physical state of the patient due to toxicity associated with the chemotherapy-based treatments.

CLL is still an incurable disease, and most patients will eventually become resistant to treatment. For physically fit patients, combination chemo-immunotherapy in the form of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care based on evidence from large randomised controlled and non-randomised trials (1-3). Updated analysis suggested an improvement in progression free survival (PFS) and overall survival (OS) in patients treated with FCR over FC(1). Hence, this combination is considered to be the gold-standard first-line treatment in patients deemed to be suitable for fludarabine-based treatment.

The addition of mitoxantrone to fludarabine-based therapy has been found to induce high response rates in a variety of lymphoproliferative disorders including follicular NHL(4) and mantle cell lymphoma(5). The addition of mitoxantrone to fludarabine and cyclophosphamide (FCM) has been assessed in a phase II clinical trial in which 69 CLL patients requiring therapy were given this combination as frontline treatment(6). This trial reported a CR rate of 64% with Minimal Residual Disease (MRD) negativity rate of 26% and Overall Response Rate (ORR) of 90%. The same group reported the combination of FCM-R in 72 previously untreated patients resulting in an ORR of 93% and a CR rate of 82% of which 46% achieved an MRD-negative CR(7) which appeared higher than expected for FCR. FCM-R has also been reported in patients with relapsed/refractory CLL. Two trials involving 60 and 29 patients with relapsed refractory CLL reported an ORR with FCM of 78% and 79%, respectively, with 30 (50%) and 9 (32%) patients, achieving a CR(8, 9). We previously reported a randomised phase II trial of 52 patients with relapsed CLL, with ORR with FCM and FCM-R of 58% and 65%, respectively(10) and an acceptable toxicity profile. Eight (15.4%) patients in this trial achieved MRD negativity.

The ADMIRE (Does the ADdition of Mitoxantrone Improve REsponse to FCR chemotherapy in patients with CLL) trial was designed to assess whether the addition of mitoxantone to FCR increases the depth of response in previously untreated patients with CLL requiring therapy in comparison to the standard FCR treatment. The current literature suggests that patients who respond to therapy and do not have detectable CLL by extremely sensitive techniques have a significantly prolonged survival (11-13). MRD with a sensitivity of 10-4 has become an important endpoint in the treatment of CLL especially in the era of chemoimmunotherapy. Indeed, attainment of MRD negativity after therapy is a desirable goal as this results in improvement of PFS and OS (14, 15). Therefore, one of the key secondary objectives was to compare MRD negativity within each treatment group.

**PATIENTS AND METHODS**

*Trial Design*

ADMIRE was a multi-center, randomized, controlled, open-label, parallel-group, phase IIB superiority trial assessing FCR (control) versus FCM-R (experimental) for previously untreated patients with CLL requiring treatment by IWCLL criteria(16). Patients were randomly allocated via a central computer-generated minimization programme that incorporated a random element 1:1 to receive oral fludarabine, cyclophosphamide and intravenous rituximab with or without intravenous mitoxantrone. Randomization was stratified to ensure balance for center, Binet Stage (Progressive A or B, C), age group (≤65, >65) and sex.

The primary objective of the trial was to assess whether the addition of mitoxantrone to FCR improved CR rates in patients with previously untreated CLL. The results would be used to determine whether a larger randomized Phase III trial to formally assess survival was appropriate.

An independent Data Monitoring Committee (DMC) was established to review the safety and ethics of the trial. The DMC reviewed unblinded safety data on a six-monthly basis and unblinded safety and trial progress reports on an annual basis. The DMC reported to an established trial steering committee (TSC) that provided general oversight for the trial.

The trial protocol was approved by the Leeds West Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial was registered as an International Standard Randomized Controlled Trial (ISRCTN42165735); and on the European Clinical Trials Database (EudraCT: 2008-006342-25).

*Patients*

The trial was planned to include 218 patients from hospitals around the United Kingdom (UK). Eligible patients had: progressive CLL requiring treatment by IWCLL criteria(16); no prior treatment for CLL; WHO performance status 0-2; Binet Stage progressive A, B or C; and provided written consent. Patients were not eligible if they had Hepatitis B or C; an active secondary malignancy (excluding basal cell carcinoma of the skin); an active infection; or past history of anaphylaxis following exposure to rat- or mouse-derived complementarity determining region (CDR)-grafted humanized monoclonal antibody. Patients with creatinine clearance greater than 30 ml/min were allowed to enter the trial with guidance on dose reduction for fludarabine. Patients with a 17p-deletion were eligible for enrollment due to lack of treatment options at the time of designing the trial. All patients provided written informed consent prior to trial enrollment and patients were able to withdraw from the trial at any time.

*Treatment and Assessments*

Treatment with FCR or FCM-R was repeated every 28 days for a total of six cycles. Fludarabine and cyclophosphamide were administered orally at doses of 24 mg/m2/day and 150 mg/m2/day, respectively, for the first five days of each cycle. These doses are pharmacologically equivalent to the doses used when FCR is given intravenously for CLL(17). This is in contrast to similar studies where intravenous doses of fludarabine and cyclophosphamide are used (1-3, 6). Mitoxantrone was administered intravenously on day 1 at a dose of 6 mg/m2 in the FCM-R group. Rituximab was administered intravenously at 375 mg/m2 on day 1 of cycle 1 and 500 mg/m2 in cycles 2-6. In participants with lymphocyte counts greater than 25x109/L, the dose of rituximab was split to 100 mg on day 1 with the remaining dose given on day 2 to reduce the risk of infusion related reactions. Participants unable to tolerate oral chemotherapy were permitted to receive equivalent intravenous doses of fludarabine (25 mg/m2/day for 3 days) and cyclophosphamide (250 mg/m2/day for 3 days). All participants were given allopurinol at least in cycle 1. PCP prophylaxis and acyclovir were given throughout the treatment. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) was recommended for patients experiencing scheduled delays due to neutropenia. Appropriate dose reductions were recommended in patients with therapy-related cytopenias.

Participants were assessed for response at 3 months post treatment and at 12, 18 and 24 months post randomization in the absence of disease progression requiring treatment. Long-term annual follow-up for survival is being performed until death.

*Endpoints*

The primary endpoint was CR rate (including CRi) at 3 months post treatment. Response was centrally assessed according to IWCLL criteria(16) by two independent, experienced CLL haematologists blinded to treatment allocation. An independent arbiter reviewed discordant reports.

Secondary endpoints at 3 months post treatment included: MRD negativity assessed in the bone marrow by highly sensitive multi-parameter flow cytometry with a level of detection below 1 CLL cell in 10 000 leukocytes(13); ORR defined as at least partial remission (PR); and safety and toxicity as graded by CTCAE V3.0(18).

Longer-term secondary endpoints included PFS, OS and time to MRD relapse in participants who became MRD negative.

*Sample Size*

The sample size was based on testing the null hypothesis of no difference in CR rates between the treatment groups. The CR rate with FCR was estimated to be 50%, with a clinically important improvement considered to be 20%. With a 2-sided 5% level of significance and 80% power, 103 participants were required in each group. Allowing for a 5% dropout rate, the recruitment target was 218 participants.

*Statistical Methods*

All analyses were conducted on the intention-to-treat (ITT) population, in which participants were included according to their randomized treatment. Safety analyses included participants according to treatment received. A 2-sided 5% significance level was used for all formal efficacy endpoint comparisons.

Methods for handling missing endpoint data were pre-specified and approved by the Chief Investigator. Participants with a missing assessment who died from CLL or treatment-related toxicity prior to their primary endpoint assessment, or discontinued treatment early due to non-response or toxicity, were treated as non-responders/MRD-positive. In the formal statistical analysis of the primary endpoint, for participants with at least a PR but missing trephine data to confirm a CR, imputation methods treated MRD-negative participants as having a CR and MRD-positive as not, although summaries also report the un-imputed data. Participants without an available endpoint assessment were not included in the formal statistical analysis of the primary endpoint. This was appropriate as it can be assumed that data are missing completely at random (MCAR), since assessments were most likely unavailable due to samples being un-assessable or missed in error, rather than participant refusal due to level of response or treatment allocation. Sensitivity analyses assessed the robustness of the assumptions regarding missing primary endpoint data.

Multivariable binary logistic regression models compared CR rates, proportions with undetectable MRD and ORR between the treatment groups, adjusted for the minimization factors, excluding center. Parameter estimates, standard errors (SEs), odds ratios (OR) and corresponding p-values for the treatment effect are reported. The differences in proportions are reported with 95% confidence intervals (CIs) and corresponding p-values.

Kaplan-Meier curves are presented for the PFS and OS endpoints. Restricted mean survival time (RMST), used in the event of non-proportional hazards (19), estimated the area under the PFS curves, and treatment groups were compared using generalized linear regression, adjusted for the minimization factors, excluding center. Parameter estimates, SEs, ORs and corresponding p-values for the treatment effect are reported. Multivariable Cox regression analysis formally compared OS between treatment groups, hazard ratios (HR), 95% CIs and corresponding p-values for the treatment effect are reported. Participants without evidence of an event at the time of analysis were censored at the last date they were known to be alive and event-free.

Safety analyses summarized the number of safety events occurring after randomization including treatment-related mortalities (within 3 months post-treatment) and incidence of secondary cancers.

Pre-specified exploratory subgroup analyses assessed the heterogeneity of the treatment effect among subgroups of interest for the primary endpoint, PFS and OS. Formal statistical testing between subgroups was not appropriate due to multiple testing errors and the reduced numbers in each subgroup. Subgroup analyses were interpreted with caution and treated as hypothesis generating.

*Code availability*

All statistical analyses were carried out using SAS software 9.4 (20). Statistical analysis programs were validated but are not available publicly.

**RESULTS:**

*Patient Characteristics*

The CONSORT diagram(21) (*Figure 1*) shows the flow of participants through the trial. A total of 420 patients were screened for eligibility. Of the 205 patients not randomized, the majority were clinically ineligible (n=112, 54.6%). Common reasons included: asymptomatic CLL, poor performance status, prior therapy for CLL, cardiac problems / unstable angina, second malignancy or not having B-CLL.

In total two-hundred and fifteen participants were recruited between July 2009 and April 2012 (FCR: 107, FCM-R: 108) from 29UK institutions with local ethical and management approval. The planned recruitment period ended before the target of 218 could be met. At the time of reporting, it has been approximately 7 years since the trial opened to recruitment, with a median follow-up of 5 years.

The baseline characteristics are displayed in *Table 1*. The median age was 62 years (range 33–77) with 74 participants (34.4%) aged >65 years. There was a male predominance [163 (75.8%)] and 27 participants (12.6%) were Binet stage progressive A, 111 (51.6%) stage B and 77 (35.8%) stage C. A majority of participants [124 (57.7%)] were WHO performance status (PS) 0, with 83 (38.6%) PS 1 and 8 (3.7%) PS 2. Overall, 98 participants (45.6%) had B-symptoms [FCR: 51 (47.7%); FCM-R: 47 (43.5%)], whilst 123 (57.2%) had a β2-microglobulin concentration of ≥4mg/L and 30 (14.0%) had creatinine clearance levels of 30-60 mls/min. Of the evaluable participants, 14/203 (6.9%) had a 17p deletion (FCR: 9/100 (9.0%); FCM-R: 5/103 (4.9%)) and 38/203 (18.7%) an 11q deletion (FCR: 18/100 (18.0%); FCM-R: 20/103 (19.4%)). 127/201 participants (63.2%) were considered to be ‘poorer risk’ in terms of VH mutational status i.e. VH unmutated or involving the VH3-21 gene [FCR: 68/101 (67.3%); FCM-R: 59/100 (59.0%)]. Twenty participants (10.0%) presented with the VH3-21 gene (FCR: 14; FCM-R: 6).

*Treatment*

Of the 215 participants, 154 (71.6%) received 6 cycles of treatment [FCR: 82 (76.6%); FCM-R: 72 (66.7%)] (*Table 2*), and 24 (11.2%) received ≤3 cycles of treatment [FCR: 11 (10.3%); FCM-R: 13 (12.0%)]. Four participants did not receive any protocol treatment [FCR: 3 (2.8%); FCM-R: 1 (0.9%)], three did not meet the eligibility criteria, and one participant allocated to receive FCR was removed by the treating clinician (*Figure 1*). Sixty-one participants (28.4%) discontinued treatment prematurely [FCR: 25 (23.4%); FCM-R: 36 (33.3%)] (*Table 2*). Reasons included: toxicity (n=43); progressive disease (n=2); stable disease with no/minimal response (n=2); ineligibility (n=4); participant choice (n=3); clinician decision (n=5); other (n=2). Overall, 129 (60.0%) participants received G-CSF during treatment as recommended in the protocol as secondary prophylaxis, with a higher proportion in the FCM-R group [FCR: 60 (56.1%); FCM-R: 69 (63.9%)]. Twenty participants unable to tolerate oral chemotherapy received equivalent intravenous doses [FCR: 8 (7.5%), FCM-R: 12 (11.1%)].

*Efficacy*

Overall, 8.4% (n=18) of participants were lost to follow-up for the primary endpoint (FCR: 10.3%; FCM-R: 6.5%), reasons are presented in *Figure 1*. Of the 215 participants, 125 (58.1%) achieved a CR [FCR: 60 (56.1%); FCM-R: 65 (60.2%)] (*Table 3*). In the formal analysis of the primary endpoint including imputation based on MRD outcome, 137/197 (69.5%) achieved a CR, with a similar proportion in each treatment group [FCR: 67/96 (69.8%); FCM-R: 70/101 (69.3%)] (*Table 3*). The difference in response rates (FCM-R – FCR) was -0.5% (95% CI: -13.3%, 12.4%), p-value=0.941. In the multivariable logistic regression analysis, the odds ratio (OR) for achieving a CR with FCM-R compared to FCR was 0.97 (95% CI: 0.53, 1.79), p-value=0.932, concluding that the difference between the treatment groups is not significant at the 5% level. The sensitivity analyses (including assessment of CR without any imputation) did not alter the findings.

There were no large differences in proportion of participants achieving a CR by gender [Male: 100/148 (67.6%), Female: 37/49 (75.5%)], age group [≤65: 91/130 (70.0%), >65: 46/67 (68.7%)], Binet stage [Progressive A/B: 93/130 (71.5%), C: 44/67 (65.7%)] or creatinine clearance levels (mL/min) [30-60: 22/30 (73.3%), >60: 111/160 (69.4%)]. A significantly higher proportion of participants who received >3 cycles of treatment achieved a CR [>3cycles: 135/183 (73.8%); ≤3 cycles: 2/14 (14.3%); difference (95%CI): -59.5% (-78.9%, -40.1%)]. There were no large differences for the primary endpoint for those participants receiving G-CSF during treatment cycles 2 to 6 [G-CSF received: 81/121 (69.9%), No G-CSF: 51/71 (71.8%)].

Lower proportions of participants with a 17p-deletion, 11q-deletion and ‘poorer risk’ VH mutational status achieved a CR [17pdel: 5/11 (45.5%); no 17pdel: 124/176 (70.5%)], [11qdel: 23/37 (62.2%); no 11qdel: 106/150 (70.7%)], [VH unmutated or VH3-21: 76/117 (65.0%); VH mutated: 52/69 (75.4%)].

Of the 215 participants, 191 (88.8%) achieved at least a PR [FCR: 93 (86.9%), FCM-R: 98 (90.7%)] Of the assessable participants, the ORR was 97.0% (191/197), with a similar proportion in each treatment group [FCR: 93/96 (96.9%), FCM-R: 98/101 (97.0%), with a difference (FCM-R – FCR) of 0.15% (95% CI: -4.6%, 5.0%). A binary logistic regression analysis was unable to be performed due to the small number of participants in the non-responders group.

Of the 215 participants, 101 (47.0%) achieved MRD negativity assessed in the bone marrow three-months post-therapy [FCR: 54 (50.5%); FCM-R: 47 (43.5%) (*Table 3*). In the formal analysis of MRD (excluding participants with a missing MRD assessment), 101/184 (54.9%) achieved MRD negativity [FCR: 54/91 (59.3%), FCM-R: 47/93 (50.5%)]. The difference in response rates (FCM-R – FCR) was -8.8% (95% CI: -23.1%, 5.5%), p-value=0.230. In the multivariable logistic regression analysis, the adjusted OR for achieving MRD-negativity with FCM-R compared to FCR was: 0.70 [95% CI: (0.39, 1.26), p=0.231] concluding that the difference between the treatment groups is not significant at the 5% level (*Table 3*).

At the time of analysis (4-years post-randomization of the final participant), 42 (19.5%) participants have died [FCR: 24 (22.4%), FCM-R: 18 (16.7%)], and 89 (41.4%) have either progressed or died [FCR: 44 (41.1%), FCM-R: 45 (41.7%)]. *Table 4* presents the primary cause of death by treatment group. Of the 42 participants deaths, 20 (47.6%) were due to CLL i.e. infection due to CLL, overwhelming tumor load, or high-grade transformation of CLL. [FCR: 13 (54.2%), FCM-R: 7 (38.9%)]. Eight (19.0%) were treatment-related including treatment related MDS/AML and infection due to treatment [FCR: 6 (25.0%), FCM-R: 2 (11.1%)]. *Figure 2* presents the PFS and OS Kaplan-Meier curves by treatment group. The mean PFS time up to a restricted time of 72 months post randomization was 51.7 and 52.3 months in the FCR and FCM-R groups, respectively. The difference in the restricted mean survival between the treatment groups was not significant [FCM-R vs FCR: parameter estimate: 0.48, SE: 3.23, *p*=0.8823]. For OS, the hazard ratio (HR) (FCM-R vs FCR) was not significant in the adjusted Cox regression model [HR&95%CI: 0.75 (0.41, 1.39), p=0.3596].

Of the 101 participants who were MRD negative in the bone marrow at 3 months post treatment (*Table 3*), 23 (22.8%) have either relapsed at the MRD level in the peripheral blood or progressed [FCR: 11/54 (20.4%), FCM-R: 12/47 (25.5%)]. The curves are not presented due to the small number of events.

For the planned subgroup analyses, Kaplan-Meier curves demonstrated an improved PFS for participants who achieved a CR or MRD negativity at 3 months post-treatment, and for those with a VH mutated gene (and not VH3-21) i.e. ‘standard risk’ patients (*Figure 3*). Both sensitivity analyses for CR status without any imputation and subgroup analyses for OS show similar trends.

*Safety and Toxicity*

The safety population included 212 participants (*Figure 1*). 156 SAEs were reported from 97 (45.8%) participants, a lower proportion receiving FCR (41.9%) compared to FCM-R (49.5%). 116 Serious Adverse Reactions (SARs) were reported from 76 (35.8%) participants [FCR: 55 events from 36 (34.3%); FCM-R: 61 events from 40 (37.4%)]. The most commonly reported SARs, 65.5% of events (n=76) were infections and infestations. Ninety-two (43.4%) participants required hospitalization for an SAE [FCR: 43 (41.0%); FCM-R: 49 (45.8%)] (*Table 5*).

One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported from a participant receiving all 6 cycles of FCM-R. They experienced prolonged myelosuppression and had a hypoplastic marrow on their 3-month post-treatment bone marrow aspirate. The event was suspected to be related to F, C and M.

Non-serious adverse events (AEs) were reported from 210 (99.1%) participants, with similar proportions in each treatment group. Of the 2914 AEs reported, 468 (16.1%) were graded as CTCAE grade 3 or above [FCR: 222 (15.9%); FCM-R: 246 (16.2%)] (*Table 5*).

There was one treatment-related mortality reported within 3 months of the end of protocol treatment from a participant receiving FCR.

Within 5 years of participants ending treatment, 39 participants (18.4%) had been diagnosed with a secondary cancer [FCR: 19 (18.1%); FCM-R: 20 (18.7%)]. The most commonly reported secondary cancers were non-melanoma skin cancers in 6.1% (n=13) of participants, followed by non-hematological solid tumors in 5.7% of participants (n=12) (*Table 5*). There have been two reports of myelodysplastic syndrome (MDS), one from each treatment group.

**DISCUSSION**

This multi-center collaborative trial demonstrates that oral FCR results in extremely high response and MRD negative rates (ORR: 97%, CR: 70%, MRD negativity: 59%). Trial follow-up is at a median of 5 years and there are a high number of censored observations but to date the PFS and OS are favorable compared to previous studies. The mean PFS for both trial arms is similar with no significant difference. PFS was improved in participants achieving CR and MRD negativity. Participants with mutated VH genes (excluding VH3-21) had improved PFS compared to those with unmutated VH genes or using VH3-21. The PFS curves for VH mutated genes (excluding VH3-21) plateau at a PFS probability of approximately 35%. Similar plateaus for PFS for this subgroup have been observed in previous studies (1, 22). The FCM-R group results appear equivalent, but the depth of responses was no higher with the addition of mitoxantrone to FCR (ORR: 97%; CR: 69%; MRD negativity: 51%). The median age of participants was 62 years, which is comparable to other front-line CLL trials of fludarabine-based therapies. 89% of the participants received greater than three cycles of treatment, and 72% of the participants received all six cycles of treatment. PCP and acyclovir prophylaxis was recommended for all participants. Secondary prophylaxis with G-CSF was administered to 60% of participants, enabling the delivery of a maximum number of treatment cycles. This may explain the high response and MRD-negative rates in our trial. The dose of fludarabine was reduced by 50% in participants with creatinine clearance between 30-60 mls/min. The 30 (14%) participants with creatinine clearance levels of 30-60 mls/min had a similar CR/CRi rate of 73.3% to those with levels >60mls/min. This might suggests that selected participants considered unfit for FCR due to renal dysfunction can tolerate dose-modified FCR with high response rates.

The addition of mitoxantrone to FCR does not appear to have substantially increased toxicity rates with 34.3% of participants experiencing a SAR with FCR compared to 37.4% with FCM-R. A similar proportion of grade 3 or 4 AEs were experienced in each treatment group (FCR: 15.9% vs FCM-R: 16.2%).

In summary, we have demonstrated that the addition of mitoxantrone to frontline FCR did not improve responses but slightly increased toxicity. In view of this, FCM-R will not be taken forward into a larger definitive Phase III trial. The trial demonstrated that oral FCR given at an equivalent dose to intravenous FCR yields extremely high response rates compared to historical series and was well tolerated. This is consistent with the outcome of its companion trial ARCTIC comparing FCR with FCM-miniR (reported in the companion paper). The explanation for the high response rates is not certain but is possibly due to the fact that in the oral regime the same dose of chemotherapy is spread over 5 rather than 3 days and that the duration of therapy exposure per cycle may be critical. In addition, dose intensity was optimised by mandating primary prophylaxis with acyclovir and co-trimoxazole, and secondary prophylaxis with G-CSF. It was also possible to use dose adjusted FCR for participants with impaired renal function.

FCR therefore remains the gold-standard therapy for CLL in participants considered fit for fludarabine-based therapy against which the novel targeted therapies must be tested, with oral administration of FC giving results at least as good as those obtained with IV administration.

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**CONFLICT OF INTEREST**

Prof. Hillmen received research funding and speakers' fees from Roche Pharmaceuticals. Dr. Rawstron reports personal fees from Roche Pharmaceuticals. Dr. Munir reports personal fees from Roche Pharmaceuticals. Dr. Bloor reports personal fees, consultancy/advisory fees and speakers’ fees from Roche Pharmaceuticals. Dr. Fegan reports personal fees from Roche Pharmaceuticals. Dr. Hamblin reports personal fees from Roche Pharmaceuticals. Prof. Gribben reports personal fees and expenses from Roche Pharmaceuticals.

There are no other conflicts of interest to declare in relation to the work described.

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**FIGURE AND TABLE LEGENDS**

Figure 1: CONSORT Diagram

Figure 2: Kaplan Meier Curves for Progression-Free and Overall Survival

 a. Progression-Free Survival by treatment group

 b. Overall Survival by treatment group

Figure 3: Kaplan-Meier Curves for Progression-Free Survival Subgroup Analyses

 a. PFS by CR status at three months post-treatment

 b. PFS by MRD status at three months post-treatment (assessed in the bone marrow)

 c. PFS by VH mutational risk status

Table 1: Baseline Characteristics

Table 2: Treatment Summaries

Table 3: Efficacy Summaries

Table 4: Primary Cause of Death

Table 5: Safety and Toxicity Summaries

**FIGURES**

**TABLES**