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Abstract

Clinical effectiveness and cost-effectiveness results from the randomised, Phase IIB trial in previously untreated patients with chronic lymphocytic leukaemia to compare fludarabine, cyclophosphamide and rituximab with fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab: the Attenuated dose Rituximab with ChemoTherapy In Chronic lymphocytic leukaemia (ARCTIC) trial

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Background: The conventional frontline therapy for fit patients with chronic lymphocytic leukaemia (CLL) is fludarabine, cyclophosphamide and rituximab (FCR). Rituximab (Mabthera®, Roche Products Ltd) targets the CD20 antigen, which is expressed at low levels in CLL. The standard dose of rituximab in CLL (375 mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2–6) was selected based on toxicity data only. Small doses of rituximab (as low as 20 mg) have biological activity in CLL, with an immediate reduction in circulating CLL cells and down-regulation of CD20. Phase II trials had suggested improved efficacy with the addition of mitoxantrone to FCR. The key assumption for the Attenuated dose Rituximab with ChemoTherapy In CLL (ARCTIC) trial was that the addition of mitoxantrone to fludarabine, cyclophosphamide and low-dose rituximab would be more effective than conventional FCR.

Objectives: To assess whether fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab (FCM-miniR) (100 mg of rituximab per cycle) was non-inferior to FCR in frontline CLL. Complete response (CR) rate was the primary end point, with the secondary end points being progression-free survival (PFS), overall survival (OS), overall response rate, eradication of minimal residual disease (MRD), safety and cost-effectiveness.

Design: ARCTIC was a UK multicentre, randomised, controlled, open, Phase IIB non-inferiority trial in previously untreated CLL. A total of 206 patients with previously untreated CLL who required treatment, according to the International Workshop on Chronic Lymphocytic Leukaemia criteria, were to be

randomised to FCR or FCM-miniR. There was an independent Data Monitoring and Ethics Committee (DMEC) with a pre-planned interim efficacy assessment on 103 participants.

Results: The DMEC's interim analysis led to early trial closure. Although the response rates in both arms were higher than anticipated, FCM-miniR had a lower CR rate than FCR. This was partly attributable to the higher toxicity associated with mitoxantrone. A total of 100 participants completed FCR, 79 completed FCM-miniR and 21 commenced FCM-miniR but switched to FCR following DMEC recommendations. The CR rate for participants receiving FCR was 76%, compared with 55% for FCM-miniR (adjusted odds ratio 0.37; 95% confidence interval 0.19 to 0.73). Key secondary end points also showed that FCR was superior, with more participants achieving MRD negativity (57% for FCR vs. 46% for FCM-miniR). More participants experienced a serious adverse reaction with FCM-miniR compared with FCR (50% vs. 41%). At a median of 37.3 months' follow-up, the PFS and OS rates are good compared with previous studies, with no significant difference between the treatment arms. The economic analysis indicates that because FCM-miniR is less effective than FCR, FCM-miniR is not expected to be cost-effective over a lifetime horizon, producing a mean cost-saving of –£7723, a quality-adjusted life-year loss of –0.73 and a resulting incremental net monetary loss of –£6780.

Conclusions: FCM-miniR is less well tolerated, with poorer response rates, than FCR, partly owing to the additional toxicity associated with mitoxantrone. In view of this, FCM-miniR will not be taken forward into a larger definitive Phase III trial. The trial demonstrated that oral FCR yields extremely high response rates compared with historical series with intravenous chemotherapy.

Future work: We shall compare the results of ARCTIC with those of the ADMIRE (Does the ADdition of Mitoxantrone Improve Response to FCR chemotherapy in patients with CLL?) trial, which compared FCR with FCM-R to assess the efficacy of low- versus standard-dose rituximab, allowing for the toxicity associated with mitoxantrone.

Trial registration: Current Controlled Trials ISRCTN16544962.

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List of abbreviations

β_2M	β_2-microglobulin
AE	adverse event
ARCTIC	Attenuated dose Rituximab with ChemoTherapy In CLL trial
B-CLL	B-cell chronic lymphocytic leukaemia
BNF	*British National Formulary*
BSA	body surface area
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete marrow recovery
CTCAE	Common Terminology Criteria for Adverse Events
CTRU	Clinical Trials Research Unit
DCT	direct Coombs test
DMEC	Data Monitoring and Ethics Committee
EQ-5D™	European Quality of Life-5 Dimensions
EVPI	expected value of perfect information
EVPPI	expected value of perfect parameter information
FC	fludarabine and cyclophosphamide
FCM	fludarabine, cyclophosphamide and mitoxantrone
FCM-miniR	fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab
FCM-R	fludarabine, cyclophosphamide, mitoxantrone and rituximab
FCR	fludarabine, cyclophosphamide and rituximab
GCLLSG	German CLL study group
GCSF	granulocyte colony-stimulating factor
HMDS	Haematological Malignancy Diagnostic Service
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IMP	Investigational Medicinal Product
INB	incremental net monetary benefit
ITT	intention to treat
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NB	net monetary benefit
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Care Excellence
NIHR	National Institutes of Health Research
OD	once daily
OR	odds ratio
ORR	overall response rate
OS	overall survival
PCP	*Pneumocystis carinii* pneumonia
PD	progressive disease
PFS	progression-free survival
PP	per-protocol
PPI	patient and public involvement
PR	partial remission

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RDM	Remission Duration Model
REC	Research Ethics Committee
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SE	standard error
SF-12	Short Form questionnaire-12 items
SF-6D	Short Form questionnaire-6 Dimensions
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VH	heavy-chain variable-region
WHO	World Health Organization
WTP	willingness to pay

Plain English summary

What was the problem?

The first treatment that patients with chronic lymphocytic leukaemia (CLL) usually receive is a combination of the drugs fludarabine, cyclophosphamide and rituximab (Mabthera®, Roche Products Ltd) (FCR). However, research suggested that adding a fourth drug called mitoxantrone to FCR would improve response rates and that a lower dose of rituximab would work just as well as the standard dose.

What did we do?

We established the Attenuated dose Rituximab with ChemoTherapy In CLL trial to compare fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab (FCM-miniR) with the standard FCR treatment. The trial recruited 200 participants.

What did we find?

Three months after the end of treatment, participants were assessed to see how well they had responded. Part-way through the trial we looked at how half of the participants had responded and we found that participants who had received FCR had better response rates and fewer side effects than participants who had received FCM-miniR. The trial was, therefore, closed early and participants who were still receiving FCM-miniR were offered the chance to have FCR instead.

Follow-up assessments are ongoing but, to date, disease progression and overall survival data are good for all participants compared with previous studies.

What does this mean?

The results of this trial show that FCR is a more effective treatment than FCM-miniR, and the addition of mitoxantrone to FCR increases side effects. FCR remains the best available therapy for CLL in patients who are considered fit for treatment with fludarabine.

Scientific summary

Background

The conventional therapy for patients with chronic lymphocytic leukaemia (CLL) who require therapy and are considered fit for fludarabine-based treatment is the combination of fludarabine, cyclophosphamide and rituximab (FCR) (Mabthera®, Roche Products Ltd). Rituximab is a monoclonal antibody targeting the CD20 antigen, which is expressed on B-cells (both normal and malignant). CD20 is characteristically expressed at a low level in CLL. The standard dose of rituximab used in FCR for CLL (375 mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2–6) was selected based on the dose approved as a single agent in follicular lymphoma. The problem with identifying the dose of rituximab, as with many other monoclonal antibodies, is that the maximum tolerated dose is not reached in Phase I trials owing to the specificity of this type of targeted therapy. In effect, the maximum tolerated dose is governed by the volume that can be infused rather than the toxicity of the molecule. The standard dose of rituximab as a single agent in follicular lymphoma of four weekly doses of 375 mg/m^2 was selected pragmatically depending on the amount of available rituximab and the number of patients required in the original follicular lymphoma trial. The same dose was then used when rituximab was combined with various different chemotherapy regimes in lymphoma, with no further Phase I data to define this more accurately. The dose upon which the CLL dose was derived was 375 mg/m^2 but, as the expression of CD20 in CLL is characteristically lower than in the other B-cell malignancies and in normal B-cells, the rituximab dose per cycle of chemotherapy in CLL was arbitrarily increased to 500 mg/m^2. When higher doses of rituximab [three doses of 500 mg/m^2 per cycle of fludarabine and cyclophosphamide (FC) compared with a single dose, which is conventional; so-called FCR3] were used in combination with fludarabine plus cyclophosphamide in a small Phase II trial, there was no evidence that the responses were any higher. However, there is good evidence that small doses of rituximab have biological activity in CLL. Even small doses of rituximab, as low as 20 mg, lead to an immediate reduction in circulating CLL cells by the end of the infusion. This is associated with a marked reduction in the expression of CD20 on the CLL cells, which becomes apparent during the infusion. If a similar, or larger, dose of rituximab is then given on the following day there is often no further evidence of a fall in lymphocyte count owing to the lack of CD20 antigen expression on the CLL cells. There is evidence that this reduction in CD20 expression may be attributable to the 'shaving' of CD20 from the CLL cell. The idea behind the mechanism for CD20 shaving is that, initially, cells coated in rituximab are removed by the reticuloendothelial system, but given the large number of CLL cells, this mechanism is rapidly saturated. At this point, the rituximab bound to the CLL cells coalesces and these aggregates are removed by the reticuloendothelial system, a process called trogocytosis. Therefore, bound and unbound CD20 antigens are removed from the CLL cells, making them non-responsive to further doses of rituximab. A possible consequence of this would be that higher doses of rituximab would remain in the plasma and as soon as any CD20 antigen returns, the same mechanism of shaving would apply until the free rituximab was exhausted or excreted. At this point, CD20 expression would return, allowing further doses of rituximab to be effective. If the above is true then giving ever-increasing doses of rituximab would not be effective and, in fact, lower doses that had biological activity but did not lead to high free plasma levels might allow the more rapid return of the CD20 antigen, thereby enabling subsequent doses of rituximab to have biological activity again. This would suggest that repeated lower doses of rituximab may be equally, or even more, effective, particularly when there is a large amount of tumour antigen present (at the initiation of therapy). The cost of rituximab constitutes approximately 80% of the acquisition costs of FCR, and the infusions last several hours, creating logistic problems for both patients and hospitals. If the dose of rituximab were to be reduced by several fold, then both of these issues would be ameliorated.

Two earlier Phase II trials in both previously untreated and relapsed CLL patients have suggested that the addition of mitoxantrone to FCR results in greater efficacy and is well tolerated, although neither of the trials was randomised to validate this.

There were two key assumptions in the design of the Attenuated dose Rituximab with ChemoTherapy In CLL (ARCTIC) trial. First, it was assumed that the efficacy of a low dose of rituximab [100 mg (i.e. one vial)] was comparable to the conventional dose (500 mg/m^2) when combined with combination chemotherapy in CLL. Second, it was assumed that the addition of mitoxantrone to FC would increase the response rates and be tolerable. Mitoxantrone was, therefore, added to the chemotherapy backbone of FC in order to allow for the possibility that low-dose rituximab might be inferior to the conventional dose. It would then follow that FCM-miniR should be at least non-inferior and, therefore, cost-effective when compared with FCR.

Objectives

The objective of the ARCTIC trial was to assess whether the combination of fludarabine, cyclophosphamide and mitoxantrone with a low dose of rituximab (FCM-miniR; 100 mg per cycle) was non-inferior to the conventional FCR therapy in patients with CLL requiring therapy for the first time. This included the complete remission (CR) rate as the primary end point, with important secondary end points including progression-free survival (PFS), overall survival (OS), overall response rate (ORR), eradication of minimal residual disease (MRD) following treatment, safety and toxicity, and cost-effectiveness. The objective was to use the results of ARCTIC, assuming they were positive, to help design a larger, definitive, Phase III trial.

Methods

The ARCTIC trial was a multicentre, randomised, controlled, open, Phase IIB non-inferiority trial including patients with previously untreated CLL who required treatment by International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria. Patients were randomised on a 1 : 1 basis to receive FCR or FCM-miniR. The intention was to include 206 patients from hospitals around the UK. The trial was monitored by an independent Data Monitoring and Ethics Committee (DMEC) and a Trial Steering Committee (TSC), and there was a pre-planned interim assessment of efficacy after 103 participants had completed therapy.

Primary end point (response assessment) data were centrally reviewed by an independent panel of CLL clinicians who determined, using IWCLL criteria, whether or not a CR had been achieved. A formal analysis of the primary end point used an adjusted logistic regression model, and time-to-event analyses were performed using adjusted Cox regression analyses. The economic evaluation used a within-trial analysis, in which cost-effectiveness was assessed within the 24-month trial period using individual patient data collected during the trial, and a decision analytic model analysis, in which cost-effectiveness was assessed over a lifetime horizon using standard modelling techniques applied to the trial data in order to extrapolate the trial results.

Results

A total of 200 of the planned 206 patients were entered into the ARCTIC trial between December 2009 and September 2012 from 34 centres across the UK. There were nine withdrawals (4.5%) during the trial, which were balanced across the treatment arms. A total of 141 participants (70.5%) completed the recommended six cycles of treatment, with slightly more in the FCR arm than the FCM-miniR arm (70.0% vs. 64.6%). The majority of participants discontinuing treatment did so because of toxicity. At the DMEC's pre-planned interim analysis, 82.9% of participants achieved a CR in the FCR arm compared with 61.4% of participants in the FCM-miniR arm. Although the difference between the two arms was not significant (at the adjusted 0.5% level) the experimental treatment had the lower CR rate. As the results were approaching significance in favour of the control group, and there was evidence of additional toxicity in the FCM-miniR arm, the trial was closed early at the recommendation of the DMEC, and participants still

receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles.

At the final analysis of the primary end point (at 3 months post treatment) 100 participants had completed FCR, 79 had completed FCM-miniR and 21 had initially received FCM-miniR but crossed over to receive FCR at some point in their treatment following the advice of the DMEC recommendation. A total of 76.1% of participants achieved a CR in the FCR arm compared with 54.7% in the FCM-miniR arm. The difference in proportions (FCM-miniR – FCR) was –21.4% [95% confidence interval (CI) –35.8% to –7.0%] and the adjusted analysis gave an odds ratio of 0.37 for the treatment effect (95% CI 0.19 to 0.73), indicating that participants in the FCM-miniR were significantly less likely to achieve a CR. Therefore, at the final analysis there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates at 3 months post treatment, and that it is, in fact, significantly inferior. The analysis of the per-protocol population and the sensitivity analyses support this conclusion.

The ORR was high at 92.6%, with 7.5% fewer participants achieving at least a partial response in the FCM-miniR arm compared with the FCR arm (95% CI –15.6% to 0.6%).

The eradication of MRD in the bone marrow at the end of therapy is a strong predictor of outcome in CLL. At 3 months post treatment, 53% of participants were MRD negative, with a higher percentage of participants in the FCR arm than the FCM-miniR arm (57.0% vs. 46.4%). The difference in proportions between FCR and FCM-miniR was not statistically significant ($\chi^2 = 1.97$; $p = 0.160$), although it was approaching significance.

There was no significant difference between the treatment arms with respect to PFS, nor was there a significant difference in OS. However, there was a non-significant trend towards the FCM-miniR participants performing worse in terms of both PFS and OS. At 24 months post randomisation, 89.4% of the FCR participants remained progression-free compared with 79.1% of the FCM-miniR participants. In terms of OS at 24 months, 95.8% of the FCR participants remained alive compared with 88.5% of the FCM-miniR participants.

In the exploratory subgroup analyses, PFS and OS were significantly improved for participants who were MRD negative or who had achieved a CR at 3 months post treatment, or who received more than three cycles of treatment. In addition, of those participants who were MRD positive, OS was worse in participants who received FCM-miniR than in those who received FCR, suggesting that after progression the participants initially treated with FCM-miniR may respond more poorly to, or be too unwell to receive, salvage therapies. Longer follow-up data are required to be able to assess reliably the time-to-event outcomes, and these will be updated in future.

More participants experienced a serious adverse event (SAE) in the FCM-miniR arm compared with the FCR arm (58.2% vs. 49.0%), as well as a serious adverse reaction (49.4% vs. 41.0%). More participants in the FCM-miniR arm were hospitalised for a SAE during the trial (51.9% vs. 46.0%) and six SAEs were deemed to be life-threatening or resulted in death compared with three in the FCR arm. A similar proportion of participants experienced an adverse event (AE) in each treatment arm, but a higher proportion of Common Terminology Criteria for Adverse Events grade 3 and 4 AEs were reported in the FCM-miniR arm (22.4% vs. 15.0%). There were no treatment-related mortalities within 3 months of completing protocol treatment.

The results of the economic analysis indicate that FCM-miniR is cost-effective in the short term, but only as a result of saving money at the expense of worse health outcomes, and is unlikely to be cost-effective in the long term. Over the 24-month trial period, FCM-miniR produced a mean cost saving of £6619 and a mean quality-adjusted life-year (QALY) loss of –0.059 compared with FCR. The incremental cost-effectiveness ratio (ICER) was £112,193, indicating that for every £112,193 saved by adopting FCM-miniR, one QALY would be lost. At a willingness-to-pay threshold of £20,000 per QALY, this leads to a net benefit gain of £5439

(equivalent to 0.27 QALYs), and there was a 100% probability that FCM-miniR is cost-effective. However, the cost-effectiveness of FCM-miniR was not sustained in the long-term analysis. Results of the decision model indicate that over a lifetime horizon, FCM-miniR produces a mean cost saving of £7723 and a mean QALY loss of –0.73. The associated ICER is £10,651, indicating that for every £10,651 saved by adopting FCM-miniR, one QALY would be lost. At a £20,000 per QALY threshold, this leads to a net loss of –£6780 (–0.34 QALYs), with a 19% chance that FCM-miniR is cost-effective.

Conclusions

Participants randomised to FCM-miniR had a significantly lower CR rate than those randomised to FCR (FCM-miniR 55% vs. FCR 76%), indicating that FCR is the more effective treatment. This seemed, at least in part, to be attributable to the higher toxicity associated with the addition of mitoxantrone to FCR. Key secondary end points also indicated that FCR had greater efficacy, with a higher proportion of participants achieving eradication of MRD (57% for FCR compared with 46% for FCM-miniR). The follow-up in the trial is still immature (median 37.3 months from randomisation) but, to date, the PFS and OS are good compared with previous studies and there is no significant difference between the two treatment arms, although there is a possible trend towards FCR patients having improved PFS and OS. The cost-effectiveness analysis indicates that, although FCM-miniR is expected to be cost-effective in the short term, it is unlikely to be cost-effective when taking into account long-term costs and health benefits.

In summary, there is strong evidence to suggest that FCM-miniR is not non-inferior to FCR in terms of CR at 3 months post treatment and that the addition of mitoxantrone adds toxicity to FCR. Although FCM-miniR was found to be cost-effective over the trial period, it is unlikely to be cost-effective in the long term. In view of this, FCM-miniR will not be taken forward into a larger, definitive, Phase III trial.

The trial demonstrated that oral FCR yields extremely high response rates compared with historical series in which the chemotherapy was given intravenously and it remains the gold-standard therapy for CLL in patients considered fit for fludarabine-based therapy.

Trial registration

The trial is registered as ISRCTN16544962.

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Chapter 1 Introduction

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Scientific background

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia, affecting approximately 6.9 per 100,000 of the population. The incidence of CLL increases with age and twice as many men are affected as women. CLL results from the clonal proliferation of B-cells and is diagnosed by the pattern of expression of various cell surface antigens on the CLL cells. Patients most commonly present with lymphocytosis, lymphadenopathy, splenomegaly and systemic symptoms, such as fatigue, weight loss and malaise. The clinical course of CLL is highly variable, with a median survival from diagnosis in the region of 7 years. Patients with more advanced disease (Binet stages B, C and stage A progressive) have a significantly worse survival.

Standard therapy for chronic lymphocytic leukaemia

Fludarabine combined with cyclophosphamide is one of the more frequently used combinations of drugs for treating CLL in second and subsequent line use. The MD Anderson Cancer Center reported the use of fludarabine and cyclophosphamide combined with rituximab (Mabthera®, Roche Products Ltd) (FCR) in both previously untreated and refractory CLL.[2,3] The response rates for FCR are very impressive and compare extremely positively with historical controls treated with fludarabine, either alone or in combination with cyclophosphamide. In previously untreated patients, complete remission was demonstrated in 217/300 (72%) patients, nodular partial remission in 31 (10%), partial remission in 37 (12%), no response in 13 (4%) and early death in 2 (< 1%) patients.[2] The same group also reported their experience with FCR in 284 patients with previously treated CLL.[3] The estimated median progression-free survival (PFS) was 21 months, with a median overall survival (OS) of 47 months. The median number of prior treatments was two: 67 patients were alkylating agent refractory, 52 were fludarabine refractory and 98 patients had prior rituximab. Using National Cancer Institute (NCI) criteria, 30% of patients achieved a complete remission rate, 14% achieved nodular partial remission and 30% had partial response (PR), giving an overall response rate (ORR) of 74%.

The German CLL Study Group (GCLLSG) completed the German CLL8 trial, which compared FCR with fludarabine and cyclophosphamide (FC) in patients with CLL who had previously been untreated and required therapy according to conventional criteria.[4] It was reported that 811 patients were entered into the GCLLSG CLL8 trial and randomly assigned to receive either FC or FCR. The ORR was significantly higher in the FCR arm (95%; 370/390 patients) than the FC arm (88%; 328/371) ($p = 0.001$). The complete response (CR) rate of the FCR arm was 52% compared with 27.0% in the FC arm ($p < 0.0001$). PFS was 65% at 3 years in the FCR arm and 45% in the FC arm ($p < 0.0001$). Updated data showed that at a median follow-up of 5.9 years, the PFS was 38% in the FCR group compared with 27.4% in the FC group ($p < 0.0001$). A total of 69.4% of the patients were alive in the FCR group versus 62.3% in the FC group. The median OS was 86 months in the FC group but the median OS was not reached in the FCR arm ($p < 0.001$).[5] In 2009, the European Medicines Evaluation Agency granted a product licence for rituximab combined with FC in previously untreated CLL.

Rituximab dose

The dose of rituximab has not been established systematically in CLL. It has been extrapolated from the earlier trials with use of rituximab in B-cell malignancies. However, rituximab monotherapy at a dose of 375 mg/m^2 induced an ORR of 13% in previously treated CLL/small lymphocytic lymphoma (SLL).[6,7] This poor response was thought to be attributable to low CD20 expression on CLL cells and binding of rituximab to CD20 positive cellular debris. Subsequent studies investigating thrice weekly doses of rituximab (375 mg/m^2) and higher

weekly doses of rituximab (500–2250 mg/m^2) in previously untreated patients induced modest ORRs of 43% and 40%, respectively.[8–10] The combination of intravenous FC along with rituximab at variable dose (375 mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2–6) was used in the Phase III CLL8 trial, showing an excellent ORR, PFS and OS.[5] However, the rationale of using higher doses of rituximab has not been formally assessed.

Rituximab binds specifically to the transmembrane antigen CD20, a non-glycosylated phosphoprotein located on pre-B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas. CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. The phenomenon of CD20 shaving on CLL cells with rituximab has been established in CLL. Most of the CLL cells were cleared after 30 mg of rituximab followed by recrudescence of CLL cells which have lost > 90% of CD20 expression. These data suggested that low-dose rituximab thrice weekly at much lower doses of 20–60 mg/m^2 may promote enhanced clearance of CLL cells by preserving CD20 expression.[11] Subcutaneous rituximab at a dose of 20 mg three times a week resulted in the reduction of CD20 expression on CLL cells, but sufficient expression was maintained during the course of 6–12 weeks in another study.[12] A combination of low-dose rituximab (20 mg/m^2 three times a week), alemtuzumab (Lemtrada®, Genzyme Therapeutics) and pentostatin (Nipent®, Hospira UK Ltd) in high-risk CLL showed that this low dose of rituximab is able to opsonise and clear the majority of circulating cells, but the loss of CD20 is less pronounced. There was also evidence of complement activation owing to C3d deposition on CLL cells and natural killer cell activation owing to down-modulation of CD16, up-regulation of CD54 and a decrease in the number of natural killer cells.[13] Hence, there is considerable evidence that rituximab at doses as low as 20 mg/m^2 can be effective and can reduce the phenomenon of CD20 shaving, as seen with the higher dosing of rituximab used in CLL.

Rituximab has also been used in lower doses in a variety of autoimmune conditions, such as refractory systemic lupus erythematosus and rheumatoid arthritis, where it is standard to use two intravenous doses of 1000 mg 2 weeks apart.[14–17] Rituximab at a dose of 100 mg once a week for 4 weeks has been used in autoimmune haemolytic anaemia and immune thrombocytopenic purpura with relative similar efficacy to the standard dose of 375 mg/m^2, although there are no randomised controlled trials to compare the two doses.[18,19] Furthermore, two infusions of 250 mg/m^2 of rituximab in mixed cryoglobulinaemia are as effective as four infusions of standard-dose rituximab.[20]

In summary, the dose of rituximab in the treatment of CLL has not been systematically established and there is good evidence to suggest that low-dose rituximab would be effective in combination with chemotherapy.

Addition of mitoxantrone

Mitoxantrone is a synthetic anthracenedione that is structurally similar to doxorubicin and daunorubicin. It was synthesised with the aim of reducing side effects, especially cardiotoxicity. It is indicated, either in combination therapy or as a single agent, in the treatment of acute non-lymphocytic leukaemia, metastatic breast cancer, hepatoma, lymphoma and paediatric sarcoma.

The addition of mitoxantrone to the fludarabine-based therapy has been found to result in high response rates in a variety of indolent lymphoproliferative disorders, including follicular lymphoma[21] and mantle cell lymphoma.[22] The combination of fludarabine, cyclophosphamide and mitoxantrone (FCM) has been reported in 60 patients who have relapsed or resistant CLL.[23] The ORR in this series was of 78% with 30 patients (50%) achieving a complete remission. It was of considerable importance that 10 of the patients in CR had an eradication of detectable minimal residual disease (MRD) by a sensitive four-colour flow cytometric test, and that these patients had a significantly prolonged survival compared with the other patients in this series. In addition, FCM plus rituximab (FCM-R) appears to be a very promising combination in Phase II trials for CLL. The Barcelona group have reported the use of FCM-R in a non-randomised Phase II trial reporting a complete remission rate of 82% and an ORR of 93% in previously untreated CLL.[24] In this study, 46% of the CR patients had undetectable MRD. The National Cancer Research Institute (NCRI) CLL subgroup has recently completed a randomised Phase II study

including FCM and FCM-R in previously treated patients with CLL. This study recruited 52 patients, with 26 in each arm, and reported a 65% CR rate for FCM-R compared with a 58% CR rate for FCM, with five and three patients, respectively, achieving eradication of MRD following FCM-R and FCM.[25]

Rationale for design

As we previously demonstrated that the combination of fludarabine, cyclophosphamide, mitoxantrone and rituximab can be delivered safely[25] and that there is evidence of synergistic effect in this combination, the aim of this trial was to test the hypothesis that the low dose of rituximab (100 mg per cycle) in combination with FCM would be as effective as the current standard care, which is the combination of FCR. The data from the use of low-dose rituximab suggest that it can result in effective B-cell depletion with relative preservation of CD20 expression on CLL cells, which would be important in terms of maintaining the efficacy of rituximab. The higher dose of rituximab used in CLL is based primarily on the efficacy of the drug as a single agent where higher doses resulted in better ORRs. However, it can be postulated that higher doses are required as a single agent owing to the tumour burden. The combination of chemotherapy with rituximab might not require the higher dose of rituximab as there is effective clearance of tumour load, and preservation of CD20 expression on CLL cells may be important to maintain the efficacy of rituximab.

Based on scientific rationale, another important aspect in the design of the trial was to assess the cost-effectiveness of delivering the combination of FCM and rituximab at a low dose. The total cost of six cycles of rituximab at the current recommended dose in the UK is estimated to be £10,128 for an average body surface area (BSA) of 1.93m^2 (average BSA in CLL8 trial).[17] This does not include the hospital cost for delivery of the infusion. The cost of six cycles of rituximab at a standard dose of 100 mg would be £1048. The infusion time to deliver this dose will be considerably lower than the standard dose. It can be suggested that the chances of developing infusion-related reactions requiring hospital admission would be lower at the lower dose of rituximab. The cost of six cycles of mitoxantrone at a dose of 6 mg/m^2 intravenously with this combination is estimated to be £600. The cost-effectiveness analysis of comparing the two arms of the trial would be crucial in establishing whether or not the use of a lower dose of rituximab is a reasonable alternative to the standard-arm FCR. Also, the non-inferiority design of the trial helps to ascertain whether lowering the dose of rituximab, and hence reducing the cost of treatment, does not affect the efficacy in terms of CR rates, as well as the longer-term outcomes of PFS and OS.

In summary, the trial answers a critical scientific question of whether or not reducing the dose of rituximab and using a combination of mitoxantrone with oral FC would be as effective as standard care, and whether or not this would, in turn, have an effect on the toxicity and cost-effectiveness of the regimes.

Chapter 2 Methods

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Aims and objectives

The aim of the ARCTIC trial was to establish whether the addition of mitoxantrone, with a low dose of rituximab, to fludarabine and cyclophosphamide (i.e. FCM-miniR), is as effective as FCR in terms of response in patients with previously untreated CLL.

The primary objective of the statistical analysis was to compare the CR rates as defined by IWCLL criteria[26] in each treatment group, in order to determine whether FCM-miniR was non-inferior to FCR.

The secondary objectives were:

- to assess the rate of eradication of detectable MRD following treatment with FCR or FCM-miniR
- to assess the ORR (complete or partial remission defined by IWCLL criteria) between the treatment groups
- to assess the safety and toxicity of low-dose rituximab and mitoxantrone in combination with FC
- to evaluate PFS
- to evaluate OS
- to evaluate time to MRD relapse.

The primary objective of the economic evaluation was to evaluate the incremental cost-effectiveness of treating patients with CLL with FCM-miniR compared with the standard treatment of FCR. Two economic evaluations were undertaken in this phase:

- a within-trial analysis comparing the outcomes and costs up to 24 months' follow-up
- a long-term cost-effectiveness analysis modelling outcomes and costs over a lifetime horizon.

The evaluation followed the reference case guidance for technology appraisals set out by the National Institute for Health and Care Excellence (NICE).[27]

Trial design

The ARCTIC trial is a multicentre, randomised, controlled, open, Phase IIB non-inferiority trial in patients who are newly diagnosed with B-cell chronic lymphocytic leukaemia (B-CLL). Patients were randomised on a 1 : 1 basis to receive one of two trial interventions, FCR or FCM-miniR.

The trial was reviewed and approved by the National Research Ethics Service Leeds (East) Research Ethics Committee (REC) (reference 09/H1306/54) and was registered as an International Standard Randomised Controlled Trial, number ISRCTN16544962. The trial was registered on the European Clinical Trials Database (EudraCT), number 2009–010998–20.

Patient and public involvement

The trial was overseen by the NCRI CLL Subgroup Committee which includes two patient and public involvement (PPI) representatives. Trial updates were presented to this committee three times per year and

the PPI representatives would provide feedback on the trial during these meetings. There was involvement from a PPI representative on the Trial Steering Committee (TSC) who provided input into the initial production of, and any amendments to, the Participant Information Sheet and other trial documentation intended for use by participants. Through membership of the TSC the PPI representatives also provided input into the design and conduct of the trial through annual meetings. The Plain English summary has been reviewed by a PPI representative who is part of the Trial Management Group (TMG).

Participants

The trial sought to recruit 206 participants with previously untreated CLL from ethically approved hospitals around the UK. Participants had to meet the following eligibility criteria in order to participate in the trial:

Inclusion criteria

- At least 18 years of age.
- B-CLL with a characteristic immunophenotype, including SLL.
- Binet's stage A progressive or B, or stage C.
- Requiring therapy by the IWCLL criteria in that they must have at least one of the following:
    - evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
    - massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
    - massive nodes (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
    - progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time of < 6 months as long as the lymphocyte count is over $30 \times 109/l$
    - a minimum of any one of the following disease-related symptoms must be present:
        - unintentional weight loss more than or equal to 10% within the previous 6 months
        - significant fatigue (i.e. Eastern Cooperative Oncology Group performance status 2 or worse; cannot work or unable to perform usual activities)
        - fevers of greater than 38.0 °C for 2 or more weeks without other evidence of infection
        - night sweats for more than 1 month without evidence of infection.
- No prior therapy for CLL.
- World Health Organization (WHO) performance status of 0, 1 or 2.
- Able to provide written informed consent.

Exclusion criteria

- Prior therapy for CLL.
- Active infection.
- Past history of anaphylaxis following exposure to rat- or mouse-derived complementarity determining region-grafted humanised monoclonal antibodies.
- Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception while receiving treatment and for 12 months after treatment has finished.
- Men whose partners are capable of having children but who are not willing to use appropriate medically approved contraception while receiving treatment and for 12 months after treatment has finished, unless they are surgically sterile.
- Central nervous system involvement with CLL.
- Mantle cell lymphoma.

- Symptomatic cardiac failure not controlled by therapy or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded).
- Other severe, concurrent diseases or mental disorders.
- Known to be human immunodeficiency virus (HIV)-positive.
- Patient has active or prior hepatitis B or C.
- Active secondary malignancy excluding basal cell carcinoma.
- Persisting severe pancytopenia (neutrophils $< 0.5 \times 10^9$/l or platelets $< 50 \times 10^9$/l) or transfusion-dependent anaemia unless attributable to direct marrow infiltration by CLL.
- Active haemolysis (patients with haemolysis controlled with prednisolone at a dose of 10 mg or less per day can be entered into the trial).
- Patients with a creatinine clearance of < 30 ml/minute (either measured by or derived from the Cockcroft–Gault formula).

Recruitment procedure

Participants were recruited from multiple research centres around the UK. Research centres were identified via a feasibility assessment to determine the most appropriate centres to participate in the trial. Research centres were required to have obtained ethical and management approvals and undertaken a site initiation meeting with the Clinical Trials Research Unit (CTRU) based at the University of Leeds prior to the start of recruitment into the trial. Potential participants were identified by the clinical team at participating centres and were approached to participate in the trial during standard clinic visits. Each participating centre was required to maintain a log of all patients screened for eligibility and to record reasons for non-randomisation.

Randomisation

Participants who fulfilled the eligibility criteria were randomised on a 1 : 1 basis to receive either FCR or FCM-miniR. A computer-generated minimisation program that incorporated a random element was used to ensure that treatment groups were well-balanced for the following characteristics:

- centre
- Binet staging (A progressive or B, C)
- age (≤ 65 years, > 65 years)
- sex (male, female).

Informed consent

A verbal explanation of the trial was provided by the attending medical staff and a Participant Information Sheet and Informed Consent Document was provided for the patient to consider. This included detailed information about the rationale, design and personal implications of the trial. Following information provision, participants had as long as they needed to consider participation (normally a minimum of 24 hours) and were given the opportunity to discuss the study with their family and other health-care professionals before they decided whether they would be willing to take part in the study.

Assenting patients were then invited to provide informed, written consent and to be formally assessed for eligibility. A record of the consent process including the date of consent and all those present was to be kept in the participants' medical notes. The original consent form was kept at the research centre, filed in the Investigator Site File, and copies of the consent form were given to the participant and the CTRU at the University of Leeds.

Participants were free to withdraw from the trial at any time. The specific wishes of any participant wanting to withdraw consent for further involvement in the trial, be that from further treatment and/or follow-up data collection, was documented to ensure appropriate processes were followed after withdrawal.

Interventions

Participants were randomised to receive six cycles of either FCR or FCM-miniR according to the regimens outlined below (*Tables 1* and *2*).

Cycles of FCR and FCM-miniR were repeated every 28 days for a total of six cycles.

Participants who experienced nausea and vomiting or diarrhoea were given FC via the intravenous route owing to concerns over drug absorption. Intravenous fludarabine was given at a dose of 25 mg/m^2/day for 3 days (bioequivalent to 24 mg/m^2/day for 5 days given orally) and cyclophosphamide was given at a dose of 250 mg/m^2/day for 3 days.

Routine concomitant medications

Participants received prophylaxis against *Pneumocystis carinii* pneumonia (PCP) with 960 mg of co-trimoxazole bi-daily on Monday/Wednesday/Friday or 480 mg on a daily basis. Participants who were allergic to co-trimoxazole received an alternative, such as dapsone (Dapsone, Actavis UK Ltd) [100 mg once daily (OD)] or nebulised pentamidine (Pentacavinat, Sanofi) (monthly). PCP prophylaxis continued throughout treatment and for at least 2 months after the last course of treatment. Aciclovir (400 mg bi-daily) was recommended as prophylaxis against herpes virus reactivation for all participants. Allopurinol at a dose of 300 mg/day was recommended for all participants for at least the first 28 days of therapy.

TABLE 1 Fludarabine, cyclophosphamide and rituximab

Drug name	Entry route	Dosage	Number of days
Fludarabine	Oral	24 mg/m^2/day	Days 1–5
Cyclophosphamide	Oral	150 mg/m^2/day	Days 1–5
Rituximab	Intravenous	375 mg/m^2	Day 1 (Cycle 1)
Rituximab	Intravenous	500 mg/m^2	Day 1 (Cycles 2–6)

TABLE 2 Fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab

Drug name	Entry route	Dosage	Number of days
Fludarabine	Oral	24 mg/m^2/day	Days 1–5
Cyclophosphamide	Oral	150 mg/m^2/day	Days 1–5
Mitoxantrone	Intravenous	6 mg/m^2/day	Day 1
Low-dose rituximab	Intravenous	100 mg	Day 1

Dose delays and reductions

Treatment was delayed or reduced in the following circumstances:

Rituximab-related infusion reactions

The infusion was temporarily stopped until the reaction was resolved and then restarted at half the speed of infusion.

Impaired renal function

Fludarabine was not to be given to participants with a creatinine clearance of < 30 ml/minute. Participants with a creatinine clearance of < 30 ml/minute could have a delay of treatment for up to 4 weeks but were withdrawn from the trial treatment if their creatinine clearance did not improve. Participants with a creatinine clearance of between 30 and 60 ml/minute were permitted to have a 50% dose of fludarabine at the discretion of the treating clinician.

Neutropenia

If neutrophils were $< 1.0 \times 10^9$/l owing to trial chemotherapy rather than bone marrow involvement, treatment was delayed for up to 2 weeks, with a 25% dose reduction of FC in subsequent treatment cycles. Participants who had a neutrophil count of $< 1.0 \times 10^9$/l at day 28 of any cycle of therapy received granulocyte colony-stimulating factor {GCSF [lenograstim (Granuocyte, Chungai Pharma UK Ltd)]} at a recommended dose of 263 µg/day from days 7–13 for the next and all subsequent cycles of chemotherapy. Further dose reductions were permitted if neutropenia recurred after the 25% dose reduction. If the neutrophil count recovered to $> 1.0 \times 10^9$/l the doses of chemotherapy were re-escalated with continuing GCSF support.

Other haematological toxicities

If platelets were $< 75 \times 10^9$/l as a result of trial chemotherapy rather than bone marrow involvement, treatment was delayed for up to 2 weeks, with a 25% dose reduction of FC in subsequent treatment cycles. If on subsequent cycles of therapy platelets had recovered to over 100×10^9/l, the chemotherapy doses were re-escalated. If further haematological toxicity occurred after the 25% dose reduction further dose reductions were permitted.

Data collection and management

Data collection took place via paper case report forms (CRFs), which centres returned to the CTRU for entry onto a central database. Initial validation checks of the forms were carried out and the trial database also validated most dates and data in line with pre-programmed validation rules.

Safety monitoring

All AEs, both related and unrelated to the treatment of CLL, were collected for all patients and evaluated for duration and intensity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. AEs were collected from randomisation until 30 days after the last dose of treatment with FCR or FCM-miniR.

Serious adverse events (SAEs) were defined as any untoward medical occurrence or effect that:

- resulted in death
- was life-threatening
- required inpatient hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability or incapacity

- consisted of a congenital anomaly or birth defect
- may have jeopardised the patient and required medical or surgical intervention to prevent one of the outcomes listed above.

Where a SAE was deemed to have been related to an Investigational Medicinal Product (IMP) used within the trial (fludarabine, cyclophosphamide, rituximab or mitoxantrone) the event was termed as a serious adverse reaction (SAR).

A Suspected Unexpected Serious Adverse Reaction (SUSAR) was defined as a SAR that also demonstrated the characteristics of being unexpected, the nature and severity of which was not consistent with the information about the medicinal product in question set out in the summary of product characteristics for that product.

Serious adverse events were collected from the time of randomisation until 30 days post treatment. SARs and SUSARs were collected from the time of randomisation and for the duration of the trial.

All SAEs, SARs and SUSARs were reported by the CTRU to the Chief Investigator of the trial as they occurred. A summary of how many SAEs and SUSARs had been received was reported at each TMG meeting. A summary of all SAEs and SUSARs was presented by treatment arm to the DMEC at all annual meetings and in an interim report every 6 months, with any safety concerns being fed back to the TSC.

Outcome measures

Primary outcome measure

- Proportion of participants achieving a CR at 3 months post therapy, as assessed by IWCLL criteria.[26]

Secondary outcome measures

- Proportion of participants with eradicated MRD at 3 months post therapy: MRD is defined as negative or undetectable owing to the presence of $< 0.01\%$ CLL cells in the blood or bone marrow by IWCLL criteria.[26]
- Overall response rate at 3 months post therapy: defined as complete or partial remission by IWCLL criteria.[26]
- Safety and toxicity: reported based on AEs (as graded by CTCAE V3.0), SAEs, SUSARs and treatment-related mortalities within 3 months of discontinuing protocol treatment. Determined by routine clinical assessments at each centre.
- Economic evaluation: quality-adjusted life-years (QALYs) were used to measure health benefit. Health-related quality of life was estimated using responses to health economics participant questionnaires, which included the European Quality of Life-5 Dimensions (EQ-5D™) and Short Form questionnaire-12 items (SF-12) [converted to Short Form questionnaire-6 Dimensions (SF-6D)].[28]
- Progression-free survival at 2 years: time from randomisation to first documented evidence of disease progression or death. Participants without evidence of disease progression at the time of analysis are censored at the last date on which they were known to be alive and progression free. The initial analysis was planned once all participants had been followed for 2 years post randomisation.
- Overall survival: time from randomisation to date of death. Participants still alive at the time of analysis are censored at the date on which they were last followed up. The initial analysis was planned once all participants had been followed for 2 years post randomisation.
- Time to MRD relapse in participants who are MRD negative 3 months post treatment: time from the 3-month post-treatment visit, for those participants who became MRD negative, to when the

participant became MRD positive. Participants who were alive and MRD negative at the time of analysis, or participants dying from causes unrelated to CLL, were censored. If participants were lost to follow-up, their MRD relapse-free survival time was censored at the time at which they were last known to be alive and MRD negative.

Independent primary end point review

The primary end point data, response at 3 months post treatment by IWCLL criteria, was centrally reviewed by an independent panel in order to enhance the consistency and accuracy in the reporting of the primary end point, and to eliminate potential local assessment bias. The independent review panel consisted of CLL clinicians who were identified via the NCRI CLL Subgroup Committee. The independent reviews were performed using anonymised data with no information regarding which treatment was provided for each participant. Each response assessment was made by two independent clinicians and where the outcome of the assessments differed the data were sent to a third clinician, an independent arbiter, to make a final decision on response.

Sample size

A total of 206 participants were required. From previous studies it was anticipated that FCR would produce response rates of at least 50%. In particular, the results from the GCLLSG, presented at the American Society of Haematology conference 2008, showed a 52% CR rate with FCR.[4,29] It was anticipated that FCM-miniR would actually have a superior response rate to FCR. This was based on, firstly, the assumption that miniR was as good, or nearly as good, as full-dose rituximab,[30] and, secondly, the hypothesis that mitoxantrone increases the response rate when added to FCR. It was, therefore, hypothesised that FCM-miniR may increase the response rate by approximately 10%. If this was the case, and FCM-miniR really had a 10% better response rate when compared with FCR, a non-inferiority Phase IIB trial was considered practicable. Under this assumed 10% difference in favour of FCM-miniR, to have 80% power to show non-inferiority, where this is defined as FCM-miniR being not more than 10% worse in terms of response rate than FCR, the trial would require the randomisation of 98 participants per arm, 196 in total.[31]

Note that if the FCR response rate deviates in either direction from 50%, the sample size required to show that the CR rate in the FCM-miniR group is not inferior by more than 10% would decrease. Therefore, this calculation was conservative, in that deviations from this assumption increase the power to assess FCM-miniR being not more than 10% worse in terms of response rate than FCR.

To account for a 5% dropout, 206 participants (103 per arm) were sought to be randomised. This approach used a one-sided 97.5% confidence interval (CI), that is, an α (type I) error rate of 2.5%, equivalent to a conventional α of 5% for the superiority setting.[31]

Statistical analysis

A full statistical analysis plan was written and signed off in accordance with current CTRU standard operating procedures.

Analysis populations

All analyses were conducted on the intention-to-treat (ITT) population, in which participants were included according to the treatment they were randomised to.

For the outcome measures assessing response, participants without an available response assessment, who had not withdrawn for toxicity or died, were excluded from the denominators. This was felt to be appropriate

as it was strongly assumed that response end point data would be missing completely at random, given that participants were unlikely to refuse to have assessments performed owing to their level of response or treatment allocation. Assessments were more likely to be unavailable as a result of samples being un-assessable or missed in error. Reasons for missing response data were monitored and have been summarised (see *Table 24*).

A per-protocol (PP) analysis was planned for the primary end point assessment in addition to the ITT, where only participants who received at least one cycle of treatment in line with the protocol, who were not major eligibility violators and for whom primary end point data were available are included. For the primary analysis, equal weighting is given to both the ITT analysis and the PP analyses, as the ITT analysis is likely to be the least conservative approach when assessing non-inferiority.

Safety end points were assessed based on the safety population, which included participants according to the treatment they actually received and who had been exposed to at least one dose of the study treatment.

Missing data handling

In the evaluation of response for the primary end point, the analysis was based on the centrally reviewed data at 3 months post treatment. Participants without an assessment of response were treated as non-responders in the ITT and PP analyses if they either:

1. died from CLL or protocol treatment prior to the 3-month post-treatment assessment or
2. discontinued treatment early owing to non-response or toxicity.

Trephine data are required to confirm a CR in participants who are known to be at least a PR. For participants with at least a PR but with missing trephine data, the following rules, defined in advance within the Statistical Analysis Plan, were applied:

1. For participants assessed as at least a PR with no evidence that were not CR/CRi:

    i. MRD-negative participants were reported as 'CR/CRi'
    ii. MRD-positive participants were reported as 'PR'
    iii. Participants with missing MRD status were excluded from the analysis.

2. Participants assessed as PR with evidence that they were not a CR or CRi by the IWCLL criteria, or participants with stable/progressive disease (PD), were treated as non-responders in the analysis.

Evaluation of MRD was based on an assessment of the bone marrow, performed centrally at the Haematological Malignancy Diagnostic Service (HMDS), St James's University Hospital, Leeds, at 3 months post treatment. For participants with a missing MRD assessment, the next available observation based on the peripheral blood was carried backwards and imputed in place of the missing 3-month observation. This was considered to be a conservative approach as participants are not expected to improve over time without treatment.

Frequency of analyses

Interim reports presenting recruitment, demographic, safety and toxicity data along with treatment and protocol compliance were presented by treatment arm to the DMEC in strict confidence at approximately yearly intervals. In addition to the full annual reports, safety data were presented to the DMEC on a 6-monthly basis. The DMEC reported its recommendations regarding the continuation of the trial to the TSC.

A single formal interim analysis was planned on the short-term efficacy data when half the number of participants (103) had reached their primary end point; this was reported to the DMEC in September 2012. A separate formal analysis plan was written for the interim analysis and signed off before the final data download. The results and outcome of the meeting are reported below (see *Interim analysis*).

Final analyses were carried out on all but the survival end points when the response data became available for all participants, approximately 9 months after the close of recruitment. The survival end points were analysed 2 years after the close of recruitment and will be updated as appropriate.

Interim analysis

The interim analysis was carried out at a stringent alpha level in order to retain an overall 5% level (two-sided) for the final analysis. The O'Brien and Fleming[32] alpha spending function was used to adjust for multiple testing, requiring an alpha level of 0.005 (two-sided) for the interim analysis, and an alpha level of 0.048 (two-sided) for the final analysis.

Primary end point analysis

An overall one-sided 2.4% significance level was used for the final primary response analysis.

The proportion of participants who achieved at least a CR are summarised by treatment group, and the lower limit of the 95.2% CI (one-sided type I error rate of 2.4%) for the difference in the proportions of participants achieving a CR between the treatment groups reported. This was obtained using one-sided binary logistic regression to adjust for the minimisation factors: Binet stage, sex and age, but excluding centre. The treatment estimate is presented along with the odds ratio (OR) and 95.2% Wald CI around the OR estimate. In order to determine whether FCM-miniR was non-inferior to FCR, defined as FCM-miniR being no more than 10% worse in terms of response rates, the lower limit of the CI for the treatment effect is compared with the non-inferiority margin of 10%, expressed as an OR using the following formula:

$$\mathrm{OR} = \frac{\pi_2(1-\pi_1)}{\pi_1(1-\pi_2)} \quad (1)$$

where π_1 = the proportion of responders in the FCR arm and π_2 = proportion of responders in the FCR arm minus 10%.

For the primary end point analysis, the ITT and PP populations are of joint primacy. In the event that the analyses do not concur (i.e. one demonstrates non-inferiority and the other does not), non-inferiority cannot be concluded.

Sensitivity analyses assess the robustness of results of the primary analysis, and the assumptions regarding missing data:

1. treating all participants will miss primary end point data as non-responders
2. treating all participants will miss primary end point data as responders
3. excluding all participants will miss trephine data from the analysis.

Secondary end point analyses

A two-sided 5% significance level was used for all secondary superiority efficacy end point comparisons.

The proportion of participants with undetectable MRD following treatment, and the proportion of participants who achieved an OR of at least a PR by IWCLL criteria following treatment, are each summarised by treatment group. The differences in the proportions and exact 95% CIs are reported. Binary logistic regression is used to provide treatment estimates with corresponding standard errors (SEs) and *p*-values, along with ORs and 95% CIs around the OR estimates, after adjusting for the minimisation factors, excluding centre.

Cox regression analysis is used to analyse time to MRD relapse, progression and death, both overall and between treatment arms, accounting for the minimisation factors, excluding centre. Treatment and covariate estimates, SEs, hazard ratios (HRs) and corresponding 95% CIs and *p*-values are presented for all variables incorporated in the models. Median PFS, OS and time to MRD relapse and corresponding

95% CIs are also presented per treatment arm and overall. The proportional hazards assumption is assessed by plotting the hazards over time (i.e. the log-cumulative hazard plot) for each treatment arm, after adjusting for the minimisation factors. In addition, MRD relapse, PFS and OS curves are calculated using the Kaplan–Meier method.

Safety analyses summarise the number of AEs, SAEs and SUSARs occurring after randomisation. Safety data are presented by treatment group using the safety population. Summaries of the total numbers of SAEs/SUSARs reported and numbers of participants experiencing each event are presented, along with details of the suspected relationship with trial medication or other causality, duration of recovered SAEs/SUSARs, seriousness criteria, event outcome and Medical Dictionary for Regulatory Activities (MedDRA) body system coding. The number and causes of deaths occurring from randomisation until 3 months post treatment are summarised, and the proportion of participants with each cause of death is calculated. No statistical testing is performed between the two groups.

Subgroup analyses

Exploratory subgroup summaries are presented to assess the heterogeneity of the treatment effect among the following subgroups of interest for the primary end point and, where relevant, PFS and OS:

- sex (male, female)
- age group ($\leq$ 65 years, > 65 years)
- Binet stage (A progressive or B, C)
- creatinine clearance levels (30–60 ml/minute, > 60 ml/minute)
- β_2-microglobulin (β_2M) concentration (< 4 mg/l, $\geq$ 4 mg/l)
- number of cycles of treatment received (three or fewer, more than three)
- GCSF received (yes, no)
- 17p deletion (yes, no)
- 11q deletion (yes, no)
- heavy-chain variable-region (VH) mutation risk (poor risk, standard risk).

In addition, PFS and OS are analysed by IWCLL response and MRD response to treatment, both alone and by treatment arm.

The analyses carried out use the same populations as for the main analyses on the primary and secondary end points. Analyses on the PP population were considered unnecessary owing to the similarity with the ITT population. Subgroup analyses may, by chance, generate false-negative or false-positive results and must be interpreted with caution and treated as hypothesis generating.

Economic evaluation

An economic evaluation was conducted to assess the cost-effectiveness of FCM-miniR compared with FCR from a UK NHS and Personal Social Services (PSS) perspective. The evaluation consists of two components: a within-trial analysis, in which cost-effectiveness is assessed within the 24-month trial period using individual participant data collected in the trial, and a decision analytic model analysis, in which cost-effectiveness is assessed over a lifetime horizon using standard modelling techniques applied to the trial data in order to extrapolate the trial results.

Measurement of outcomes

The economic analysis used QALYs to measure health benefit. Health-related quality of life was estimated using responses to health economics participant questionnaires, which included the EQ-5D.[28] QALYs

represent a quality-weighted survival value in which one QALY is equivalent to 1 year of full health. All participants were asked to complete these questionnaires at the following time points:

- baseline
- after three cycles of therapy
- at the end of therapy
- 3 months after the end of therapy
- every 3 months after the end of therapy until 24 months post randomisation (i.e. at 6, 9, 12, 18 and 24 months post randomisation).

Standard UK tariff values were applied to these responses at each time point to obtain participant utility values for the within-trial period. QALYs were calculated using the 'area under the curve' method and formed the primary outcome measure of the cost-effectiveness study. As NICE currently recommends the use of EQ-5D derived utilities in its reference case, EQ-5D utilities were used in all base-case analyses; sensitivity analysis using SF-12 (converted to SF6D) utilities was also conducted.[27]

Measurement of costs

Participant-reported data on resource usage were collected in the trial using the health economics participant questionnaires at similar time points as the health outcomes, except at baseline. For the 3-month follow-up data, the recall period was 3 months (i.e. participants were asked to provide information on their use of health-care resources over the previous 3-month period). For all other cases, the recall period was either since entering the study or since the last questionnaire was completed. The questionnaires included the number and length of hospital inpatient stays, the number of outpatient visits, and the number of primary/community care visits. Participants were also asked to report on the use of PSS related to their treatment (such as the number of visits of carers and social workers).

Costs were estimated by combining participant-reported resource usage with unit cost data obtained from national databases such as the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care and *British National Formulary* (BNF).[33,34]

The analyses took the perspective of the NHS including the costs of health and social care. All costs are reported in 2013 GBP (£) and future costs were discounted at an annual rate of 3.5%, as per the NICE Methods Guide.[27]

Missing data

Missing data for participant-reported health-related quality of life were dealt with by using the multiple imputation method.[35,36] This method assumes that data are missing at random; missing data values are replaced with plausible substitutes based on the distribution of observed data, with uncertainty around the observed data values incorporated using iterative multivariable regression techniques. A set of baseline variables and cost data from that time point were used to impute missing health outcomes data. This approach is recommended for economic analyses alongside clinical trials as it reflects the uncertainty inherent in missing data.[37]

Within-trial analysis

Main characteristics of the analysis

The within-trial analysis aimed to determine the cost-effectiveness of FCM-miniR compared with FCR over the 24-month trial period. Individual participant data collected in the trial were used to determine the cost and QALYs associated with each treatment arm. QALYs were derived using participant EQ-5D questionnaire responses, and cost-effectiveness is assessed as the incremental cost per incremental QALY.

Following the trial interim analysis, carried out on the first half of participants randomised to the trial ($n = 103$), 21 participants randomised to FCM-miniR transferred over to treatment with FCR. The difference

in the CR rates at the interim analysis between the treatment arms, although not statistically significant, was deemed by the DMEC to be clinically relevant in favour of the control group. In light of this, and evidence of additional toxicity in the FCM-miniR arm, the trial was closed early at the recommendation of the DMEC and all participants still receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles. The economic evaluation base-case analysis was therefore conducted using the trial sample with these 21 participants removed, as the treatment transfer occurred as a result of the planned interim analysis rather than as a result of an independent participant or clinician decision, which does not meet the definition of ITT. Sensitivity analyses were conducted to assess the impact of removing these participants.

As the analysis spans more than 1 year, future costs and health outcomes (beyond one year) were discounted at an annual rate of 3.5% as per the NICE Methods Guide.[27] Cost-effectiveness is measured in terms of the incremental cost-effectiveness ratio (ICER), which is calculated by dividing the mean difference in cost between the two arms by the mean difference in QALYs between the two arms, as follows:

$$\begin{aligned} \text{ICER} &= \frac{(\text{Mean Cost}_{\text{FCM-miniR}} - \text{Mean Cost}_{\text{FCR}})}{(\text{Mean QALY}_{\text{FCM-miniR}} - \text{Mean QALY}_{\text{FCR}})} \\ &= \frac{\Delta C}{\Delta E} < \lambda \end{aligned} \tag{2}$$

where ΔC is the incremental cost of FCM-miniR and ΔE is the incremental health benefit of FCM-miniR and λ is the societal willingness to pay (WTP) for one QALY. The ICER represents the additional cost per one unit of outcome gained. This indicates the trade-off between total cost and effectiveness when choosing between FCM-miniR and FCR therapies. When compared against the marginal trade-off for the NHS as a whole – the cost-effectiveness threshold – this gives an indication of whether spending money on FCM-miniR is an efficient use of resources. As a guideline rule, we used the NICE implicit WTP threshold of £20,000–30,000 per QALY to determine cost-effectiveness. In general, a new intervention is considered cost-effective so long as its ICER is within or below the £20,000–30,000 per QALY range.

Uncertainty

Non-parametric bootstrapping was used to determine the level of sampling uncertainty around the ICER by generating 10,000 estimates of incremental costs and benefits from the trial results. The bootstrap approach is a non-parametric method that considers the original sample as though it were the population and draws multiple random samples from the original sample. Results are presented using cost-effectiveness scatterplots to illustrate the uncertainty surrounding the cost-effectiveness estimates. On the cost-effectiveness plane (which plots incremental QALYs against incremental costs), a result is considered cost-effective if it falls on or below the given cost-effectiveness threshold. The cost-effectiveness acceptability curve (CEAC) is derived by calculating the proportion of bootstrapped estimates which are cost-effective across a range of WTP thresholds, to show the probability that FCM-miniR is cost-effective across different threshold values.[37]
The CEACs were constructed using the net benefit approach. The net monetary benefit (NB) is a simple rearrangement of the ICER decision formula as shown:

$$\begin{aligned} \text{ICER} &= \frac{\Delta C}{\Delta E} < \lambda \\ \text{NB} &= \lambda * \Delta E - \Delta C \end{aligned} \tag{3}$$

where ΔC is the incremental cost of the treatment strategy, ΔE is the incremental benefit of the treatment strategy, and λ is the societal WTP per QALY threshold. Across any number of alternative interventions, the intervention with the highest NB is considered cost-effective [i.e. an intervention is cost-effective if the incremental net monetary benefit (INB) is positive].[27] Using the NB statistic, the cost-effectiveness of each of the bootstrap estimates can be determined in order to derive the overall probability of cost-effectiveness for the CEAC.

Mean INBs between the two arms were reported with 95% bootstrap CIs calculated using the bias-corrected method.[38]

Sensitivity analysis

To investigate the appropriateness of the EQ-5D as the principal outcome measure, a sensitivity analysis using SF-6D utility values derived from the SF-12 trial data was conducted.

In addition, to assess the potential impact of participant crossover in the trial, two additional sensitivity analyses were conducted:

1. An ITT analysis was conducted, in which any transfer of participants between arms was ignored and participants who crossed over from FCM-miniR to FCR were retained in the analysis of the FCM-miniR arm.
2. Participants who were transferred are deemed to have been in the FCR treatment arm from randomisation.

Decision economic model analysis

Decision analytical modelling was used to compare FCR and FCM-miniR therapies over a lifetime horizon. A discrete-time state-transition (modified-Markov) model was developed to estimate the long-term cost-effectiveness of treating participants with CLL with FCM-miniR compared with the standard treatment of FCR. In line with the within-trial economic evaluation, the model analysis adopts a UK NHS and PSS perspective and future costs and QALYs were discounted at an annual rate of 3.5% in line with NICE guidance.[27] The model was built in Microsoft Excel version 2010 (Microsoft Corporation, Redmond, WA, USA).

Model structure and parameters

The model structure is presented in *Figure 1*. The model included three possible health states: PFS, PD and death.

Markov models describe patient progression over time through a pathway of health states, with movement between the health states being triggered by events such as disease progression or death. Resource use and costs are associated with each health state and patients accumulate costs and health benefits in each state over 3-monthly cycles. As 2-year individual patient cost and utility data were available from the trial data, the model runs from the end of the trial in order to estimate long-term costs and health benefits. The lifetime cost and QALY results are calculated as the sum of the trial 2-year results and the model lifetime estimates (truncated at age 100 years).

The model inputs were derived using information from a range of sources. Where possible, data from the trial were used directly, and published literature was used to inform remaining parameters. Where published literature was required, focused non-systematic reviews were conducted to identify potential sources of information. Appropriate distributions were applied using observed or published variance data; where no such data were available, the standard deviation was assumed to be equal to the mean. As for the within-trial analysis, the model base-case analysis excludes participants who crossed over from the FCM-miniR arm to the FCR arm; a sensitivity analysis was conducted to assess the impact of this. The proportion of participants

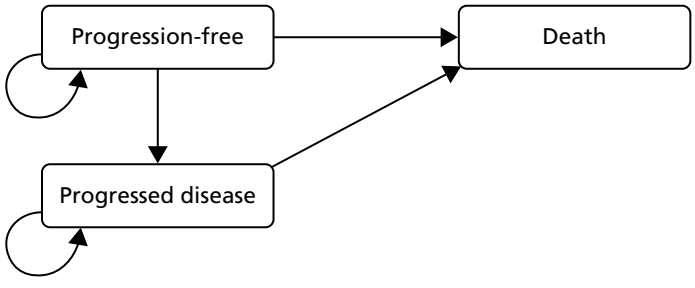

FIGURE 1 Three-state Markov model.

beginning in each health state in the model was derived directly from the proportion of participants in the trial who remained progression-free and mortality-free at the last follow-up (24 months). Derivation of the post-24-month rate of transition between the progression-free state and progressed disease state required significant extrapolation beyond the relatively short follow-up period of the trial, which contained low numbers of progression events upon which to base the extrapolation. Owing to the short follow-up of the trial, the usual practice of fitting survival curves to the trial data in order to extrapolate results over time is likely to produce highly uncertain, and most likely implausible, results. An alternative approach was therefore adopted that involved fitting a parametric survival model using the Remission Duration Model (RDM) model. The RDM model is based on a plausible biological rationale for the mechanism of disease progression.[39] The model was fitted, using maximum likelihood estimation, to the control arm of the CLL8 trial conducted in Germany which represents a comparable patient population treated with a comparable FCR regimen.[4,40] The fitted model parameters were then calibrated to the PFS curve from the FCR arm of ARCTIC (*Figure 2*).

As chemotherapy is expected to exert its effect on PFS only during the treatment period, which was captured within the trial follow-up period, the progression-free event rate beyond 2 years (i.e. in the model) was assumed to be the same between arms. In a sensitivity analysis, the transition rate for FCM-miniR was derived by applying the HR observed in the trial period to the FCR survival curve over various durations to allow for the possibility of a carry-over effect.

Adverse events (AEs) relating to each of the treatment strategies were assumed to occur only within the trial follow-up period (2 years post randomisation to treatment). The cost of AEs has therefore been captured in the within-trial analysis period (in which AEs were costed separately for each arm based on the trial individual patient data) and has not been included within the model follow-up period.

The probability of dying from the PF state was assumed to be equivalent to the general population age- and sex-specific mortality. The probability of dying from the PD state was derived from the literature and assumed to be identical between arms.

Death was assumed to be associated with zero utility and zero cost. For the PF health state, the associated 3-month cost and utility values were derived directly from the trial second-year data, using available data on participants prior to disease progression. Cost and utility values were calculated using second-year data only in order to avoid using data from participants' primary treatment period, which would bias the results. For the PD state, a combination of a lack of progression events and lack of completed questionnaires at the time of progression in the trial meant that cost and utility estimates for this health state had to be derived from the literature. For the cost of the PD, the 3-month health state cost was taken from a previously conducted cost–utility analysis which looked at the cost-effectiveness of bendamustine (Levact,

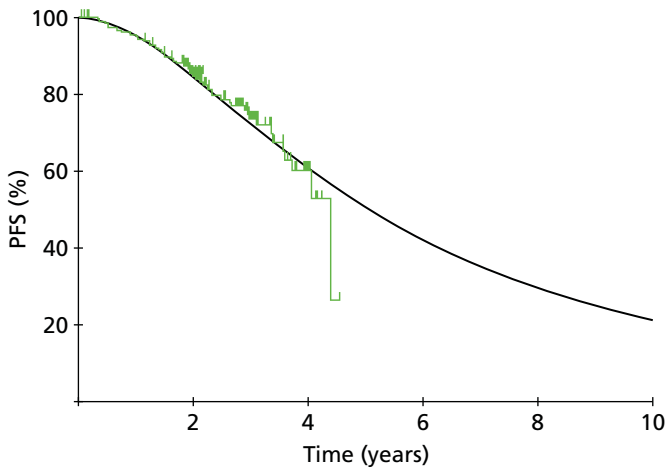

FIGURE 2 Progression-free survival in the FCR arm.

Napp Pharmaceuticals) versus chlorambucil (Leukeven, Aspen) for the first line treatment of CLL in England and Wales. Woods *et al.* derived resource use for CLL health states (including PD) from an advisory board conducted in January 2010, which consisted of five haematologists who worked in the UK NHS and were experienced in treating CLL. The reported 3-month progressed disease state cost was £1924, based on 2009 NHS reference costs; this cost was inflated to a 2013 price for use in the current model.[41] For the PD state utility, a decrement was applied to the PF state, using data from Beusterien *et al.*[42] This was a cross-sectional study in which 89 members of the general population in the UK (England and Scotland) were asked to value health states describing CLL response status using standard gamble methodology.[42]

A full list of model parameters and distributions applied in the model is given in *Table 3*.

TABLE 3 Model input parameters

Model parameter		Mean	Distribution	SE	Source
Global parameters	Annual discount rate	0.035	Fixed	–	NICE[27]
	Start age, years	62.38	Fixed	–	ARCTIC trial data
	Proportion male, %	0.66	Fixed	–	
Starting distribution	PF (FCR)	0.894	Dirichlet	0.03	ARCTIC trial distribution at 24-month follow-up
	PD (FCR)	0.064	Dirichlet	0.04	
	Dead (FCR)	0.042	Dirichlet	0.02	
	PF (FCM-miniR)	0.791	Dirichlet	0.05	
	PD (FCM-miniR)	0.094	Dirichlet	0.06	
	Dead (FCM-miniR)	0.115	Dirichlet	0.04	
Health state costs (3 months), £	PF	268	Gamma	43	ARCTIC trial data
	PD	2146	Gamma	2146	Woods *et al.*, 2012[41]
	Dead	0.00	Fixed	–	–
Health state utilities (3 months)	PF (EQ-5D)	0.82	Beta	0.01	ARCTIC trial data
	PF (SF-6D)	0.70	Beta	0.03	
	PD utility decrement applied to PF state value	–0.16	Log-normal	0.02[a]	Beusterien *et al.*, 2010[42]
	Dead	0.00	Fixed	–	–
Transition probabilities/ effects (3 months)	Risk of progression (PF to PD) in FCR arm	Varies (drawn from survival curve figure)	Fixed	–	Survival analysis of ARCTIC within-trial data (see *Figure 2*)
	Risk of progression (PF to PD) in FCM-miniR arm	Varies (drawn from survival curve figure)	Fixed	–	
	Mortality in PF state	Varies (age- and sex-dependent)	Fixed	–	Office for National Statistics, 2013 age- and sex-standardised rates[43]
	Mortality in PD state	0.14	Beta	0.03	Wierda *et al.*, 2010[44]
	Log of HR for risk of progression in FCM-miniR arm vs. FCR arm (used in SA only)	0.33	Normal	0.30	ARCTIC trial data

a Standard deviation.

Sensitivity analyses

Probabilistic sensitivity analyses were conducted to assess the impact of joint parameter uncertainty on the results. Probabilistic analysis accounts for joint parameter uncertainty in non-linear models by assigning probability distributions to each of the input parameters and randomly drawing from these probabilities over 10,000 Monte Carlo model simulations to produce different cost and QALY estimates in each simulation of the model. As for the bootstrap within-trial analysis, the results are presented on the cost-effectiveness plane as a scatterplot, and using CEACs to show the probability that the two arms are cost-effective across different WTP per additional QALY thresholds.

Deterministic sensitivity analysis was used to assess the impact of individual parameter uncertainty on the results. Parameters were independently varied between upper and lower bands of plausible values, based on increasing and decreasing each parameter by 25% of its initial value.

Three additional sensitivity analyses were conducted to assess the impact of key model assumptions:

1. SF-6D utilities. The base-case analysis was conducted using utilities derived from participant responses to the EQ-5D questionnaire (which NICE recommends). A sensitivity analysis was conducted using utilities derived from participant responses to the SF-12 questionnaire. For a discussion on the relative merits of SF-12 versus EQ-5D please see *Chapter 5, Economic evaluation discussion*.
2. Intention to treat analysis. In the base-case analysis participants who crossed over from FCM-miniR to FCR as a result of the trial interim analysis were excluded from the cost-effectiveness analysis. A sensitivity analysis was conducted in which these participants were instead retained in the analysis of the FCM-miniR arm.
3. Treatment effect. As chemotherapy is expected to exert its effect on PFS only during the treatment period, which was captured within the trial follow-up period, the progression-free event rate beyond 2 years was assumed to be the same between arms in the base case. In a sensitivity analysis, the transition rate for FCM-miniR was derived by applying the HR observed in the trial to the FCR survival curve over various durations to allow for the possibility of a carry-over effect; in addition to the base-case analysis, in which a differential rate of progression occurs in the initial 2-year trial period only, analyses were conducted extending the observed HR over 3, 5, 10 years and a lifetime horizon in the FCM-miniR arm.

Value of information analysis

Any model is subject to uncertainty around model parameters and assumptions, which may result in a wrong decision being made based on the model results. If an incorrect decision is made, there will be consequences in terms of health benefit and resources lost. The maximum amount the NHS should be willing to invest to reduce uncertainty in the decision can be informed by the expected value of perfect information (EVPI).[45] The EVPI evaluates the expected opportunity cost of current uncertainty by assessing the probability that a decision based on current information is wrong, multiplied by the costs of making a wrong decision. It is calculated by applying non-parametric methods to the output from the Monte Carlo simulation of the model.[46] It is the difference between the expected value (E) of the decision made with perfect information across j interventions and θ parameters, $E_\theta \max_j NB(j,\theta)$, and the expected value of the decision made on the basis of existing evidence, $\max_j E_\theta NB(j,\theta)$:

$$\text{EVPI} = E_\theta \max_j NB(j,\theta) - \max_j E_\theta NB(j,\theta) \quad (4)$$

Additional research should be considered only if the EVPI exceeds the expected cost of research. The EVPI therefore provides an upper limit on the amount that the NHS should be willing to spend on further research in order to resolve current uncertainties.

The value of future research can be further explored using the expected value of perfect parameter information (EVPPI). The EVPPI is a calculation of the maximum value attributable to specific components (parameters) of the evidence base. The EVPPI is calculated as the difference between the expected value of the decision made with perfect information for a particular parameter or set of parameters, ϕ, across the

remaining uncertain parameters, ψ, and the expected value of the decision made on the basis of existing evidence:

$$\text{EVPPI}_{\phi} = E_{\phi}\max_j E_{\phi/\psi} NB(j, \phi, \psi) - \max_j E_{\theta} NB(j, \theta) \quad (5)$$

The EVPPI represents the maximum cost the NHS should be willing to spend on further research to resolve uncertainty for the given parameter or set of parameters evaluated. It is useful for isolating which specific parameters of the decision model are fuelling the overall EVPI, and thereby indicates in what direction future research should be focused.

The formulae above give the per-person EVPI and EVPPI values. To generate population value of information statistics, the per-person estimates must be multiplied by the population expected to be affected by the new treatment. This value is derived from the annual incidence of disease multiplied by the number of years the treatment decision is expected to be relevant. Based on cancer research statistics, the annual incidence of CLL across England and Wales is expected to be 2943.[47] In the absence of quantitative data it was assumed that the period over which the current decision problem will be relevant (i.e. the effective lifetime over which the new treatment will be used) was 10 years. An annual discount factor of 3.5% was applied to the population estimate.

Summary of changes to the protocol

From the time of initial ethical approval (25 June 2009), four substantial amendments to the protocol were submitted to and subsequently approved by the REC.

Amendment 1, dated 5 November 2009 and approved 26 November 2009, included the following key changes:

- introduction of a participant diary card to collect compliance with oral treatments
- addition of a health economics participant questionnaire
- clarification regarding data collection and storage in the participant information sheet.

Amendment 2, dated 21 February 2011 and approved 17 March 2011, included the following key changes:

- amending inclusion criteria to allow participants with SLL to enter the trial
- allowing two schedules for splitting the dose of rituximab
- stipulating the re-escalation of chemotherapy after dose reductions
- making the 6-month post-treatment blood sample compulsory for all participants
- adding information to include participant name on all samples sent to HMDS.

Amendment 3, dated 15 July 2011 and approved 29 July 2011, included the following key changes:

- correcting an error in one of the rituximab dose-splitting schedules.

Amendment 4, dated 1 October 2012 and approved 13 November 2012, included the following key changes:

- noting the early trial closure
- updating the end of trial definition
- providing clarifications to the pharmacovigilance reporting and review requirements.

Chapter 3 Statistical trial results

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Recruitment

Between December 2009 and September 2012, 200 of a planned 206 patients were recruited into the ARCTIC trial (*Figure 3*), with 100 participants randomly allocated to the FCR control arm and 100 to the FCM-miniR intervention arm. Written informed consent was received from all participants.

Thirty-eight centres across the UK received local ethical and management approval for the trial and had permission to randomise patients, of which 34 centres were recruited into the trial. *Table 4* summarises recruitment per centre and by allocated treatment arm. The top five recruiting centres were the Oxford Cancer and Haematology Centre ($n = 25$), Birmingham Heartlands Hospital ($n = 16$), St James's University Hospital (Leeds) ($n = 15$), Southampton General Hospital ($n = 13$) and Castle Hill Hospital (Hull) ($n = 12$).

Early closure to recruitment

The ARCTIC trial closed early to recruitment in September 2012 owing to an urgent safety measure, on advice from the DMEC and the TSC. This decision was made following the planned interim analysis of the short-term efficacy data for the first half of participants randomised to the trial ($n = 103$).

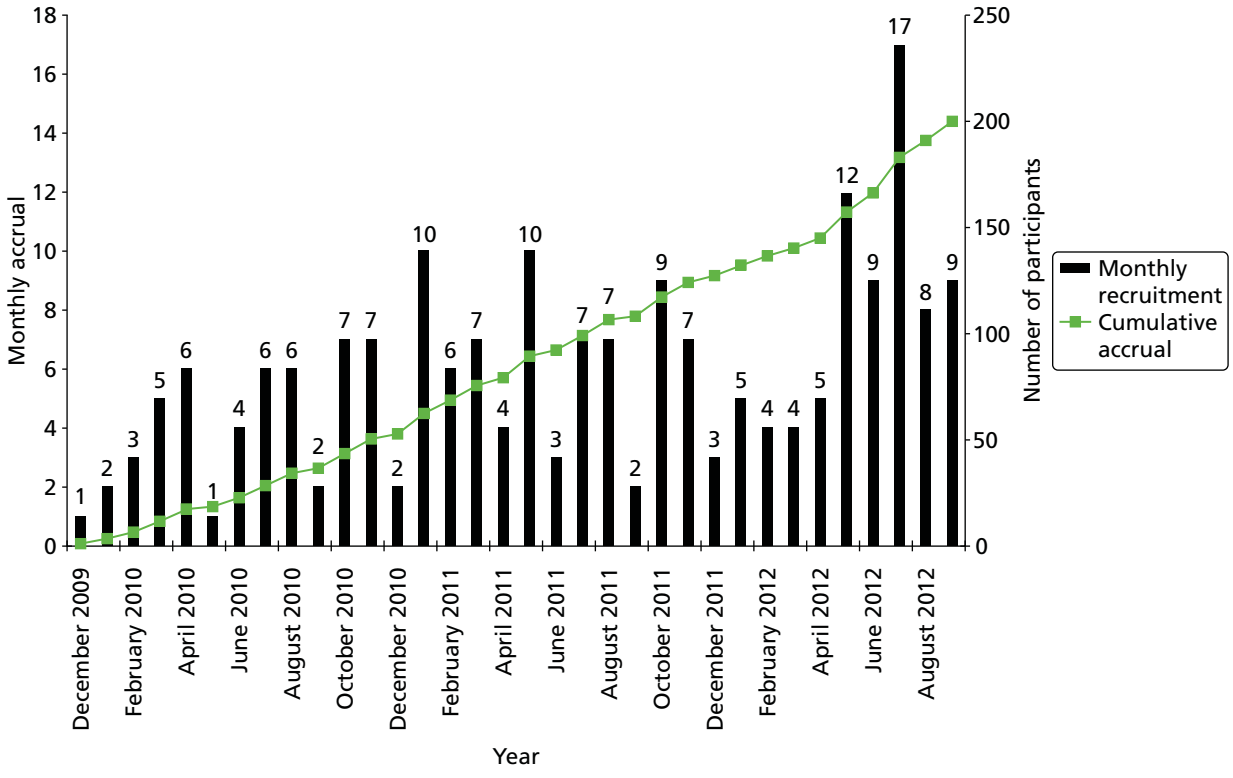


FIGURE 3 Cumulative and monthly recruitment.

TABLE 4 Recruitment per centre and by allocated treatment arm

Randomising centre	FCR ($n = 100$) *n* (%)	FCM-miniR ($n = 100$) *n* (%)	Total ($n = 200$) *n* (%)
Arrowe Park Hospital, Upton	0 (0.0)	1 (1.0)	1 (0.5)
Birmingham Heartlands Hospital, Birmingham	8 (8.0)	8 (8.0)	16 (8.0)
Borders General Hospital, Melrose	3 (3.0)	3 (3.0)	6 (3.0)
Buckinghamshire Hospitals NHS Trust, Wycombe and Stoke Mandeville	6 (6.0)	5 (5.0)	11 (5.5)
Castle Hill Hospital, Hull	6 (6.0)	6 (6.0)	12 (6.0)
Christie Hospital, Manchester	1 (1.0)	0 (0.0)	1 (0.5)
Colchester General Hospital, Colchester	2 (2.0)	1 (1.0)	3 (1.5)
Epsom St Helier University Hospital NHS Trust, Epsom and Carshalton	1 (1.0)	0 (0.0)	1 (0.5)
Glan Clwyd Hospital, Rhyl	4 (4.0)	4 (4.0)	8 (4.0)
Good Hope Hospital, Birmingham	6 (6.0)	5 (5.0)	11 (5.5)
Great Western Hospital, Swindon	2 (2.0)	2 (2.0)	4 (2.0)
Harrogate District Hospital, Harrogate	1 (1.0)	1 (1.0)	2 (1.0)
King's College Hospital, London	0 (0.0)	2 (2.0)	2 (1.0)
Manchester Royal Infirmary, Manchester	2 (2.0)	3 (3.0)	5 (2.5)
Northwick Park Hospital, London	0 (0.0)	2 (2.0)	2 (1.0)
Oxford Cancer and Haematology Centre, Oxford	12 (12.0)	13 (13.0)	25 (12.5)
Pinderfields Hospital, Wakefield	3 (3.0)	5 (5.0)	8 (4.0)
Princess Royal University Hospital, London	2 (2.0)	0 (0.0)	2 (1.0)
Queen Elizabeth Hospital, Birmingham	1 (1.0)	1 (1.0)	2 (1.0)
Queen Elizabeth Hospital, Gateshead	2 (2.0)	3 (3.0)	5 (2.5)
Queen Elizabeth Hospital, Woolwich	2 (2.0)	0 (0.0)	2 (1.0)
Royal Blackburn Hospital, Blackburn	2 (2.0)	4 (4.0)	6 (3.0)
Royal Liverpool University Hospital, Liverpool	2 (2.0)	2 (2.0)	4 (2.0)
Royal Marsden Hospital, London	1 (1.0)	0 (0.0)	1 (0.5)
Royal United Hospital, Bath	2 (2.0)	3 (3.0)	5 (2.5)
Russells Hall Hospital, Dudley	2 (2.0)	0 (0.0)	2 (1.0)
St Batholomew's Hospital, London	0 (0.0)	1 (1.0)	1 (0.5)
St James's University Hospital, Leeds	8 (8.0)	7 (7.0)	15 (7.5)
Southampton General Hospital, Southampton	6 (6.0)	7 (7.0)	13 (6.5)
Southmead Hospital, Bristol	3 (3.0)	0 (0.0)	3 (1.5)
Sunderland Royal Hospital, Sunderland	3 (3.0)	3 (3.0)	6 (3.0)
University Hospital of North Tees, Stockton-on-Tees	1 (1.0)	1 (1.0)	2 (1.0)
Western General Hospital, Edinburgh	3 (3.0)	3 (3.0)	6 (3.0)
Ysbyty Gwynedd Hospital, Bangor	3 (3.0)	4 (4.0)	7 (3.5)

The unblinded CR and ORRs (based on an independent assessment of response following the IWCLL criteria[26]) were presented along with baseline demographic, treatment compliance, MRD eradication and safety and toxicity data. The data presented showed higher CR rates in the control arm (FCR) than were expected, and the difference in the CR rates between the treatment arms, although not statistically significant, was deemed by the DMEC to be clinically significant in favour of FCR over FCM-miniR. In addition, there appeared to be an increased toxicity rate and increased number of dose omissions and reductions in the FCM-miniR arm. A detailed summary of the interim analysis results is presented in *Statistical trial results*.

Interim analysis recommendations

The primary aim of this Phase IIB trial was to determine whether FCM-miniR should continue to be investigated in a Phase III trial. Given the strength and robustness of the interim data, the DMEC felt that continuing this trial was futile, as it was highly unlikely that the data would warrant continued investigation of the experimental treatment. As such, they recommended that recruitment into the trial should stop with immediate effect, and these recommendations were ratified by the TSC. It was agreed that the local site investigators should be informed of the findings of the interim analysis as soon as possible. All participants receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles, although this was not mandated. The decision was to be made by the participant following detailed discussions with their clinician. It was also agreed that participants should continue to be followed up as per the protocol.

At the time of trial closure, 200 participants had been recruited. Twenty-one out of the 23 participants still receiving FCM-miniR at the time of trial closure chose to transfer over to receive treatment with FCR on discussion with their treating clinician. Where appropriate, the results will categorise participants into three treatment categories: FCR, FCM-miniR and FCM-miniR/FCR for the patients randomised to FCM-miniR who were recommended to transfer. It is not appropriate to include the participants who transferred to FCR in either of the other categories according to the ITT analysis, because the decision to stop FCM-miniR was on recommendation from the DMEC, rather than a decision from the treating clinician or participant, which violates the ITT assumption.

Participant flow

Figure 4 presents the Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow through the trial. In total, 548 patients were reported as having been assessed for eligibility and, of these, 200 (36.5%) provided written informed consent and were randomised into the trial. Of the 348 patients who were reported as having been assessed for the trial but who were not randomised, 177 of these were from a single centre which used a very broad screening process which was inconsistent with other centres. The majority of patients were excluded owing to being clinically ineligible ($n = 228$, 65.5%). Again, this is biased towards the single centre which assessed 172 of these patients as being ineligible as they did not meet key eligibility criteria such as having had no prior therapy for CLL. If this centre is excluded from the screening data, a total of 371 patients were reported as having been assessed for eligibility with 56 (15.1%) being excluded owing to clinical ineligibility. A total of 100 participants were randomised to the FCR control arm and 100 to the FCM-miniR intervention arm.

In the FCR arm, all but two participants received their allocated treatment ($n = 98$, 98.0%). One participant was ineligible (owing to prior therapy for CLL) and went on to receive FCR off trial. The other participant withdrew from the trial on the advice of the treating clinician as they had a 17p deletion and were treated with a more 'appropriate regime' off trial. In the FCM-miniR arm, 79 participants (79.0%) received their allocated intervention throughout the trial, with 21 participants transferring over to receive treatment with FCR as a result of the interim analysis, two from their first cycle of treatment.

A total of nine participants (4.5%) withdrew their consent for the trial (five in the FCR arm and four in the FCM-miniR arm). *Table 5* summarises the number of participants who withdrew consent from the trial, the type of withdrawal and reason for withdrawal. Two participants withdrew their consent for further trial

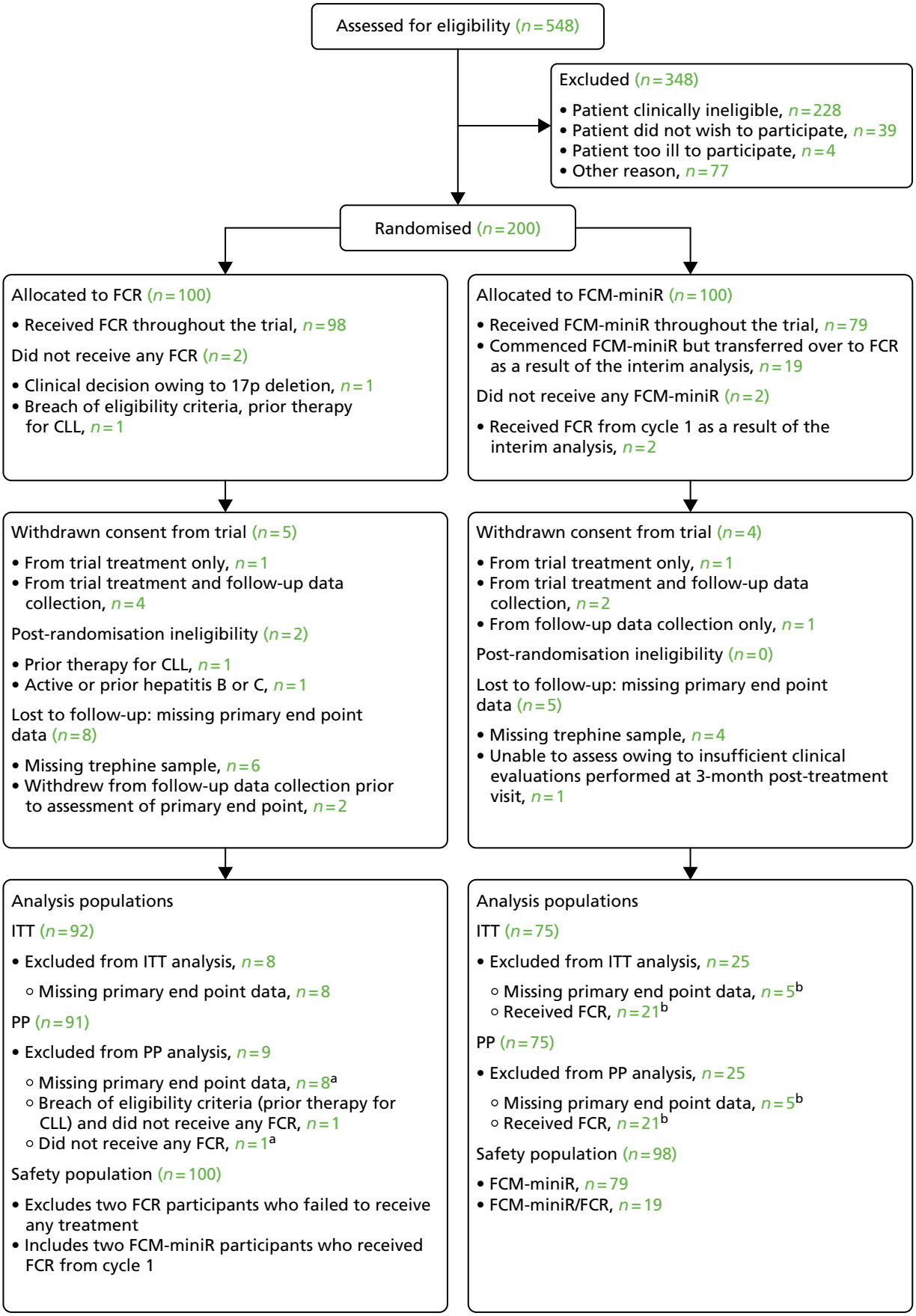


FIGURE 4 Consolidated Standards of Reporting Trials diagram. a, One participant did not receive any FCR and also had missing primary end point data and is therefore recorded twice; and b, one participant received FCR and had missing primary end point data and is therefore recorded twice. Reproduced from Howard *et al.*[1] with permission.

TABLE 5 Participant withdrawals

Participant withdrawal details	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
Participant withdrawn, *n* (%)	5 (5.0)	4 (4.0)	9 (4.5)
Type of withdrawal,* n *(%)			
Withdrawn from trial treatment only	1 (1.0)	1 (1.0)	2 (1.0)
Withdrawn from trial treatment and follow-up data collection	4 (4.0)	2 (2.0)	6 (3.0)
Withdrawn from follow-up data collection only	0 (0.0)	1 (1.0)	1 (0.5)
Reason for withdrawal			
Unwilling to continue with treatment, owing to toxicity	0 (0.0)	2 (2.0)	2 (1.0)
Unwilling to continue with treatment, owing to being too unwell	0 (0.0)	1 (1.0)	1 (0.5)
Unwilling to continue with treatment	1 (1.0)	0 (0.0)	1 (0.5)
Unwilling to continue with visits	1 (1.0)	1 (1.0)	2 (1.0)
Non-response to treatment	1 (1.0)	0 (0.0)	1 (0.5)
Clinician decision	1 (1.0)	0 (0.0)	1 (0.5)
Other reason	1 (1.0)	0 (0.0)	1 (0.5)
Trial duration (months) from randomisation to withdrawal			
Mean (SD)	2.2 (2.0)	9.6 (8.8)	5.4 (6.8)
Median (range)	1.8 (0.4–5.7)	8.1 (1.4–20.7)	2.0 (0.4–20.7)
N	5	4	9

SD, standard deviation.

treatment only (one each in the FCR and FCM-miniR arms). Six participants withdrew their consent from further trial treatment and follow-up data collection (four in the FCR arm and two in the FCM-miniR), of which one ineligible participant in the FCR arm did not receive any trial treatment. Primary end point data are available for the two FCM-miniR participants, but all participants in the FCR arm who withdrew from follow-up did so prior to the assessment of the primary end point. One participant in the FCM-miniR arm withdrew their consent for further follow-up data collection only after the assessment of the primary end point, having received all six cycles of treatment.

Three participants in the FCM-miniR arm withdrew because they were unwilling to continue with trial treatment as a result of either toxicity or being too unwell. In the FCR arm, one participant withdrew owing to non-response to treatment, another participant felt that 'Not enough information was given regarding neutropenic sepsis' and that their 'GCSF injections were delayed due to the trial' (categorised as 'Other reason' in *Table 5*). The median time from randomisation to withdrawal was 2.0 months (range: 0.4–20.7 months) with a shorter median time to withdrawal in the FCR arm (1.8 months) compared with the FCM-miniR arm (8.1 months).

Two participants in the FCR arm were found to be ineligible for the trial post randomisation. One participant had received prior therapy for CLL; they received FCR off-trial and continued to be followed up as per the protocol and therefore had available primary end point data within the definition of the ITT population, although they were excluded from the PP population. The second participant had been previously infected with hepatitis B; they continued on the trial under the approval of the Chief Investigator, with the justification that the participant had 'antibodies but no infection' and, therefore, the eligibility deviation was felt to be minor. They received all six cycles of treatment and were followed up for their primary end point.

A total of 13 participants (6.5%) were lost to follow-up and were classed as participants with missing primary end point data, with a similar proportion in each treatment arm ($n = 8$, 8.0% FCR; $n = 5$, 5.0% FCM-miniR). Ten participants (six in the FCR arm and four in the FCM-miniR arm) had a missing trephine sample at 3 months post treatment, which is required to confirm a CR. Four participants (one in the FCR arm and three in the FCM-miniR arm) missed their 3-month post-treatment visit, and one FCM-miniR participant failed to have sufficient clinical evaluations performed. Four participants in the FCR arm withdrew from further follow-up prior to their assessment of response; however, two did so owing to toxicity and non-response to treatment and were therefore included in the ITT analysis as non-responders. For further information on the reasons for missing trephine samples, missed clinic visits, withdrawals and how participants have been handled in the analysis, see *Final analysis: primary end point*.

Overall, 167 participants (83.5%) were included in the ITT analysis, with a higher proportion coming from the FCR arm ($n = 92$, 92.0%) than the FCM-miniR arm ($n = 75$, 75.0%). Participants were excluded from both trial arms owing to missing primary end point data ($n = 13$) and a further 21 participants were excluded from the FCM-miniR arm as a result of receiving treatment with FCR following the closure of the FCM-miniR arm. The PP population was similar to that of the ITT, with an additional participant excluded from the FCR arm owing to breaching the eligibility criteria and not receiving any of their randomised treatment. The participant who had previously been infected with hepatitis B was not excluded from the PP population as this was not classed as a major protocol violation.

Baseline characteristics

Tables 6–10 summarise the baseline characteristics, including the minimisation factors, participant characteristics, assessment of disease, clinical details and genetic markers for all randomised participants.

Overall, 62.5% ($n = 125$) of the trial population were aged 65 years or less, 67.5% ($n = 135$) were male and 68.0% ($n = 136$) had Binet stage A progressive or B (*Table 6*). The median age of a trial participant was 63 years (range 36–80 years) and 20.0% ($n = 40$) were aged 70 years or more. Of the trial population, 97.0% ($n = 194$) were of white ethnicity (*Table 7*). The two treatment arms were well balanced for the minimisation factors and participant characteristics.

Table 8 summarises the baseline assessments of disease. The median duration of disease was approximately 2 years, with a range of less than 1 month to approximately 23 years. A total of 35.5% of participants ($n = 71$) were Binet stage C, with a higher proportion in the FCR arm ($n = 39$, 39.0%) than in the FCM-miniR arm ($n = 32$, 32.0%). These proportions are slightly different from those presented in

TABLE 6 Minimisation factors (all participants)

Minimisation factors	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
Age group (years),* n *(%)			
≤ 65	63 (63.0)	62 (62.0)	125 (62.5)
> 65	37 (37.0)	38 (38.0)	75 (37.5)
Sex,* n *(%)			
Male	68 (68.0)	67 (67.0)	135 (67.5)
Female	32 (32.0)	33 (33.0)	65 (32.5)
Binet stage,* n *(%)			
A progressive or B	67 (67.0)	69 (69.0)	136 (68.0)
C	33 (33.0)	31 (31.0)	64 (32.0)

TABLE 7 Baseline participant characteristics (all participants)

Participant characteristics	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
Age summaries, years			
Mean (SD)	61.8 (8.3)	62.6 (8.3)	62.2 (8.3)
Median (range)	63 (41–77)	63 (36–80)	63 (36–80)
Age categories (years),* n *(%)			
30–39	0 (0.0)	1 (1.0)	1 (0.5)
40–49	9 (9.0)	5 (5.0)	14 (7.0)
50–59	24 (24.0)	25 (25.0)	49 (24.5)
60–69	48 (48.0)	48 (48.0)	96 (48.0)
≥ 70	19 (19.0)	21 (21.0)	40 (20.0)
Ethnicity,* n *(%)			
White	98 (98.0)	96 (96.0)	194 (97.0)
Mixed: white and black Caribbean	0 (0.0)	1 (1.0)	1 (0.5)
Asian: Indian	1 (1.0)	0 (0.0)	1 (0.5)
Black: Caribbean	0 (0.0)	1 (1.0)	1 (0.5)
Black: African	0 (0.0)	1 (1.0)	1 (0.5)
Other ethnic group	1 (1.0)	1 (1.0)	2 (1.0)

SD, standard deviation.

TABLE 8 Baseline assessment of disease (all participants)

Baseline assessment	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
Duration of CLL (years)			
Mean (SD)	3.37 (3.60)	2.81 (3.32)	3.09 (3.46)
Median (range)	2.47 (0.01–22.74)	1.64 (0.03–17.88)	2.17 (0.01–22.74)
Binet criteria,* n *(%)			
A progressive	20 (20.0)	14 (14.0)	34 (17.0)
B	41 (41.0)	54 (54.0)	95 (47.5)
C	39 (39.0)	32 (32.0)	71 (35.5)
B symptoms,* n *(%)			
Yes	46 (46.0)	57 (57.0)	103 (51.5)
No	54 (54.0)	43 (43.0)	97 (48.5)
Signs of extranodal/extramedullary CLL,* n *(%)			
Yes	11 (11.0)	14 (14.0)	25 (12.5)
No	88 (88.0)	85 (85.0)	173 (86.5)
Missing	1 (1.0)	1 (1.0)	2 (1.0)
WHO performance status,* n *(%)			
0	55 (55.0)	61 (61.0)	116 (58.0)
1	40 (40.0)	37 (37.0)	77 (38.5)
2	5 (5.0)	2 (2.0)	7 (3.5)

SD, standard deviation.

TABLE 9 Baseline clinical assessments (all participants)

Baseline assessment	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
β_2M concentration (mg/l),* n *(%)			
< 4	37 (37.0)	35 (35.0)	72 (36.0)
≥ 4	53 (53.0)	62 (62.0)	115 (57.5)
Missing	10 (10.0)	3 (3.0)	13 (6.5)
Creatinine clearance (ml/minute),* n *(%)			
30–60	17 (17.0)	14 (14.0)	31 (15.5)
> 60	83 (83.0)	86 (86.0)	169 (84.5)
DCT,* n *(%)			
Positive	19 (19.0)	15 (15.0)	34 (17.0)
Negative	71 (71.0)	73 (73.0)	144 (72.0)
Missing	10 (10.0)	12 (12.0)	22 (11.0)
Paraprotein type,* n *(%)			
None	71 (71.0)	68 (68.0)	139 (69.5)
IgA	0 (0.0)	1 (1.0)	1 (0.5)
IgG	17 (17.0)	23 (23.0)	40 (20.0)
IgM	2 (2.0)	4 (4.0)	6 (3.0)
Missing	10 (10.0)	4 (4.0)	14 (7.0)
Hepatitis B,* n *(%)			
Previously infected	1 (1.0)	0 (0.0)	1 (0.5)
Vaccinated	4 (4.0)	1 (1.0)	5 (2.5)
Negative	94 (94.0)	98 (98.0)	192 (96.0)
Missing	1 (1.0)	1 (1.0)	2 (1.0)
Hepatitis C,* n *(%)			
Negative	100 (100)	100 (100)	200 (100)

DCT, direct Coombs test; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

Table 4 because, for a minor number of cases, the incorrect Binet staging was provided at randomisation. Overall, 51.5% ($n = 103$) of the trial population had B symptoms, with a higher proportion in the FCM-miniR arm ($n = 57$, 57.0%) than in the FCR arm ($n = 46$, 46.0%). Twenty-five (12.5%) participants had signs of extranodal or extramedullary CLL and the majority of participants ($n = 116$, 58.0%) were WHO performance status 0, with 38.5% and 3.5% at performance status 1 and 2, respectively.

Table 9 summarises the baseline clinical assessments, which are reasonably well balanced between the treatment arms. Seventy-two participants (36.0%) had a β_2M concentration of < 4 mg/l and 31 (15.5%) participants had a creatinine clearance between 30 and 60 ml/minute. Overall, 34 participants (17.0%) had a positive direct Coombs test (DCT) and immunoglobulin G was the predominant paraprotein type after 'None' in 20% of participants. Results of the clinical assessments are in line with what would be expected for this population of patients. One participant in the FCR arm was assessed as being previously infected with hepatitis B, as described in *Participant flow*.

TABLE 10 Baseline genetic markers (all participants)

Genetic markers	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
17p deletion*, n *(%)			
Yes (poorer risk)	4 (4.0)	3 (3.0)	7 (3.5)
No (standard risk)	88 (88.0)	88 (88.0)	176 (88.0)
Missing	8 (8.0)	9 (9.0)	17 (8.5)
11q deletion*, n *(%)			
Yes (poorer risk)	10 (10.0)	20 (20.0)	30 (15.0)
No (standard risk)	83 (83.0)	75 (75.0)	158 (79.0)
Missing	7 (7.0%)	5 (5.0)	12 (6.0)
VH *mutation risk group*, n *(%)*			
Poor risk[a]	52 (52.0)	52 (52.0)	104 (52.0)
Standard risk[b]	30 (30.0)	31 (31.0)	61 (30.5)
Missing	18 (18.0)	17 (17.0)	35 (17.5)
CD38 *status*, n *(%)*			
Positive (poorer risk)	41 (41.0)	46 (46.0)	87 (43.5)
Negative (standard risk)	55 (55.0)	52 (52.0)	107 (53.5)
Missing	4 (4.0)	2 (2.0)	6 (3.0)

a Poor risk: VH unmutated, or involving the VH3–21 gene.
b Standard risk: VH mutated and not involving the VH3–21 gene.

Table 10 summarises the genetic markers which were assessed at baseline and considered to be prognostic for response. Seven (3.5%) participants had a 17p deletion and 30 (15.0%) participants had an 11q deletion, a higher proportion in the FCM-miniR arm ($n = 20$, 20.0%) than in the FCR arm ($n = 10$, 10.0%). This chance difference might be important, as 11q-deleted CLL may be sensitive to rituximab and so this imbalance could affect the results.

Overall, 52.0% ($n = 104$) of participants were assessed to be within the VH mutation poor risk group and 43.5% ($n = 87$) had a positive CD38 status, a slightly higher proportion in the FCM-miniR arm ($n = 46$, 46.0%) than in the FCR arm ($n = 41$, 41.0%).

Treatment received

Tables 11–14 summarise the treatment details including treatment received, treatment discontinuations and modifications and GCSF usage by randomisation allocation (FCR, FCM-miniR). After the interim analysis, 21 participants still receiving FCM-miniR transferred over to receive treatment with FCR. Of these, two participants received a full six cycles of FCR; four received FCR from cycle 2; four from cycle 3; six from cycle 4; four from cycle 5; and one participant received FCR for their final cycle of treatment, cycle 6. These participants are summarised in addition to those who received FCR and FCM-miniR throughout the trial.

TABLE 11 Treatment details (all participants)

Treatment details	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
Number of treatment cycles received,* n *(%)				
0	2 (2.0)	0 (0.0)	0 (0.0)	2 (1.0)
1	1 (1.0)	7 (8.9)	0 (0.0)	8 (4.0)
2	9 (9.0)	3 (3.8)	0 (0.0)	12 (6.0)
3	3 (3.0)	6 (7.6)	0 (0.0)	9 (4.5)
4	6 (6.0)	5 (6.3)	0 (0.0)	11 (5.5)
5	9 (9.0)	7 (8.9)	1 (4.8)	17 (8.5)
6	70 (70.0)	51 (64.6)	20 (95.2)	141 (70.5)
Treatment cycles received,* n *(%)				
≤ 3	15 (15.0)	16 (20.3)	0 (0.0)	31 (15.5)
> 3	85 (85.0)	63 (79.7)	21 (100.0)	169 (84.5)
Summary statistics				
Mean (SD)	5.2 (1.5)	5.0 (1.7)	6.0 (0.2)	5.2 (1.5)
Median (range)	6 (0–6)	6 (1–6)	6 (5–6)	6 (0–6)

SD, standard deviation.

TABLE 12 Early discontinuation of protocol treatment (all participants)

Early discontinuation details	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
Number of participants discontinuing treatment early, *n* (%)	30 (30.0)	28 (35.4)	1 (4.8)	59 (29.5)
Reason for early discontinuation of treatment,* n *(%)				
Disease progression, requiring further treatment	0 (0.0)	3 (10.7)	0 (0.0)	3 (5.1)
Toxicity	22 (73.3)	21 (75.0)	1 (100)	44 (74.6)
A prior eligibility criteria has been violated (discussed with CTRU/CI)	1 (3.3)	0 (0.0)	0 (0.0)	1 (1.7)
Stable disease with no or minimal response	1 (3.3)	2 (7.1)	0 (0.0)	3 (5.1)
Participant decision	2 (6.7)	1 (3.6)	0 (0.0)	3 (5.1)
Clinician decision	3 (10.0)	1 (3.6)	0 (0.0)	4 (6.8)
Other reason discontinued	1 (3.3)	0 (0.0)	0 (0.0)	1 (1.7)

Overall, 31 participants (15.5%) received three or fewer cycles of treatment ($n = 15$, 15.0% FCR; $n = 16$, 20.3% FCM-miniR; $n = 0$, 0.0% FCM-miniR/FCR), with 70.5% of participants receiving all six cycles ($n = 70$, 70.0% FCR; $n = 51$, 64.6% FCM-miniR; $n = 20$, 95.2% FCM-miniR/FCR) (*Table 11*). Two participants randomised to FCR did not receive any trial treatment. One was found to be ineligible post randomisation as they had received prior therapy for CLL; they went on to receive FCR off trial and continued to be followed up as per the protocol. The other participant withdrew from the trial (treatment and follow-up) on the advice of the treating clinician as they had a 17p deletion and were treated with a more 'appropriate regime' off trial.

TABLE 13 Treatment modifications (all participants)

Treatment modifications	FCR (*n* = 100)	FCM-miniR (*n* = 79)	FCM-miniR/FCR (*n* = 21)	Total (*n* = 200)
Number of participants experiencing at least one dose modification, *n* (%)	67 (67.0)	52 (65.8)	16 (76.2)	135 (67.5)
Dose modification,* n *(%)				
Dose omission	6 (6.0)	9 (11.4)	2 (9.5)	17 (8.5)
Dose reduction	31 (31.0)	28 (35.4)	11 (52.4)	70 (35.0)
Dose delay	53 (53.0)	47 (59.5)	14 (66.7)	114 (57.0)
Dose stopped early	11 (11.0)	7 (8.9)	1 (4.8)	19 (9.5)
Alternative route of administration	7 (7.0)	5 (6.3)	1 (4.8)	13 (6.5)

TABLE 14 Granulocyte colony-stimulating factor usage during treatment (all participants)

GCSF usage	FCR (*n* = 100)	FCM-miniR (*n* = 79)	FCM-miniR/FCR (*n* = 21)	Total (*n* = 200)
Received GCSF during the first three cycles,* n *(%)				
Yes	31 (31.0)	28 (35.4)	9 (42.9)	68 (34.0)
No	57 (57.0)	41 (51.9)	12 (57.1)	110 (55.0)
Unknown	12 (12.0)	10 (12.7)	0 (0.0)	22 (11.0)
Received GCSF during treatment,* n *(%)				
Yes	42 (42.0)	40 (50.6)	12 (57.1)	94 (47.0)
No	53 (53.0)	34 (43.0)	9 (42.9)	96 (48.0)
Unknown	5 (5.0)	5 (6.3)	0 (0.0)	10 (5.0)

Fifty-nine participants (29.5%) discontinued treatment early: 30 of those participants who were receiving FCR (30.0%), 28 of those participants receiving FCM-miniR (35.4%) and one of those participants in the FCM-miniR/FCR group. Toxicity was the majority reason for early discontinuation of treatment (74.6% of cases), with a similar proportion in the FCR and FCM-miniR treatment arms (FCR: *n* = 22, 73.3%; FCM-miniR: *n* = 21, 75.0%) (*Table 12*).

Table 13 summarises the number and proportion of participants experiencing at least one modification to their protocol-defined dose of treatment (i.e. dose omission, reduction, delay, stopped early or alternative route of administration). A total of 135 participants (67.5%) experienced at least one modification to their protocol treatment with a similar proportion in the FCR (*n* = 67, 67.0%) and FCM-miniR (*n* = 52, 65.8%) treatment arms. Overall, 57.0% (*n* = 114) of participants experienced a delay to at least one of their doses of treatment and 35.0% (*n* = 70) experienced a dose reduction with a higher proportion in the FCM-miniR arm.

Overall, 68 participants (34.0%) received treatment with GCSF during the cycles of therapy with a higher proportion in the FCM-miniR arm (35.4%, *n* = 28) than the FCR arm (31.0%, *n* = 31) and the FCM-miniR/FCR arm (42.9%, *n* = 9). Throughout the whole of the treatment period (cycles 1–6), 94 participants (47.0%) received GCSF at some stage (FCR: 42%, *n* = 42; FCM-miniR: 50.6%, *n* = 40; and FCM-miniR/FCR: 57.1%, *n* = 12) (*Table 14*). Rates are in line with what would be expected for these treatments.

Of the 68 participants known to have received treatment with GCSF at some stage during the first three cycles, 88.2% (*n* = 60) received four or more cycles of treatment; in contrast, 98.2% (*n* = 108) of those who did not receive GCSF received four or more cycles of treatment (*Table 15*).

TABLE 15 Granulocyte colony-stimulating factor usage by number of treatment cycles received

Number of treatment cycles received	Received GCSF within first three cycles ($n = 68$), *n* (%)	Did not receive GCSF within first three cycles ($n = 110$), *n* (%)	Unknown ($n = 20$), *n* (%)	Total ($n = 198$), *n* (%)
1	0 (0.0)	0 (0.0)	8 (40.0)	8 (4.0)
2	2 (2.9)	0 (0.0)	10 (50.0)	12 (6.1)
3	6 (8.8)	2 (1.8)	1 (5.0)	9 (4.5)
4	5 (7.4)	6 (5.5)	0 (0.0)	11 (5.6)
5	5 (7.4)	12 (10.9)	0 (0.0)	17 (8.6)
6	50 (73.5)	90 (81.8)	1 (5.0)	141 (71.2)

Interim analysis

An interim analysis of the short-term efficacy data was performed on the first 103 participants randomised into the study: 51 allocated to the FCR control arm and 52 allocated to the FCM-miniR intervention arm. The results of the interim analysis were presented to the DMEC in September 2012.

The interim analysis was based on all data received and entered into the trial database up to 30 August 2012. Owing to the ongoing nature of the trial, the DMEC was aware that the data on which the interim analysis was based may not have been fully validated and could be subject to change by the time of the final analysis. This report summarises the data as they were reported to the DMEC, even if there were changes to these results prior to the final, clean, analysis data set.

By the time the final participant to be included in the interim analysis had reached their primary end point (i.e. 3 months post treatment), 191 participants out of a target of 206 had been randomised from 32 UK centres. The primary aim of the formal interim analysis was to be able to release information on any potential large differences in efficacy between the treatment arms earlier than would have been the case with the final analysis.

Treatment received

Of the first 103 participants randomised, 72 (69.9%) received all six cycles of treatment, with a higher proportion of participants coming from the FCR arm ($n = 38$, 74.5%) than the FCM-miniR arm ($n = 34$, 65.4%) (*Table 16*). Thirty-one participants (30.1%) had discontinued treatment early (FCR: 25.5%, $n = 13$; FCM-miniR: 34.6%, $n = 18$).

Table 17 summarises the number and proportion of participants experiencing at least one modification to their protocol-defined dose of treatment. A higher proportion of participants in the FCM-miniR arm experienced at least one dose omission, dose reduction and dose delay than in the FCR arm.

TABLE 16 Treatment details (interim analysis population)

Treatment details	FCR ($n = 51$)	FCM-miniR ($n = 52$)	Total ($n = 103$)
Number of treatment cycles received,* n *(%)			
1	0 (0.0)	3 (5.8)	3 (2.9)
2	5 (9.8)	1 (1.9)	6 (5.8)
3	1 (2.0)	2 (3.8)	3 (2.9)
4	3 (5.9)	5 (9.6)	8 (7.8)
5	4 (7.8)	7 (13.5)	11 (10.7)
6	38 (74.5)	34 (65.4)	72 (69.9)

TABLE 17 Treatment modifications (interim analysis population)

Treatment modifications	FCR ($n = 51$)	FCM-miniR ($n = 52$)	Total ($n = 103$)
Dose modification,* n *(%)			
Dose omission	1 (2.0)	7 (13.5)	8 (7.8)
Dose reduction	15 (29.4)	20 (38.5)	35 (34.0)
Dose delay	23 (45.1)	28 (53.8)	51 (49.5)

Efficacy

An independent central assessment of response was carried out in order to assess formally the primary end point data on response to treatment as defined by IWCLL criteria.[26] The interim analysis of the primary end point data was based on the ITT population, which included participants for whom written informed consent had been received and for which primary end point data were available. A PP analysis was not performed as, out of the first 103 participants, all received at least one cycle of their randomised treatment. The FCR participant who had been previously infected with hepatitis B was not excluded as this was not classed as a major protocol violation.

Of the 103 participants assessed in the interim analysis, 18 (17.5%) were excluded from the formal analysis of the primary end point, with a slightly higher proportion coming from the FCR arm (FCR: $n = 10$, 19.6%; FCM-miniR: $n = 8$, 15.4%) (*Table 18*). Fifteen participants had a missing trephine sample (7 FCR; 8 FCM-miniR), which is required by the IWCLL criteria to confirm a CR, with no further evidence that they were definitely not a CR/CRi. Of these, two trephine samples were taken but were inadequate for analysis. Thirteen samples were not taken owing to a sample being missed in error ($n = 4$); a clinician's decision ($n = 2$); a participant's decision ($n = 2$); a participant being unwell ($n = 1$); it being too painful/difficult to sample a participant ($n = 4$).

In the FCR arm, two participants withdrew their consent for further trial treatment and follow-up data collection prior to the assessment of the primary end point, and one participant discontinued treatment after their second cycle and was subsequently lost to follow-up.

Table 19 presents the number of participants achieving a CR and the difference in response rates between the treatment arms. Overall, 71.8% ($n = 61$) of participants achieved a CR, with a higher proportion in the FCR arm ($n = 34$, 82.9%) than in the FCM-miniR arm ($n = 27$. 61.4%). The difference in the CR rates was 21.6% in favour of the FCR arm, with a 99.5% CI (–48.0% to 4.8%).

TABLE 18 Exclusions from the interim analysis of the primary end point (interim analysis population)

Exclusion	FCR ($n = 51$)	FCM-miniR ($n = 52$)	Total ($n = 103$)
Participants excluded from the primary end point analysis, *n* (%)	10 (19.6)	8 (15.4)	18 (17.5)
Reasons for exclusion,* n *(%)			
Missing 3-month post-treatment trephine sample	7 (13.7)	8 (15.4)	15 (14.6)
Withdrew from further trial treatment and follow-up data collection	2 (3.9)	0 (0.0)	2 (1.9)
Lost to follow-up	1 (2.0)	0 (0.0)	1 (1.0)

TABLE 19 Proportion of participants achieving a CR/CRi at 3 months post treatment (ITT population)

Achievement of the primary end point	FCR ($n = 41$)	FCM-miniR ($n = 44$)	Total ($n = 85$)	Difference in response rates (FCM – miniR-FCR)	99.5% CI for difference in response rate
Achieved a CR/CRi, *n* (%)	34 (82.9)	27 (61.4)	61 (71.8)	–21.6	–48.0% to 4.8%
Did not achieve a CR/CRi, *n* (%)	7 (17.1)	17 (38.6)	24 (28.2)		

A binary multivariate logistic regression model was used to assess formally the effect of treatment on the proportion of participants achieving a CR at 3 months post treatment, adjusting for the minimisation factors, excluding centre (*Table 20*). The O'Brien and Fleming[32] alpha spending function was used to adjust for multiple testing, requiring an alpha level of < 0.005 (two-sided) to indicate significance, in order to preserve the alpha for the final analysis.

The OR for achieving a CR in the FCM-miniR arm compared with the FCR arm was 0.32 (99.5% CI: 0.07 to 1.48). With a *p*-value of 0.037, the difference between the treatment arms in terms of CR rates was not significant at the reduced 0.5% significance level, although it was noted that the experimental treatment was somewhat worse in terms of response.

Of the 103 participants included in the interim analysis, 51.5% ($n = 53$) had undetectable MRD at 3 months post treatment, with a higher proportion of participants in the FCR arm ($n = 29$, 56.9%) than in the FCM-miniR arm ($n = 24$, 46.2%) (*Table 21*).

TABLE 20 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (ITT population)

Parameter	df	Parameter estimate	SE	Wald χ^2	Pr > χ^2	OR (99.5% CI)
Intercept	1	0.81	0.31	6.86	0.009	
Treatment group: FCM-miniR vs. FCR	1	–0.56	0.27	4.34	0.037	0.32 (0.07 to 1.48)
Sex: female vs. male	1	0.31	0.31	1.02	0.312	1.87 (0.33 to 10.55)
Age group: > 65 years vs. ≤ 65 years	1	–0.56	0.28	3.91	0.048	0.32 (0.07 to 1.60)
Binet stage: C vs. A progressive or B	1	–0.42	0.28	2.35	0.125	0.43 (0.09 to 2.02)

df, degrees of freedom.

TABLE 21 Proportion of participants achieving MRD negativity at 3 months post treatment (interim analysis population)

MRD assessment	FCR ($n = 51$)	FCM-miniR ($n = 52$)	Total ($n = 103$)
Assessment of MRD, **n** ***(%)***			
MRD negative	29 (56.9)	24 (46.2)	53 (51.5)
MRD positive	19 (37.3)	22 (42.3)	41 (39.8)
Unknown, samples not taken	0 (0.0)	5 (9.6)	5 (4.9)
Early death	0 (0.0)	1 (1.9)	1 (1.0)
Withdrew from further trial treatment and follow-up data collection	2 (3.9)	0 (0.0)	2 (1.9)
Lost to follow-up	1 (2.0)	0 (0.0)	1 (1.0)

Safety and toxicity

A total of 103 SAEs were reported from 60 participants out of the first 103 randomised into the trial. Of the 103 reported SAEs, 44 events (42.7%) were from 26 participants receiving FCR and 59 events (57.3%) were from 34 participants receiving FCM-miniR. The mean number of SAEs reported per participant (1.7) was the same in both treatment arms (*Table 22*).

Of the 103 SAEs reported, 85 (82.5%) were suspected to be related to trial treatment (51 reported from participants receiving FCM-miniR and 34 reported from participants receiving FCR). One SUSAR was reported from a participant in the FCR arm. The participant received all six cycles of treatment and was diagnosed with a 'squamous cell carcinoma' approximately 4 months after their last cycle of treatment. The event was felt by the Principal Investigator at the site to be related to trial treatment (F, C and R) and unexpected. The majority of SAEs required hospitalisation ($n = 89$, 86.4%); three participants died as a result of their SAE (one in the FCR arm and two in the FCM-miniR arm) (*Table 23*).

A total of 1469 AEs were reported from 101 participants. A total of 669 events were from 49 participants receiving FCR and 770 events from 52 participants receiving FCM-miniR.

TABLE 22 Number of participants experiencing an SAE and total number of SAEs reported (interim analysis population)

SAE summary	FCR ($n = 51$)	FCM-miniR ($n = 52$)	Total ($n = 103$)
Has the participant experienced an SAE?*, n *(%)			
Yes	26 (51.0)	34 (65.4)	60 (58.3)
No	25 (49.0)	18 (34.6)	43 (41.7)
Number of participants with one or more SAE	26	34	60
Number of SAEs reported	44	59	103
Number of SAEs per participant			
Mean (SD)	1.7 (1.2)	1.7 (1.1)	1.7 (1.1)
Median (range)	1 (1–5)	1 (1–5)	1 (1–5)

SD, standard deviation.

TABLE 23 Suspected relationship with experimental treatment (interim analysis population)

SAE relationship and seriousness criteria	FCR, *N* (%)	FCM-miniR, *N* (%)	Total, *N* (%)
Relationship to experimental treatment			
Suspected, unexpected	1 (2.3)	0 (0.0)	1 (1.0)
Suspected, expected	33 (75.0)	51 (86.4)	84 (81.6)
Not suspected	10 (22.7)	8 (13.6)	18 (17.5)
Total	44 (100)	59 (100.0)	103 (100)
Seriousness criteria (not mutually exclusive)			
Participant died as a result of the SAE	1 (2.3)	2 (3.4)	3 (2.9)
Life-threatening	1 (2.3)	3 (5.1)	4 (3.9)
Congenital anomaly/birth defect	0 (0.0)	0 (0.0)	0 (0.0)
Required/prolonged hospitalisation	39 (88.6)	50 (84.7)	89 (86.4)
Persistent or significant disability/incapacity	1 (2.3)	0 (0.0)	1 (1.0)
Jeopardised patient/required intervention to prevent one of the above criteria	6 (13.6)	10 (16.9)	16 (15.5)
Missing	1 (2.3)	0 (0.0)	1 (1.0)

Conclusions from the Data Monitoring and Ethics Committee

The difference in the CR rates between the treatment arms (82.9% FCR; 61.4% FCM-miniR), although not statistically significant, was deemed by the DMEC to be clinically relevant. In light of this, and the indication of an increased toxicity rate and increased number of dose omissions and reductions in the FCM-miniR arm, the DMEC recommended that the trial should close the recruitment with immediate effect, and all participants receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles. At the time of trial closure, 200 participants had been recruited into the trial.

Final analysis: primary end point

The final participant's clinic visit to assess their primary end point (3 months post treatment) was carried out on 31 July 2013; the data lock for the analysis of the primary end point was performed on 30 October 2013. Owing to the non-inferiority nature of the primary end point, the primary analysis was carried out on both the ITT and PP populations.

Participants randomised to FCM-miniR who transferred over to receive treatment with FCR after the interim analysis (see *Interim analysis* for further details) were summarised in a separate group and excluded from any formal comparisons of the treatment arms. This was felt to be appropriate, as the decision to stop FCM-miniR was on the recommendation of the DMEC, rather than a decision from the treating clinician or participant, which violates the ITT assumption.

Central assessment of response by International Workshop on chronic lymphocytic leukaemia

Table 24 summarises the proportion of participants with a centrally reviewed IWCLL assessment of response. Of the 200 participants, a response assessment was available for 166 participants (83.0%), with the same proportion in each treatment arm. Twenty-four (12.0%) participants assessed as being at least a PR had a missing trephine sample, which is required by the IWCLL criteria to confirm a CR. Four participants in the FCR arm withdrew from follow-up and one FCM-miniR participant died prior to the assessment of response. In addition, in the FCM-miniR arm, one participant's response to treatment was unable to be assessed and four participants (one in the FCR and three in the FCM-miniR arm) missed their 3-month post-treatment visit.

TABLE 24 Number of participants with a centrally reviewed assessment of response (IWCLL) (all participants)

IWCLL assessment of response available	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
IWCLL assessment of response,* n *(%)			
Yes	83 (83.0)	63 (63.0)	146 (73.0)
Yes (received FCM-miniR/FCR)	0 (0.0)	20 (20.0)	20 (10.0)
No IWCLL assessment of response,* n *(%)			
Missing trephine sample	12 (12.0)	11 (11.0)	23 (11.5)
Missing trephine sample (received FCM-miniR/FCR)	0 (0.0)	1 (1.0)	1 (0.5)
Withdrew from follow-up prior to assessment of response	4 (4.0)	0 (0.0)	4 (2.0)
Early death	0 (0.0)	1 (1.0)	1 (0.5)
Unable to assess	0 (0.0)	1 (1.0)	1 (0.5)
Missed 3-month post-treatment visit	1 (1.0)	3 (3.0)	4 (2.0)

Numbers analysed and reasons for non-inclusion in the intention-to-treat population

Of the 200 participants randomised, 167 (83.5%) participants were included in the ITT analysis, with a higher proportion in the FCR arm ($n = 92$, 92.0% FCR; $n = 75$, 75.0% FCM-miniR) (*Table 25*). Participants who were randomised to FCM-miniR but transferred over to receive treatment with FCR after the interim analysis were excluded from the ITT population ($n = 21$). In addition to the 146 participants in the FCR and FCM-miniR arms with an assessment of response, a further 14 participants who were at least a PR but had missing trephine samples were included in the ITT analysis owing to further clinical evidence that confirmed that they were either a CR/CRi or PR, as per the pre-specified decision rules, specified in *Chapter 2*, *Missing data handling*. Two participants in the FCR arm withdrew consent for the trial owing to non-response and toxicity, and a further FCM-miniR participant died as a result of their CLL, all prior to the assessment of their primary end point (3-month post-treatment visit). Four participants (one in the FCR and three from the FCM-miniR arms) discontinued treatment early owing to non-response or toxicity and subsequently missed their 3-month post-treatment visit. All seven participants (three FCR, four FCM-miniR) were included in the ITT analysis as non-responders, as per the missing data decision rules.

A total of 33 participants were not able to be included in the ITT analysis, including the 21 treatment arm transfers:

- There were nine participants with a missing trephine sample (six in the FCR and three in the FCM-miniR arm), with no further clinical evidence they were definitely not a CR/CRi. Of these, three were missed in error; two were at the discretion of the treating clinician; two were the participants' decisions; two were a result of it being too painful/difficult to sample participants.
- Two participants withdrew their consent for further trial treatment and follow-up data collection prior to the assessment of the primary end point, both randomised to FCR. Of these, one participant had a 17p deletion and on the advice of the treating clinician was treated with a 'more appropriate regime' off trial, prior to receiving any trial treatment. The second participant withdrew consent after receiving one cycle of treatment, for non-treatment-related reasons: 'Due to other tests/treatment, the participant no longer wishes to remain on trial and feels they do not have time to continue with trial follow-up'.
- One participant, who received two cycles of treatment with FCM-miniR, was unable to be assessed for response owing to insufficient clinical evaluations performed at the 3-month post-treatment visit (i.e. missing haematology tests, liver and spleen examinations and blood/trephine samples), with no reason provided.

TABLE 25 Number of participants included in the ITT analysis, and reasons for exclusion (all participants)

Reason for exclusion, *n* (%)	FCR ($n = 100$)	FCM-miniR ($n = 100$)	Total ($n = 200$)
Participants included in the ITT population	***92 (92.0)***	***75 (75.0)***	***167 (83.5)***
IWCLL response assessment available	84 (84.0)	66 (66.0)	150 (75.0)
Missing trephine sample but clinical evidence that participant was either a CR/CRi or PR	6 (6.0)	8 (8.0)	14 (7.0)
Withdrew from follow-up prior to assessment of response owing to toxicity or non-response	2 (2.0)	0 (0.0)	2 (1.0)
Early death as a result of CLL	0 (0.0)	1 (1.0)	1 (0.5)
Participants excluded from the ITT population	***8 (8.0)***	***25 (25.0)***	***33 (16.5)***
Received FCM-miniR/FCR	0 (0.0)	21 (21.0)	21 (10.5)
Missing trephine sample with at least a PR and no evidence that participant was not a CR/CRi	6 (6.0)	3 (3.0)	9 (4.5)
Withdrew from follow-up prior to assessment of response	2 (2.0)	0 (0.0)	2 (1.0)
Unable to assess	0 (0.0)	1 (1.0)	1 (0.5)

These 33 participants were excluded from the ITT population in line with the guidance within the Statistical Analysis Plan, which was signed off prior to any analysis being conducted.

In the PP population, an additional participant with an assessment of response in the FCR arm was excluded as a result of breaching the eligibility criteria and not receiving any of their randomised treatment. The participant in the FCR arm who had been previously infected with hepatitis B was not excluded as this was not classed as a major protocol violation.

Table 26 presents the baseline characteristics for the ITT population compared with the 33 participants who were not able to be included in the analysis. In the group of participants who were not included in the ITT analysis, participants tended to be older, with a higher proportion of females and Binet stage A progressive or B disease, although these were relatively small numbers for comparison. The excluded population contained a slightly higher proportion of poorer risk participants in terms of 17p and 11q deletions.

TABLE 26 Comparison of the baseline characteristics for the ITT population and participant exclusions

Baseline characteristics	ITT population (*n* = 167)	Excluded from the ITT population (*n* = 33)	Total (*n* = 200)
Minimisation factors,* n *(%)			
Age group			
≤ 65 years	106 (63.5)	19 (57.6)	125 (62.5)
> 65 years	61 (36.5)	14 (42.4)	75 (37.5)
Sex			
Male	117 (70.1)	18 (54.5)	135 (67.5)
Female	50 (29.9)	15 (45.5)	65 (32.5)
Binet stage			
A progressive or B	111 (66.5)	25 (75.8)	136 (68.0)
C	56 (33.5)	8 (24.2)	64 (32.0)
Genetic markers			
17p deletion			
Yes (poorer risk)	6 (3.6)	1 (3.0)	7 (3.5)
No (standard risk)	147 (88.0)	29 (87.9)	176 (88.0)
Missing	14 (8.4)	3 (9.1)	17 (8.5)
11q deletion			
Yes (poorer risk)	24 (14.4)	6 (18.2)	30 (15.0)
No (standard risk)	133 (79.6)	25 (75.8)	158 (79.0)
Missing	10 (6.0)	2 (6.1)	12 (6.0)
VH risk group			
Poor risk	87 (52.1)	17 (51.5)	104 (52.0)
Standard risk	52 (31.1)	9 (27.3)	61 (30.5)
Unknown	28 (16.8)	7 (21.2)	35 (17.5)

Formal analysis of the primary end point

Overall, 66.5% ($n = 111$) of participants in the ITT population achieved a CR, a higher proportion in the FCR arm ($n = 70$, 76.1%) than the FCM-miniR arm ($n = 41$, 54.7%) (*Table 27*). The difference between the arms was 21.4%, in favour of the FCR arm (95% CI –35.8% to –7.0%), indicating that FCM-miniR appears to be performing worse in terms of response.

A binary multivariate logistic regression model was used to assess formally the primary end point: the effect of treatment on the proportion of participants achieving a CR at 3 months post treatment, after adjusting for the minimisation factors, excluding centre (*Table 28*). The OR for achieving a CR in the FCM-miniR arm compared with the FCR arm was 0.37 (95% CI: 0.19 to 0.73), indicating that participants in the FCM-miniR are less likely to achieve a CR. The trial was powered on demonstrating that FCM-miniR was no more than 10% worse in terms of CR rates than FCR. With a CR rate of 76.1% in the FCR arm, a 10% reduction gives an OR of 0.61 (see *Primary end point analysis* for further details of the derivation). As the lower limit of the 95% CI for the treatment effect is < 0.61, and even the mean OR is below this level, there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates. As the upper limit of the 95% CI is also below 1, there is evidence that FCM-miniR is significantly inferior to FCR.

The 95% CIs around the ORs for the minimisation factors all contain 1, indicating that there is no evidence that any of the minimisation factors are significantly associated with response, although there is a suggested trend towards participants who are aged over 65 years and with Binet stage C performing worse.

The analysis of the primary end point using the PP population concurred with the outcome of the ITT analysis and demonstrated inferiority of FCM-miniR to FCR with an OR of 0.38 (95% CI 0.19 to 0.75) (*Table 29*).

The analysis of the primary end point on both the ITT and PP populations strongly demonstrated that FCM-miniR is not non-inferior to FCR in terms of CR rates and, in fact, there is evidence to suggest that FCM-miniR is significantly inferior to FCR.

TABLE 27 Proportion of participants achieving a CR or CRi at 3 months post treatment (ITT population)

Achievement of the primary end point, *n* (%)	FCR ($n = 92$)	FCM-miniR ($n = 75$)	Total ($n = 167$)	Difference in CR rates and 95% CIs (FCM-miniR – FCR)
Achieved a CR/CRi	70 (76.1)	41 (54.7)	111 (66.5)	–21.4% (–35.8% to –7.0%)
Did not achieve a CR/CRi	22 (23.9)	34 (45.3)	56 (33.5)	

TABLE 28 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (ITT population)

Parameter	df	Parameter estimate	SE	OR (95% CI estimate)
Intercept	1	1.38	0.33	
Treatment group: FCM-miniR vs. FCR	1	–0.98	0.34	0.37 (0.19 to 0.73)
Sex: female vs. male	1	0.22	0.38	1.25 (0.59 to 2.63)
Age group: > 65 years vs. ≤ 65 years	1	–0.55	0.35	0.58 (0.29 to 1.15)
Binet stage: C vs. A progressive or B	1	–0.21	0.36	0.81 (0.40 to 1.63)

df, degrees of freedom.

TABLE 29 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (PP population)

Parameter	df	Parameter estimate	SE	OR (95% CI estimate)
Intercept	1	1.37	0.33	
Treatment group: FCM-miniR vs. FCR	1	–0.97	0.34	0.38 (0.19 to 0.75)
Sex: female vs. male	1	0.23	0.38	1.26 (0.60 to 2.66)
Age group: > 65 years vs. ≤ 65 years	1	–0.57	0.35	0.57 (0.28 to 1.13)
Binet stage: C vs. A progressive or B	1	–0.20	0.36	0.82 (0.41 to 1.66)

df, degrees of freedom.

Sensitivity analyses

Sensitivity analyses were performed in order to assess the reliability of the analysis of primacy and the assumptions regarding the missing primary end point data. The responses of participants that were not included in the ITT population were imputed, with the exception of those participants who received FCM-miniR/FCR after the FCM-miniR arm was closed (see *Table 25*).

The first sensitivity analysis assumed that participants who were not included in the ITT population were all non-responders, and thus these participants were treated as not having achieved a CR in the analysis of the primary end point (eight in the FCR arm and four in the FCM-miniR). A total of 179 participants were included in this analysis, with 62.0% (111/179) achieving a CR compared with 66.5% (111/167) in the analysis of primacy. A total of 70.0% (70/100) of FCR participants achieved a CR compared with 51.9% (41/79) in the FCM-miniR arm. The OR for achieving a CR in the FCM-miniR arm compared with the FCR arm was 0.46 (95% CI 0.24 to 0.86) (*Table 30*), indicating that FCM-miniR participants are less likely to achieve a CR. With a response rate of 70.0% in the control arm, a 10% reduction (i.e. the non-inferiority margin) gives an OR of 0.64. As the lower limit of the 95% CI for the treatment effect and the mean OR are both < 0.64, there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates, even after treating participants with missing data as non-responders.

The second sensitivity analysis assumed that the participants who were not included in the ITT population were all responders, and thus these participants were treated as having achieved a CR in the analysis of the primary end point (8 FCR, 4 FCM-miniR). A total of 179 participants were included in this analysis, with 68.7% (123/179) achieving a CR compared with 66.5% (111/167) in the analysis of primacy. A total of

TABLE 30 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (sensitivity analysis 1)

Parameter	df	Parameter estimate	SE	OR (95% CI estimate)
Intercept	1	1.14	0.30	
Treatment group: FCM-miniR vs. FCR	1	–0.78	0.32	0.46 (0.24 to 0.86)
Sex: female vs. male	1	0.03	0.34	1.03 (0.52 to 2.02)
Age group: > 65 years vs. ≤ 65 years	1	–0.52	0.32	0.60 (0.31 to 1.13)
Binet stage: C vs. A progressive or B	1	–0.28	0.33	0.75 (0.39 to 1.45)

df, degrees of freedom.

78.0% (78/100) of FCR participants achieved a CR compared with 57.0% (45/79) in the FCM-miniR arm. The OR for achieving a CR in the FCM-miniR arm compared with the FCR arm was 0.37 (95% CI: 0.19 to 0.72) (*Table 31*) indicating that participants in the FCM-miniR are less likely to achieve a CR. With a response rate of 78.0% in the control arm, a 10% reduction (i.e. the non-inferiority margin) gives an OR of 0.60. As the lower limit of the 95% CI for the treatment effect and the mean OR are < 0.60, there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates, even after treating participants with missing data as responders.

The third sensitivity analysis excluded all participants with missing trephine data from the ITT population and thus the analysis of the primary end point (6 FCR, 8 FCM-miniR). A total of 153 participants were included in this analysis, with 69.9% (107/153) achieving a CR compared with 66.5% (111/167) in the analysis of primacy. A total of 79.1% (68/86) of FCR participants achieved a CR compared with 58.2% (39/67) of participants in the FCM-miniR arm. The OR for achieving a CR in the FCM-miniR arm compared with the FCR arm was 0.37 (95% CI: 0.18, 0.77) (*Table 32*), indicating that participants in the FCM-miniR are less likely to achieve a CR. With a response rate of 79.1% in the control arm, a 10% reduction (i.e. the non-inferiority margin) gives an OR of 0.59. As the lower limit of the 95% CI for the treatment effect and the mean OR are < 0.59, there is very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates, even after excluding participants with missing trephine data.

The results of the sensitivity analyses are consistent with the analysis of primacy and confirm that there is strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates at 3 months post treatment. The results do not change considerably even after imputing the missing data, demonstrating the robustness of the conclusions. After excluding participants with missing trephine data, the results remained consistent with the analysis of primacy, supporting the approach to impute the response for participants with missing trephine data but who were known to be at least a PR (as described in *Missing data handling*).

TABLE 31 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (sensitivity analysis 2)

Parameter	df	Parameter estimate	SE	OR (95% CI estimate)
Intercept	1	1.45	0.33	
Treatment group: FCM-miniR vs. FCR	1	–1.00	0.34	0.37 (0.19 to 0.72)
Sex: female vs. male	1	0.32	0.37	1.38 (0.66 to 2.85)
Age group: > 65 vs. ≤ 65	1	–0.51	0.34	0.60 (0.31 to 1.18)
Binet stage: C vs. A progressive or B	1	–0.22	0.35	0.81 (0.40 to 1.60)

df, degrees of freedom.

TABLE 32 Multivariate logistic regression analysis for the proportion of participants achieving a CR or CRi at 3 months post treatment, adjusted for the minimisation factors (sensitivity analysis 3)

Parameter	df	Parameter estimate	SE	OR (95% CI estimate)
Intercept	1	1.54	0.36	
Treatment group: FCM-miniR vs. FCR	1	–0.99	0.37	0.37 (0.18 to 0.77)
Sex: female vs. male	1	0.47	0.43	1.61 (0.69 to 3.75)
Age group: > 65 vs. ≤ 65	1	–0.62	0.37	0.54 (0.26 to 1.13)
Binet stage: C vs. A progressive or B	1	–0.25	0.39	0.78 (0.36 to 1.67)

df, degrees of freedom.

Subgroup analyses

Pre-specified subgroup analyses were carried out to assess the heterogeneity of the treatment effect among subgroups of interest for the primary end point, using the ITT population. As the PP population was very similar to that of the ITT, subgroup analyses on this population were considered unnecessary. As the trial was not powered to look for differences in subgroups of participants, the results are to be treated as exploratory and should be used for hypothesis-generating purposes only.

Tables 33–36 present the subgroups of interest by whether or not a CR was achieved, the difference in response rates and 95% CIs.

Of the 163 participants included in the ITT analysis of the primary end point, a similar proportion of males and females achieved a CR (65.0% vs. 70.0%; *Table 33*). The difference in response rates between the two age groups was 11.7% (95% CI –3.3% to 26.8%), suggesting a trend towards younger participants (aged ≤ 65 years) being more likely to achieve a CR; as the CI contains zero this difference is not statistically significant. A higher proportion of participants with Binet stage A progressive or B achieved a CR than those with stage C (68.5% vs. 62.5%). The 95% CI contains zero, indicating that this difference is not statistically significant but suggesting a trend in favour of Binet stage A progressive and B participants.

TABLE 33 Minimisation factors by achievement of the primary end point (ITT population)

Minimisation factors			Difference in rates (95% CI)
Sex	***Male* (n = *117*)**	***Female* (n = *50*)**	
Achieved a CR/CRi, *n* (%)	76 (65.0)	35 (70.0)	–5.0% (–20.4% to 10.3%)
Did not achieve a CR/CRi, *n* (%)	41 (35.0)	15 (30.0)	
Age group	***≤ 65 years* (n = *105*)**	***> 65 years* (n = *58*)**	
Achieved a CR/CRi, *n* (%)	75 (70.8)	36 (59.0)	11.7% (–3.3% to 26.8%)
Did not achieve a CR/CRi, *n* (%)	31 (29.2)	25 (41.0)	
Binet stage	***Stage A progressive or B* (n = *106*)**	***Stage C* (n = *56*)**	
Achieved a CR/CRi, *n* (%)	76 (68.5)	35 (62.5)	6.0% (–9.4% to 21.3%)
Did not achieve a CR/CRi, *n* (%)	35 (31.5)	21 (37.5)	

TABLE 34 Baseline clinical details by achievement of the primary end point (ITT population)

Baseline clinical details			Difference in rates (95% CI)
Creatinine clearance levels	***30–60 ml/minute* (n = *25*)**	***> 60 ml/minute* (n = *142*)**	
Achieved a CR/CRi, *n* (%)	15 (60.0)	96 (67.6)	–7.6% (–28.3% to 13.1%)
Did not achieve a CR/CRi, *n* (%)	10 (40.0)	46 (32.4)	
β_2M concentration	***< 4 mg/l* (n = *60*)**	***≥ 4 mg/l* (n = *97*)**	
Achieved a CR/CRi, *n* (%)	43 (71.7)	60 (61.9)	9.8% (–5.1% to 24.8%)
Did not achieve a CR/CRi, *n* (%)	17 (28.3)	37 (38.1)	

TABLE 35 Treatment cycles received by achievement of the primary end point (ITT population)

Treatment cycles received	Three cycles or fewer (*n* = 25)	More than three cycles (*n* = 142)	Difference in rates (95% CI)
Achieved a CR/CRi, *n* (%)	7 (28.0)	104 (73.2)	–45.2% (–64.3% to –26.2%)
Did not achieve a CR/CRi, *n* (%)	18 (72.0)	38 (26.8)	
Received GCSF during first three cycles	***Yes* (n = *56*)**	***No* (n = *95*)**	
Achieved a CR/CRi, *n* (%)	38 (67.9)	69 (72.6)	–4.8% (–19.9% to 10.4%)
Did not achieve a CR/CRi, *n* (%)	18 (32.1)	26 (27.4)	
Received GCSF during treatment	***Yes* (n = *77*)**	***No* (n = *83*)**	
Achieved a CR/CRi, *n* (%)	50 (64.9)	59 (71.1)	–6.1% (–20.6% to 8.3%)
Did not achieve a CR/CRi, *n* (%)	27 (35.1)	24 (28.9)	

TABLE 36 Baseline genetic markers by achievement of the primary end point (ITT population)

17p deletion	Yes (poorer risk) (*n* = 6)	No (standard risk) (*n* = 147)	Difference in rates (95% CI)
Achieved a CR/CRi, *n* (%)	0 (0.0)	102 (69.4)	–69.4% (–76.8% to –61.9%)
Did not achieve a CR/CRi, *n* (%)	6 (100)	45 (30.6)	
11q deletion	***Yes (poorer risk)* (n = *24*)**	***No (standard risk)* (n = *133*)**	
Achieved a CR/CRi, *n* (%)	14 (58.3)	90 (67.7)	–9.3% (–30.6% to 11.9%)
Did not achieve a CR/CRi, *n* (%)	10 (41.7)	43 (32.3)	
VH mutation risk	***Poor risk* (n = *87*)**	***Standard risk* (n = *52*)**	
Achieved a CR/CRi, *n* (%)	54 (62.1)	36 (69.2)	–7.2% (–23.3% to 9.0%)
Did not achieve a CR/CRi, *n* (%)	33 (37.9)	16 (30.8)	

The difference in response rates between the two creatinine clearance groups was –7.6% (95% CI –28.3% to 13.1%), suggesting a trend towards participants with a creatinine clearance level between 30 and 60 ml/minute being less likely to achieve a CR than those with a creatinine clearance level of > 60 ml/minute. As the CI contains zero, this difference was not statistically significant. A higher proportion of participants achieved a CR with a β_2 M concentration < 4 mg/l compared with a concentration ≥ 4 mg/l (71.7% vs. 61.9%). The 95% CI contains zero, indicating that this difference is not statistically significant but suggesting a trend in favour of the lower β_2M concentration group (*Table 34*).

A much higher proportion of participants who received more than three cycles of treatment achieved a CR than those who received three cycles or fewer (73.2% vs. 28.0%) (*Table 35*). The difference in response rates was –45.2% (95% CI –64.3% to –26.2%), indicating a significant trend in favour of participants who received more than three cycles of treatment. Of the participants who received treatment with GCSF at some stage during the first three treatment cycles, 67.9% achieved a CR, compared with 72.6% of those who did not. This difference (–4.8%) was non-significant, with 95% CIs that contain zero (–19.9% to 10.4%). Of the participants who received treatment with GCSF during any treatment cycle, 64.9% achieved a CR compared with 71.1% of those who did not receive treatment with GCSF. This

difference (–6.1%) was non-significant, with 95% CIs that contain zero (–20.6% to 8.3%). This suggests that the use of GCSF was successful in allowing the delivery of more cycles of therapy and that this enabled participants to achieve better responses which were similar to those seen in participants not requiring GCSF.

All participants who were 17p deleted and who had an available assessment of response ($n = 6$) failed to achieve a CR. The 95% CI (–76.8% to –61.9%) is highly statistically significant. A higher proportion of participants who did not have an 11q deletion achieved a CR compared with those who did (67.7% vs. 58.3). The difference in response rates (–9.3%) was non-significant with 95% CIs which contain zero (*Table 36*). Of the 10 participants with an 11q deletion receiving FCR who had an available response assessment, a greater number achieved a CR compared with those participants receiving FCM-miniR [FCR = 8/10 (80.0%), FCM-miniR = 6/14 (42.9%)]. This might be expected as patients with 11q-deleted CLL classically have a relatively high expression of CD20 and are very sensitive to rituximab when combined with FC. Of the participants who were in the 'poor' VH mutation risk group, 62.1% achieved a CR compared with 69.2% of those who were in the 'standard' risk group. This difference (–7.2%) was non-significant with 95% CIs that contain zero (–23.3% to 9.0%).

Secondary end points

Overall response rate

At 3 months post treatment, of the 197 participants randomised and with a response assessment, a total of 184 (93.4%) achieved at least a PR, including 10 participants with missing trephine data for whom it was known that they were at least a PR (*Table 37*) but for whom it could not be confirmed if they were a CR for the primary analysis. A slightly higher proportion of participants in the FCR arm achieved at least a PR compared with the FCM-miniR arm ($n = 94$, 95.9% FCR; $n = 69$, 88.5% FCM-miniR) with all participants receiving FCM-miniR/FCR achieving at least a PR. Thirteen participants (6.6%) did not achieve an overall response, and there were three participants with missing data (*Table 37*).

Table 38 presents the proportion of participants achieving an OR (at least a PR) at 3 months post treatment and the difference in the response rates between the arms, after excluding those FCM-miniR participants ($n = 21$) who received treatment with FCR post-interim analysis. The ORR is high at 92.6% ($n = 163$), with a slightly higher proportion of participants in the FCR arm achieving at least a PR compared with participants in the FCM-miniR arm (95.9% FCR; 88.5% FCM-miniR). Approximately 7.5% fewer participants achieved at least a PR in the FCM-miniR arm (95% CI –15.6% to 0.6%). As the CI contains zero, the difference between the arms is not statistically significant, although it is bordering on significance.

TABLE 37 Overall response rate at 3 months post treatment

ORR	FCR ($n = 98$)	FCM-miniR ($n = 78$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 197$)
Achieved at least a PR, *n* (%)	94 (95.9)	69 (88.5)	21 (100)	184 (93.4)
Did not achieve at least a PR, *n* (%)	4 (4.1)	9 (11.5)	0 (0.0)	13 (6.6)

TABLE 38 Difference in the proportion of participants achieving an overall response at 3 months post treatment

ORR	FCR ($n = 98$)	FCM-miniR ($n = 78$)	Total ($n = 176$)	Difference in OR rates (95% CI) (FCM-miniR – FCR)
Achieved at least a PR, *n* (%)	94 (95.9)	69 (88.5)	163 (92.6)	–7.5% (–15.6% to 0.6%)
Did not achieve at least a PR, *n* (%)	4 (4.1)	9 (11.5)	13 (7.4)	

When the responses to treatment are broken down into categories, as per IWCLL, 128/200 (64.0%) participants achieved a CR, with 33.5% achieving complete remission and 30.5% achieving complete remission with incomplete marrow recovery at 3 months' treatment. Forty-six participants (23.0%) were assessed as achieving partial remission. Three participants were recorded as having stable disease (one FCR, two FCM-miniR) and three as having PD (three FCM-miniR). A total of 15 participants had missing response data owing to being lost to follow-up prior to the 3-month post-treatment visit ($n = 4$), insufficient clinical evaluations to be able to assess response ($n = 1$) and missing trephine data ($n = 10$). The participants with missing trephine data were known to have achieved at least a PR and so are included in the ORR analysis (*Table 39*). The participant who died as a result of their CLL, two of the participants who withdrew owing to toxicity and non-response and the four participants who discontinued treatment early owing to toxicity/non-response and were lost to follow-up are included in the CR and OR analyses as non-responders.

Minimal residual disease

Minimal residual disease was assessed in the bone marrow at 3 months post treatment. At this time, 85/200 participants (42.5%) were MRD negative and 81/200 (40.5%) were MRD positive (*Table 40*). A total of 29 participants (14.5%) had missing MRD data with proportions reasonably balanced across the treatment arms ($n = 15$, 15.0% FCR; $n = 13$, 16.5% FCM-miniR). Reasons for missing MRD data included: procedure attempted but unable to get sample ($n = 1$); participant refused to have sample taken ($n = 3$); sample not taken as participant unwell ($n = 2$); sample not taken owing to investigator's discretion ($n = 2$); sample not taken owing to an administrative error or clinical omission ($n = 10$); missed visit ($n = 3$); reasons unknown ($n = 8$).

For participants with missing MRD data at 3 months post treatment, the missing value was imputed using the next available observation, if available, as described in *Chapter 2*, *Missing data handling*. This was the case for 14 participants (10 FCR; three FCM-miniR; one FCM-miniR/FCR). Twelve MRD-negative results were imputed (eight FCR; three FCM-miniR; one FCM-miniR/FCR) and two MRD-positive results (two FCR). Of the four participants in the FCR arm who withdrew from follow-up data collection prior to the assessment of response, two did so owing to toxicity and non-response. These participants and the participant in the FCM-miniR arm who died early as a result of CLL (prior to 3 months post treatment) have been classed as 'MRD positive'.

TABLE 39 International Workshop on Chronic Lymphocytic Leukaemia response assessment at 3 months post treatment (all randomised participants)

IWCLL response assessment	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
Complete remission, *n* (%)	40 (40.0)	18 (22.8)	9 (42.9)	67 (33.5)
Complete remission with incomplete marrow recovery (CRi), *n* (%)	30 (30.0)	23 (29.1)	8 (38.1)	61 (30.5)
Partial remission, *n* (%)	18 (18.0)	25 (31.6)	3 (14.3)	46 (23.0)
Stable disease, *n* (%)	1 (1.0)	2 (2.5)	0 (0.0)	3 (1.5)
PD, *n* (%)	0 (0.0)	3 (3.8)	0 (0.0)	3 (1.5)
Early death, *n* (%)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.5)
Withdrew from further follow-up data collection prior to assessment of response, *n* (%)	4 (4.0)	0 (0.0)	0 (0.0)	4 (2.0)
Missing, *n* (%)	7 (7.0)	7 (8.9)	1 (4.8)	15 (7.5)

TABLE 40 Proportion of participants with an MRD assessment at 3 months post treatment (all randomised participants)

Assessment of MRD	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
MRD negative, *n* (%)	45 (45.0)	29 (36.7)	11 (52.4)	85 (42.5)
MRD positive, *n* (%)	36 (36.0)	36 (45.6)	9 (42.9)	81 (40.5)
Withdrew from further follow-up data collection prior to assessment of MRD, *n* (%)	4 (4.0)	0 (0.0)	0 (0.0)	4 (2.0)
Early death, *n* (%)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.5)
Missing, *n* (%)	15 (15.0)	13 (16.5)	1 (4.8)	29 (14.5)

Of the 183 participants with an assessment of MRD after imputation, over half (53.0%) were MRD negative at 3 months post treatment (*Table 41*). A total of 57.0% ($n = 53$) of FCR participants were MRD negative compared with 46.4% ($n = 32$) of FCM-miniR participants and 57.1% ($n = 12$) of those participants randomised to FCM-miniR who swapped over to receive treatment with FCR.

Table 42 presents the proportion of participants with undetectable MRD (MRD negative) at 3 months post treatment and the difference in rates between the arms, excluding those FCM-miniR participants ($n = 21$) who received treatment with FCR following the interim analysis. A higher proportion of participants in the FCR arm were MRD negative than participants in the FCM-miniR arm ($n = 53$, 57.0% FCR; $n = 32$, 46.4% FCM-miniR). Approximately 11% fewer participants were MRD negative in the FCM-miniR arm (95% CI –26.1% to 4.9%). As the CI contains zero, there is no evidence of a significant difference between the treatment arms, although the overall trend is in favour of the FCR arm.

A binary multivariate logistic regression model was used to assess formally the effect of treatment on the proportion of participants achieving MRD negativity at 3 months post treatment, after adjusting for the minimisation factors, excluding centre (*Table 43*).

The OR for achieving MRD negativity in the FCM-miniR arm compared with the FCR arm was 0.63 (95% CI 0.34 to 1.20), indicating that there is a non-significant trend towards FCM-miniR participants being less likely to achieve MRD negativity at 3 months post treatment than participants in the FCR arm.

TABLE 41 Proportion of participants achieving MRD negativity at 3 months post treatment

Assessment of MRD	FCR ($n = 93$)	FCM-miniR ($n = 69$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 183$)
MRD negative, *n* (%)	53 (57.0)	32 (46.4)	12 (57.1)	97 (53.0)
MRD positive, *n* (%)	40 (43.0)	37 (53.6)	9 (42.9)	86 (47.0)

TABLE 42 Difference in the proportion of participants with undetectable MRD at 3 months post treatment

MRD status	FCR ($n = 93$)	FCM-miniR ($n = 69$)	Total ($n = 162$)	Difference in MRD-negative rates (95% CI) (FCM-miniR – FCR)
MRD negative, *n* (%)	53 (57.0)	32 (46.4)	85 (52.5)	–10.6% (–26.1% to 4.9%)
MRD positive, *n* (%)	40 (43.0)	37 (53.6)	77 (47.5)	

TABLE 43 Multivariate logistic regression analysis for the proportion of participants with undetectable MRD at 3 months post treatment, adjusted for the minimisation factors

Parameter	df	Parameter estimate	SE	Wald χ^2	Pr > χ^2	OR (95% CI)
Intercept	1	0.54	0.29	3.47	0.062	
Treatment group: FCM-miniR vs. FCR	1	–0.46	0.32	1.97	0.160	0.63 (0.34 to 1.20)
Sex: female vs. male	1	0.10	0.35	0.08	0.775	1.10 (0.56 to 2.18)
Age group: > 65 years vs. ≤ 65 years	1	–0.67	0.34	3.93	0.048	0.51 (0.27 to 0.99)
Binet stage: C vs. A progressive or B	1	–0.12	0.34	0.13	0.721	0.89 (0.46 to 1.72)

df, degrees of freedom.

Progression-free survival

The final participant's 24-month clinic visit (after which they are followed up annually) was carried out on 13 October 2014; the data lock for the analysis of the long-term follow-up data was performed on 15 October 2014. At the time of analysis, the median follow-up time of participants who were event-free and still in follow-up was 37.3 months (range: 24.7–58.1 months). PFS was defined as the time from randomisation to the first documented evidence of disease progression or death. Overall, 38 participants (19.0%) had progressed, 17 in the FCR arm (17.0%), 19 in the FCM-miniR arm (24.1%) and two participants who received both FCM-miniR and FCR. A total of 49 (24.5%) participants had either progressed or died: 24 in the FCM-miniR arm (30.4%) compared with 22 in the FCR arm (22.0%) (*Table 44*).

Figure 5 presents the Kaplan–Meier curves for PFS in months by randomisation allocation. Participants still alive and progression-free at the time of analysis were censored at the last date on which they were known to be alive and progression-free, indicated by a cross. Participants who were randomised to FCM-miniR but transferred over to receive treatment with FCR were excluded from the analysis ($n = 21$).

The PFS curves indicate an overall trend towards an improvement in PFS for participants in the FCR arm. More early progressions are seen with FCM-miniR than with FCR within the first 12 months, but after that the curves remain roughly proportional. At 24 months post randomisation, the PFS probability in the FCR arm is 89.4% compared with 79.1% in the FCM-miniR arm. There is a high number of censored observations around and beyond the 24-month point, the time to which the majority of participants have been followed up, so care must be taken at this stage not to over-interpret the results until longer-term follow-up data are acquired.

A log-rank test was used to compare the differences between the PFS curves. There was no evidence of a significant difference between the treatment arms at the 5% significance level with respect to time to progression ($p = 0.279$). The Wilcoxon rank-sum test, which gives greater weight to earlier differences, was also non-significant ($p = 0.1081$) (*Table 45*).

In a formal Cox regression analysis, after adjusting for the minimisation factors, excluding centre, there was no evidence of a significant difference in PFS between the treatment arms at the 5% significance level with a HR of 1.39 (95% CI 0.77 to 2.49; $p = 0.2771$) (*Table 46*), although it should be noted that the CIs

TABLE 44 Proportion of participants with PD (all randomised participants)

Status	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
Number of participants with PD, *n* (%)	17 (17.0)	19 (24.1)	2 (9.5)	38 (19.0)
Number of participants with PD and/or who have died, *n* (%)	22 (22.0)	24 (30.4)	3 (14.3)	49 (24.5)

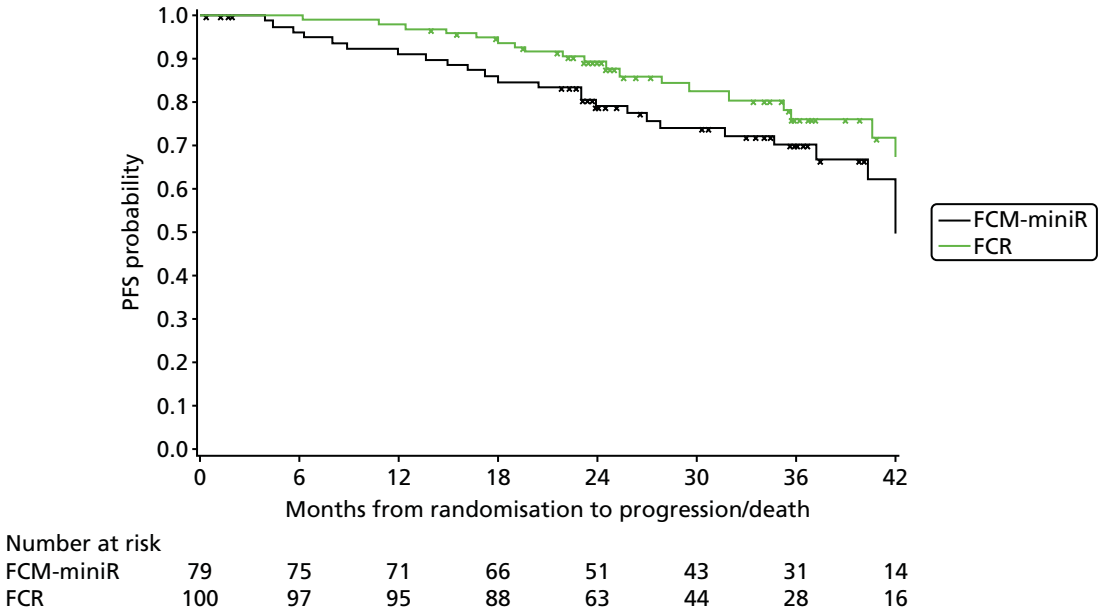


FIGURE 5 Kaplan–Meier plot of time to progression by randomisation allocation.

TABLE 45 Median time to progression and comparison between the treatment arms

Randomisation allocation	Median time to progression (months) (95% CI)	Total number of participants	Total number of events	Total number of censored observations	Test	χ^2	df	*p*-value
FCM-miniR	48.5 (40.4 to NE)	79	24	55	Log-rank	1.1719	1	0.2790
FCR	52.7 (42.9 to NE)	100	22	78	Wilcoxon rank-sum	2.5811	1	0.1081
Total	52.7 (44.5 to NE)	179	46	133				

df, degrees of freedom; NE, not estimable.

TABLE 46 Cox's proportional hazards model for the time to progression adjusted for the minimisation factors

Parameter	df	Parameter estimate	SE	χ^2	*p*-value	HR (95% CI)
Randomisation allocation: FCM-miniR vs. FCR	1	0.33	0.30	1.18	0.2771	1.39 (0.77 to 2.49)
Age group: > 65 years vs. ≤ 65 years	1	0.05	0.32	0.03	0.8702	1.05 (0.56 to 1.97)
Sex: female vs. male	1	–0.04	0.32	0.02	0.8952	0.96 (0.51 to 1.81)
Binet stage: C vs. A progressive or B	1	–0.16	0.32	0.23	0.6298	0.86 (0.45 to 1.61)

df, degrees of freedom.

are wide owing to the relatively short follow-up period. Although non-significant, a HR of 1.39 indicates that there is a trend in favour of the FCR arm, and that participants in the FCM-miniR arm are around 40% more likely to progress at each time point. The trial was not powered to detect a difference in PFS and CIs around the HR are wide, indicating a lack of precision of the HR estimate owing to the small number of events, and indicating that longer-term follow-up data are required.

The 95% CIs around the HRs for the minimisation factors all contain 1, indicating that there is no significant evidence that any of the minimisation factors are significantly associated with PFS, although it should be noted that the CIs are wide owing to the relatively short follow-up period.

Overall survival

At the time of analysis (October 2014), the median follow-up time for survivors was 37.7 months (range 24.7–58.1 months). OS was defined as the time from randomisation to death from any cause. In total, 24 participants (12.0%) had died: 10 in the FCR arm (10.0%), 13 in the FCM-miniR arm (16.5%) and one participant who received FCM-miniR followed by one cycle of FCR (*Table 47*). The most common primary cause of death was 'overwhelming tumour load' in 33.3% of cases ($n = 8$) and there was only one treatment-related death in the trial, occurring in the FCR arm.

Figure 6 presents the Kaplan–Meier curves for OS in months by randomisation allocation. Participants still alive at the time of analysis were censored at the last date on which they were known to be alive, indicated by a cross. Participants who were randomised to FCM-miniR but transferred over to receive treatment with FCR were excluded from the analysis ($n = 21$).

TABLE 47 Proportion of participants who have died and primary cause of death

Number of participants who have died, *n* (%)	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 21$)	Total ($n = 200$)
	10 (10.0)	13 (16.5)	1 (4.8)	24 (12.0)
Primary cause of death				
Treatment-related death	1 (10.0)	0 (0.0)	0 (0.0)	1 (4.2)
Overwhelming tumour load	2 (20.0)	6 (46.2)	0 (0.0)	8 (33.3)
Infection owing to CLL	3 (30.0)	4 (30.8)	0 (0.0)	7 (29.2)
Infection owing to treatment	2 (20.0)	0 (0.0)	1 (100)	3 (12.5)
High-grade transformation on the background of CLL	0 (0.0)	1 (7.7)	0 (0.0)	1 (4.2)
Other malignancies (non-haematopoietic)	0 (0.0)	1 (7.7)	0 (0.0)	1 (4.2)
Other	2 (20.0)[a]	1 (7.7)[b]	0 (0.0)	3 (12.5)

a Idiopathic thrombocytopenia; pulmonary haemorrhage.
b Acute intraparenchymal haemorrhage.

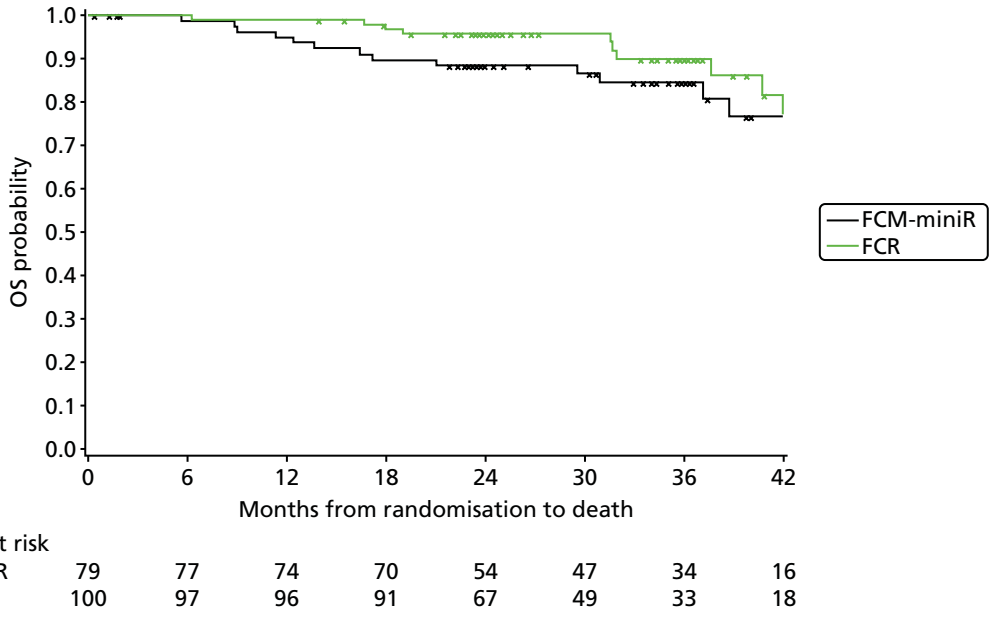


FIGURE 6 Kaplan–Meier plot of OS by randomisation allocation.

The survival curves indicate an overall trend towards an improvement in OS for participants in the FCR arm. As with PFS, there are a greater number of earlier events in participants on FCM-miniR, with the curves becoming closer to parallel after 18 months. At 24 months post randomisation, the survival probability is 95.8% in the FCR arm compared with 88.5% in the FCM-miniR arm. There are a high number of censored observations around and beyond the 24-month point, the time to which the majority of participants have been followed up, so care must be taken at this stage not to overinterpret the results until longer-term follow-up data are acquired.

The log-rank test was used to compare the difference between the survival curves. There was no evidence of a significant difference between the treatment arms at the 5% significance level with respect to OS ($p = 0.2779$). The Wilcoxon rank-sum test, which gives greater weight to earlier differences, was also non-significant ($p = 0.1013$) (*Table 48*). Note, however, that there have been few events in either arm owing to the relatively short follow-up period.

In the formal Cox regression analysis, after adjusting for the minimisation factors, excluding centre, there was no evidence of a significant difference in OS between the treatment arms at the 5% significance level with a HR of 1.57 (95% CI 0.68 to 3.58; $p = 0.2876$) (*Table 49*). Although non-significant, a HR of 1.57 indicates that there is a trend in favour of the FCR arm, and that participants in the FCM-miniR arm are around 57% more likely to not survive at any time point. The trial was not powered to detect a difference in OS and the CIs around the HR are wide, indicating a lack of precision of the HR estimate owing to the small number of events, so longer-term follow-up data would be beneficial.

The 95% CIs around the HRs for the minimisation factors all contain 1, indicating that there is no evidence that any of the minimisation factors are significantly associated with OS, although there is only a limited period of follow-up at the time of reporting. There is a suggested trend in favour of participants aged 65 years or younger to have an improved survival than those aged over 65.

TABLE 48 Median time to death and comparison between treatment arms

Randomisation allocation	Median time to death (months) (95% CI)	Total number of participants	Total number of events	Total number of censored observations	Test	χ^2	df	*p*-value
FCM-miniR	NE	79	13	66	Log-rank	1.1771	1	0.2779
FCR	NE	100	10	90	Wilcoxon rank-sum	2.6854	1	0.1013
Total	NE	179	23	156				

df, degrees of freedom; NE, not estimable.

TABLE 49 Cox's proportional hazards model for OS adjusted for the minimisation factors

Parameter	df	Parameter estimate	SE	χ^2	*p*-value	HR (95% CI)
Randomisation allocation: FCM-miniR vs. FCR	1	0.45	0.42	1.13	0.2876	1.57 (0.68 to 3.58)
Age group: > 65 vs. ≤ 65	1	0.46	0.42	1.17	0.2797	1.58 (0.69 to 3.61)
Sex: female vs. male	1	–0.29	0.48	0.36	0.5485	0.75 (0.29 to 1.92)
Binet stage: C vs. A progressive or B	1	–0.05	0.46	0.01	0.9053	0.95 (0.39 to 2.33)

df, degrees of freedom.

Time to minimal residual disease relapse

Participants who were MRD negative at 3 months post treatment were followed up 6-monthly until MRD relapse (i.e. until they became MRD positive) or until 24 months post randomisation. Longer follow-up was not possible owing to funding constraints. In the population of participants who were assessable for MRD at 3 months post treatment, 85/162 (52.5%) participants had achieved MRD negativity (see *Table 42*). At the time of analysis, it was reported that only seven participants had relapsed at the MRD level (four FCR, three FCM-miniR); however, there was a high proportion of missing MRD data at each of the follow-up visits. Owing to the small number of events, high proportion of missing data and lack of longer-term follow-up data, the time to MRD relapse analysis was unable to be performed.

Subgroup analyses

Subgroup analyses were carried out to assess PFS and OS based on IWCLL and MRD response groups, the minimisation factors, number of cycles of treatment received, GCSF usage and genetic risk groups. As the trial was not powered for survival end points or to look for differences in subgroups of participants, the results are to be treated as exploratory and used for hypothesis generating purposes only.

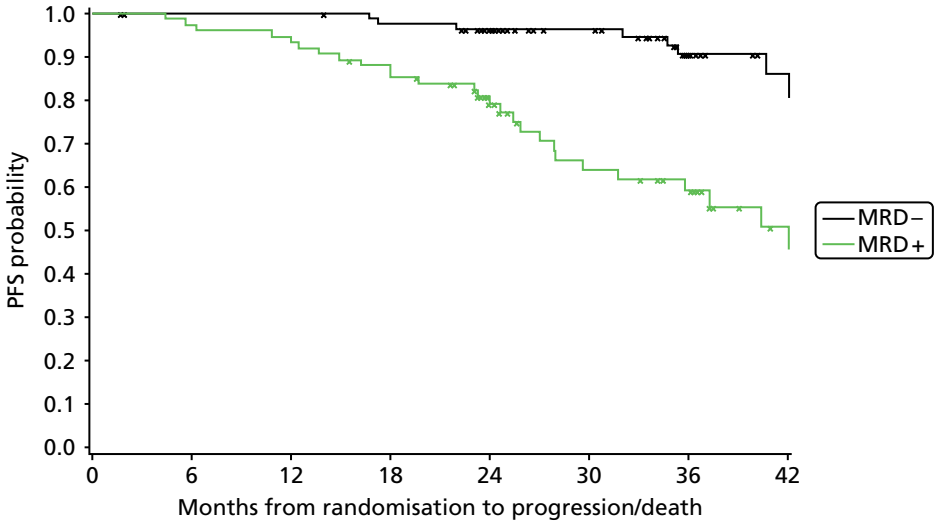
Progression-free survival by minimal residual disease response status

Figure 7 presents the Kaplan–Meier curves for time to progression by MRD status at 3 months post treatment. Of the 85 participants who were MRD negative at this time point, eight (9.4%) have reported an event (i.e. progression or death) compared with 30/77 (39.0%) who were MRD positive.

The curves show clear divergence from 6 months post randomisation, the end of treatment visit, with an overall trend towards an improvement in PFS for participants who were MRD negative at 3 months post treatment. This difference was significant at the 5% level in favour of the MRD-negative participants (log-rank: $\chi^2 = 23.20$; $p < 0.0001$). At 24 months post randomisation, the PFS probability is 96.4% for MRD-negative participants compared with 79.2% for the MRD-positive group.

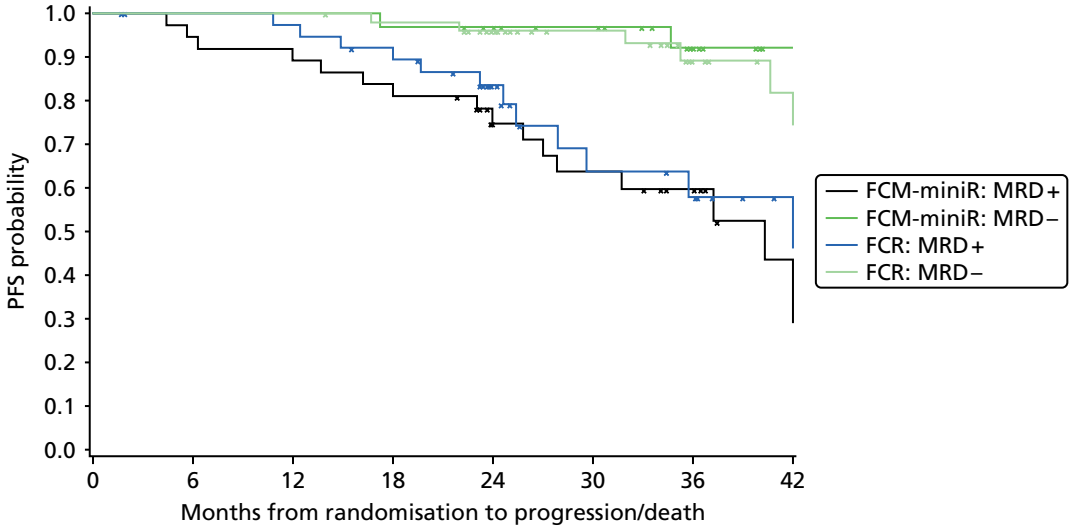
Progression-free survival by minimal residual disease response status and randomisation allocation

Figure 8 presents the Kaplan–Meier curves for time to progression by randomisation allocation and MRD status at 3 months post treatment.



Number at risk								
MRD–	85	85	85	82	69	56	35	19
MRD+	77	73	70	63	41	29	23	10

FIGURE 7 Kaplan–Meier plot of time to progression by MRD status at 3 months post treatment.



Number at risk

FCM-miniR: MRD+	37	35	33	30	21	17	13	5
FCM-miniR: MRD–	32	32	32	31	28	25	17	8
FCR: MRD+	40	38	37	33	20	12	10	5
FCR: MRD–	53	53	53	51	41	31	18	11

FIGURE 8 Kaplan–Meier plot of time to progression by randomisation allocation and MRD status at 3 months post treatment.

For the participants who became MRD negative, the PFS curves are similar for the two treatment arms. For the participants who were MRD positive, participants in the FCR arm show a trend towards a slightly improved time to progression compared with participants in the FCM-miniR arm until around 24–30 months post randomisation, at which point there are a number of censored observations, indicating that longer term follow-up would be beneficial to interpretation. At 24 months post randomisation, the PFS probabilities for the MRD-negative participants were similar between the treatment groups (96.2% FCR, 96.9% FCM-miniR). For MRD-positive participants, the PFS probability was 83.7% in the FCR arm compared with 74.9% in the FCR-miniR arm.

Progression-free survival by complete response status

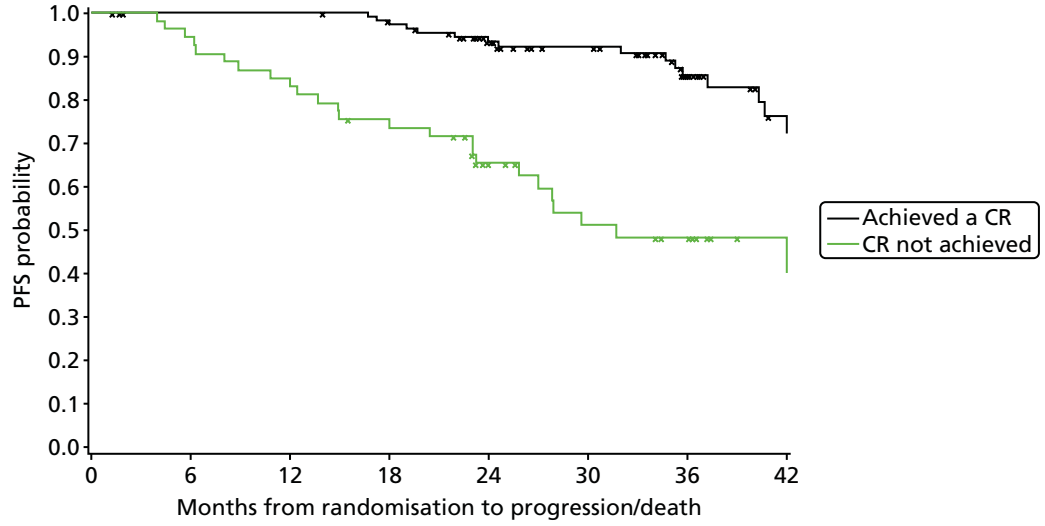
Figure 9 presents the Kaplan–Meier curves for time to progression by CR status at 3 months post treatment. Of the participants who had achieved a complete remission or CRi at this time point, 16/111 (14.4%) had an event (i.e. progression or death) compared with 27/56 (48.2%) who had not achieved at least a CR.

The curves show clear divergence from 6 months post randomisation, the end of treatment visit, with an overall trend towards an improvement in PFS for participants who achieved a CR at 3 months post treatment. This difference was significant at the 5% level in favour of participants who achieved at least a CR (log-rank: $\chi^2 = 29.41$; $p < 0.0001$). At 24 months post randomisation, the PFS probability is 93.4% for participants who achieved a CR compared with 65.4% for those who did not.

Progression-free survival by complete response status and randomisation allocation

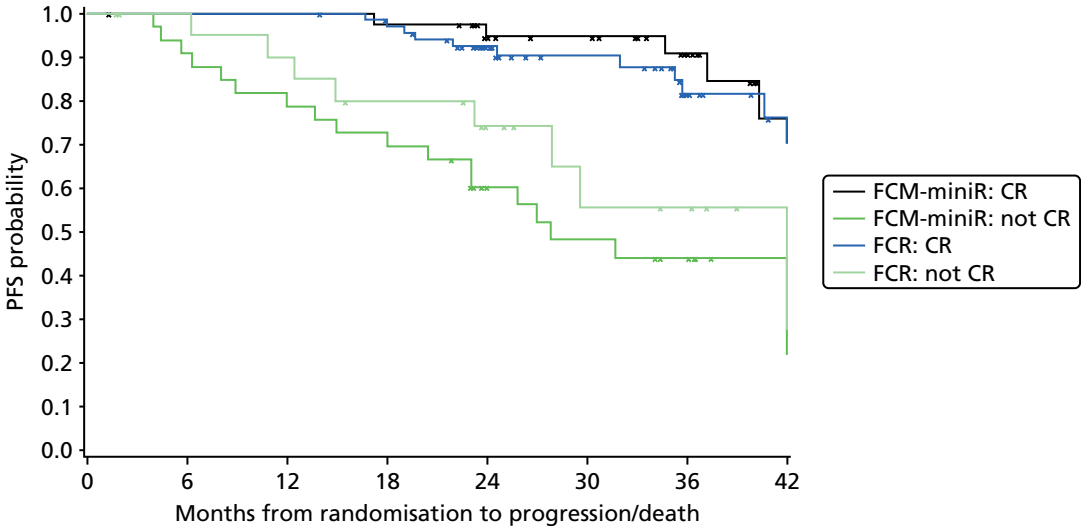
Figure 10 presents the Kaplan–Meier curves for time to progression by randomisation allocation and CR status at 3 months post treatment.

For the participants who achieved a CR, the curves are similar for the two treatment arms, with a slight trend towards the FCM-miniR participants doing better. For the participants who did not achieve a CR, participants in the FCR arm have an improved time to progression compared with FCM-miniR participants.



Number at risk								
Achieved a CR	111	111	111	106	79	65	42	22
CR not achieved	56	50	44	38	27	18	14	6

FIGURE 9 Kaplan–Meier plot of time to progression by CR status at 3 months post treatment.



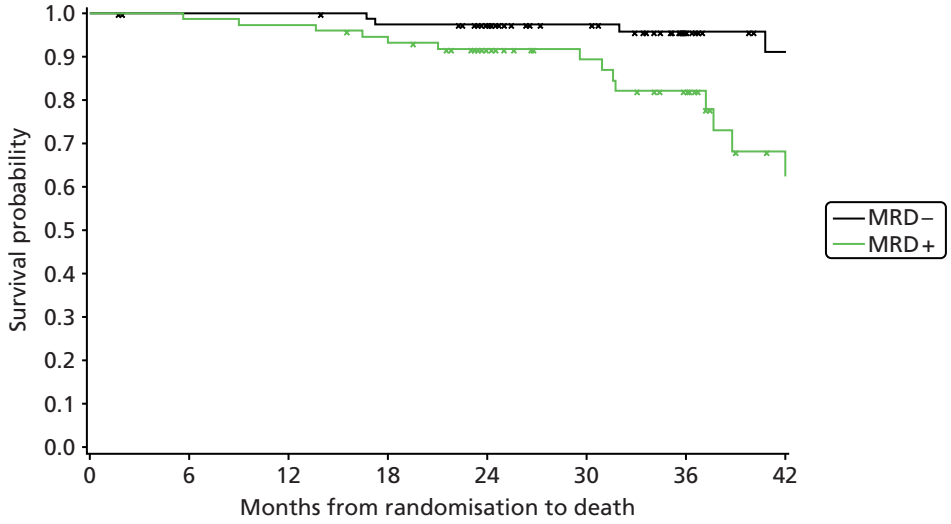
Number at risk								
FCM-miniR: CR	41	41	41	40	33	20	21	9
FCM-miniR: not CR	34	30	26	23	16	12	9	4
FCR: CR	70	70	70	66	46	35	21	13
FCR: not CR	22	20	18	15	11	6	5	2

FIGURE 10 Kaplan–Meier plot of time to progression by randomisation allocation and CR status at 3 months post treatment.

At 24 months post randomisation, the PFS probabilities for the participants who achieved a CR were similar between the treatment groups (92.6% FCR, 94.8% FCM-miniR). For participants who did not achieve a CR, the PFS survival probability was 74.3% in the FCR arm compared with 60.3% in the FCR-miniR arm.

Overall survival by minimal residual disease response status

Figure 11 presents the Kaplan–Meier curves for OS by MRD status at 3 months post treatment. Of the participants who were MRD negative at this time point, 4/85 (4.7%) had died compared with 14/77 (18.2%) who were MRD positive.



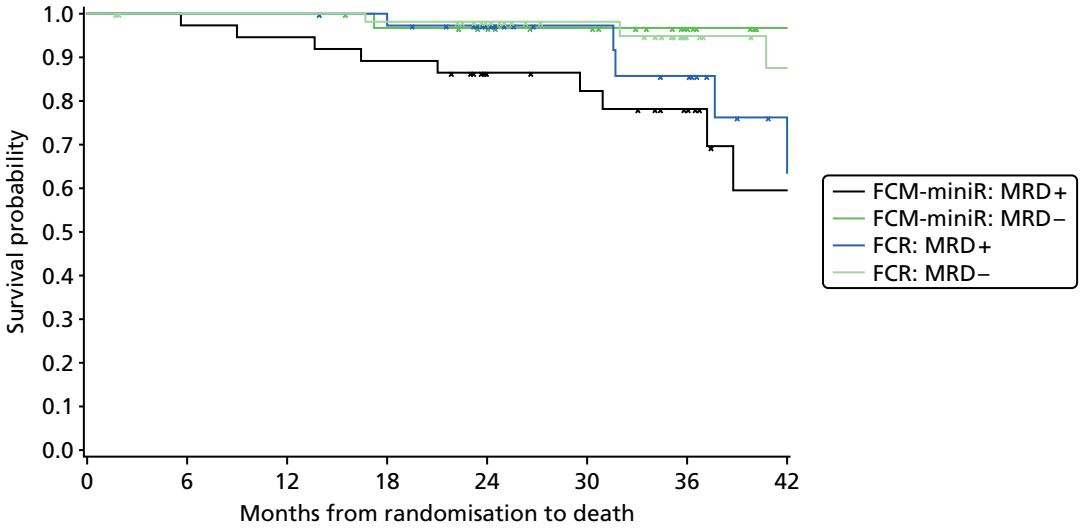
Number at risk								
MRD–	85	85	85	82	69	56	36	20
MRD+	77	74	73	69	47	37	29	12

FIGURE 11 Kaplan–Meier plot of OS by MRD status at 3 months post treatment.

The curves show clear divergence from the end of treatment visit, with an overall trend towards an improvement in OS for participants who were MRD negative at 3 months post treatment. This difference was significant at the 5% level in favour of the MRD-negative participants (log-rank: $\chi^2 = 9.25$; $p = 0.003$). At 24 months post randomisation, the OS probability for MRD-negative participants is 97.6% compared with 91.9% for the MRD-positive group.

Overall survival by minimal residual disease response status and randomisation allocation

Figure 12 presents the Kaplan–Meier curves for OS by randomisation allocation and MRD status at 3 months post treatment.



Number at risk								
FCM-miniR: MRD+	37	36	35	33	23	20	15	6
FCM-miniR: MRD–	32	32	32	31	28	25	17	8
FCR: MRD+	40	38	38	36	24	17	14	6
FCR: MRD–	53	53	53	51	41	31	19	12

FIGURE 12 Kaplan–Meier plot of OS by randomisation allocation and MRD status at 3 months post treatment.

For the participants who became MRD negative, the OS curves are similar for the two treatment arms. A similar survival pattern was observed for MRD-positive participants receiving FCR until around 30 months post randomisation, at which point survival worsened. OS was poorest for MRD-positive participants who received FCM-miniR. At 24 months post randomisation, the OS probabilities for the MRD-negative participants were similar between the treatment groups (98.1% FCR, 96.9% FCM-miniR), and for MRD-positive participants receiving FCR (97.3%). The FCM-miniR, MRD-positive group showed the poorest OS probability at 24 months (86.5%).

Overall survival by complete response status

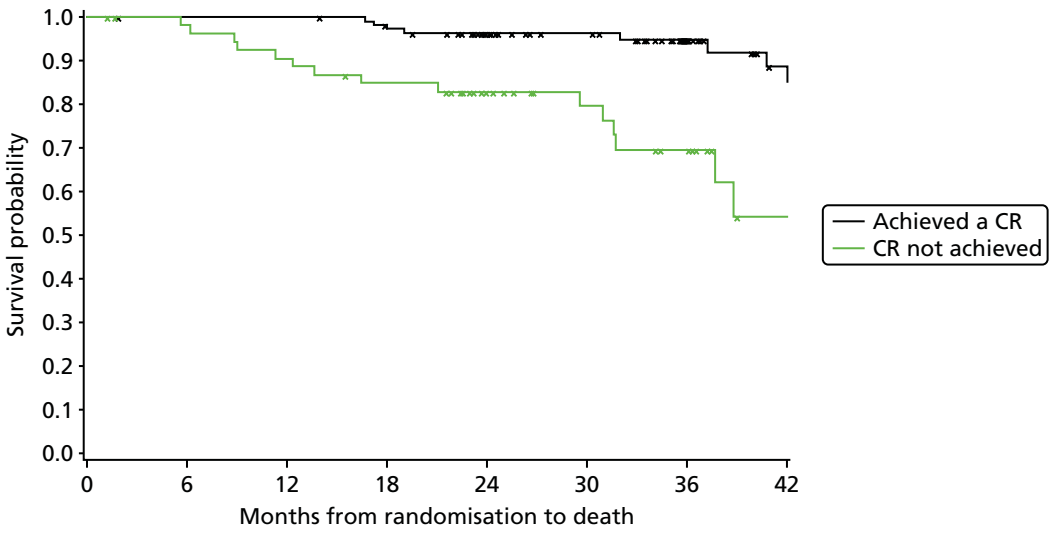
Figure 13 presents the Kaplan–Meier curves for OS by CR status at 3 months post treatment. Of the participants who had achieved a CR at this time point, 8/111 (7.2%) had died compared with 15/56 (26.8%) who had not achieved a CR.

The curves show clear divergence from 6 months post randomisation, the end of treatment visit, with an overall trend towards an improvement in OS for participants who achieved a CR at 3 months post treatment. This difference was significant at the 5% level in favour of participants who achieved a CR (log-rank: $\chi^2 = 16.92$; $p < 0.001$). At 24 months post randomisation, the OS probability for participants who achieved a CR is 96.4% compared with 82.9% for those who did not.

Overall survival by complete response status and randomisation allocation

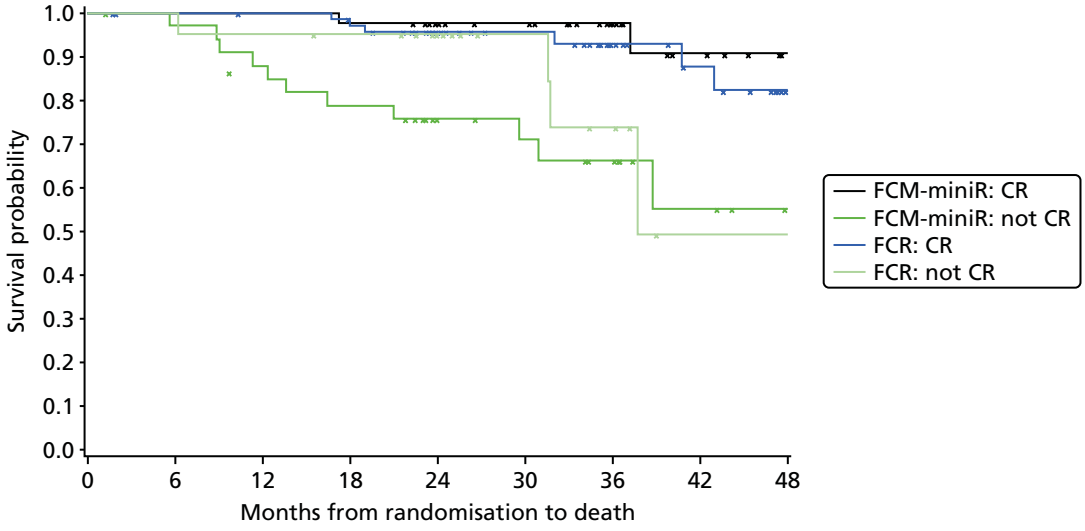
Figure 14 presents the Kaplan–Meier curves for OS by randomisation allocation and CR status at 3 months post treatment.

For the participants who achieved a CR, the curves are similar for the two treatment arms. A similar survival pattern was observed for participants who did not achieve a CR who were receiving FCR until around 30 months post randomisation, at which point survival worsened. OS was poorest for participants who did not achieve a CR and who received FCM-miniR. At 24 months post randomisation, the OS probabilities for the participants who achieved a CR were similar between the treatment groups (95.6% FCR, 97.6% FCM-miniR), and for participants who did not achieve a CR receiving FCR (95.0%). The FCM-miniR participants who did not achieve a CR showed the poorest OS probability at 24 months (75.8%).



Number at risk								
Achieved a CR	111	111	111	106	81	67	45	26
CR not achieved	56	52	48	44	32	24	18	6

FIGURE 13 Kaplan–Meier plot of OS by CR status at 3 months post treatment.



Number at risk

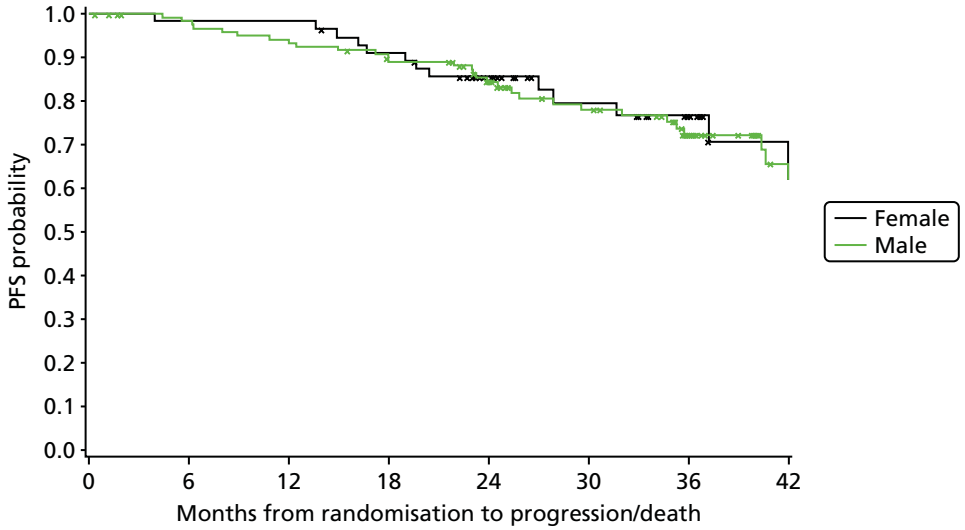
FCM-miniR: CR	41	41	41	40	34	31	21	10	5
FCM-miniR: not CR	34	32	29	26	18	15	12	5	2
FCR: CR	70	70	70	66	47	36	24	16	6
FCR: not CR	22	20	19	18	14	9	6	1	1

FIGURE 14 Kaplan–Meier plot of OS by randomisation allocation and response status at 3 months post treatment.

Progression-free survival and overall survival by minimisation factors at baseline: sex

Figure 15 presents the Kaplan–Meier curves for time to progression by participant sex. At the time of analysis, of the 123 male participants, 32 (26.0%) had reported an event (i.e. progression or death) compared with 14/56 (25.0%) female participants.

At 24 months post randomisation, the PFS probability for male participants was 84.4% compared with 85.5% for females. The difference between the PFS curves for sex was non-significant (log-rank: $\chi^2 = 0.045$; $p = 0.833$).



Number at risk

Female	56	55	55	50	38	27	19	11
Male	123	117	111	104	76	60	40	19

FIGURE 15 Kaplan–Meier plot of time to progression by sex.

Figure 16 presents the Kaplan–Meier curves for OS by participant sex. At the time of analysis, of the 123 male participants, 17 (13.8%) had died compared with 6/56 (10.7%) female participants.

At 24 months post randomisation, the OS probability for male participants was 92.4% compared with 92.8% for females. The difference between the OS curves for sex was non-significant (log-rank: $\chi^2 = 0.411$; $p = 0.522$).

Progression-free survival and overall survival by minimisation factors at baseline: age group

Figure 17 presents the Kaplan–Meier curves for time to progression by age group (≤ 65 years, > 65 years). At the time of analysis, of the 113 participants aged ≤ 65 years, 31 (27.4%) had reported an event (i.e. progression or death) compared with 15/66 (22.7%) participants aged over 65 years.

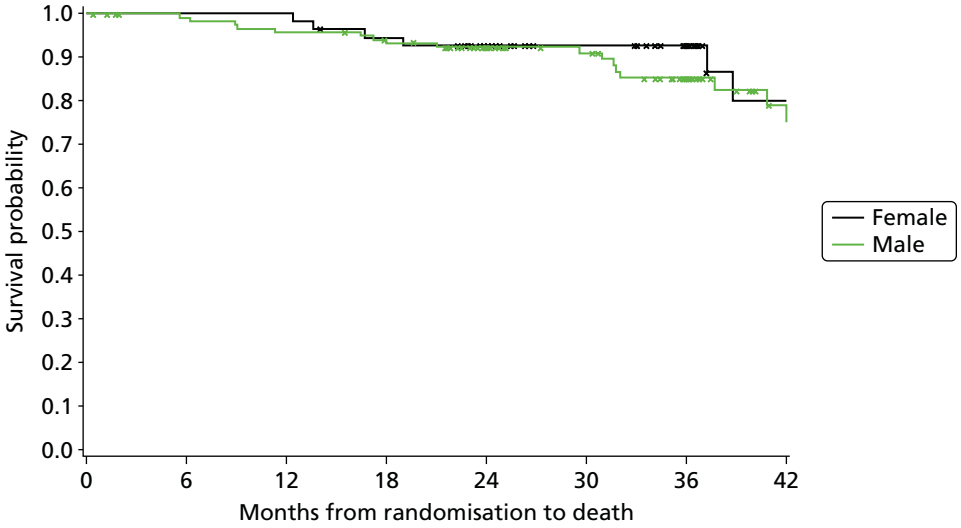


FIGURE 16 Kaplan–Meier plot of OS by sex.

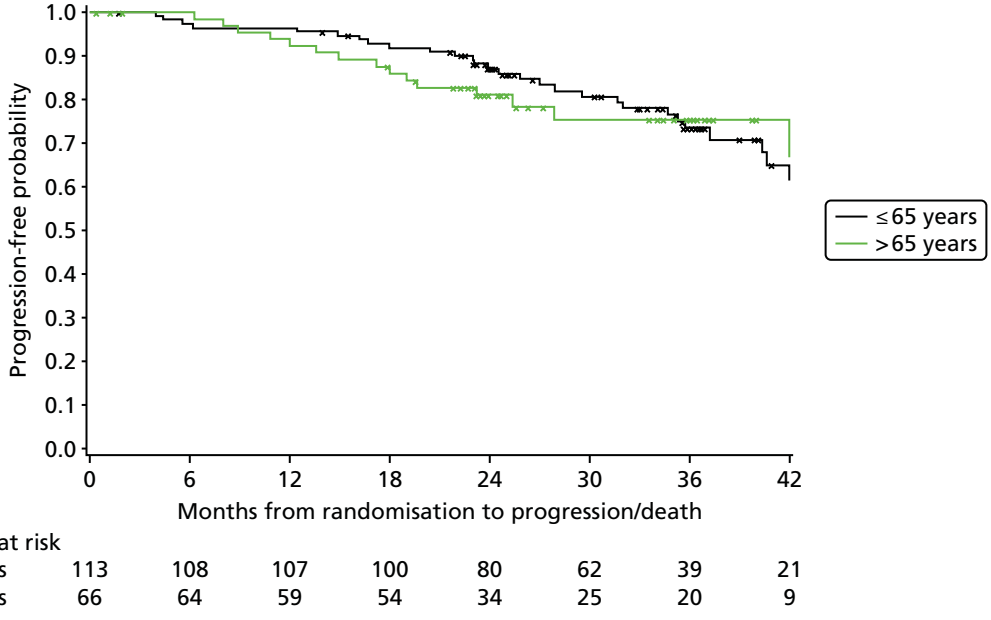


FIGURE 17 Kaplan–Meier plot of time to progression by age group.

At 24 months post randomisation, the PFS probability for participants aged ≤ 65 years was 87.0% compared with 80.9% for those older than 65 years. Although there appears to be a trend in favour of younger participants performing better in terms of PFS, the overall difference between the PFS curves for age group was non-significant (log-rank: $\chi^2 = 0.015$; $p = 0.902$).

Figure 18 presents the Kaplan–Meier curves for OS by age group (≤ 65 years, > 65 years). At the time of analysis, of the 113 participants aged ≤ 65 years, 13 (11.5%) had died compared with 10/66 (15.2%) participants aged over 65 years.

At 24 months post randomisation, the OS probability for participants aged ≤ 65 years was 94.5% compared with 89.0% for those over 65 years of age. The difference between the OS curves for age group was non-significant (log-rank: $\chi^2 = 1.106$; $p = 0.293$), although there is a suggested trend for younger participants performing better in terms of OS.

Progression-free survival and overall survival by minimisation factors at baseline: Binet stage

Figure 19 presents the Kaplan–Meier curves for time to progression by Binet stage (A progressive or B, C). At the time of analysis, of the 118 participants who were Binet stage A progressive or B, 32 (27.0%) had reported an event (i.e. progression or death) compared with 14/61 (23.0%) participants who were Binet stage C.

At 24 months post randomisation, the PFS probability for participants with Binet stage A progressive or B was 84.8% compared with 84.7% for Binet stage C participants. The difference between the PFS curves for Binet stage was non-significant (log-rank: $\chi^2 = 0.217$; $p = 0.641$).

Figure 20 presents the Kaplan–Meier curves for OS by Binet stage (A progressive or B, C). At the time of analysis, of the 118 participants who were Binet stage A progressive or B, 16 (13.6%) had died compared with 7/61 (11.5%) participants who were Binet stage C.

At 24 months post randomisation, the OS probability for participants with Binet stage A progressive or B was 91.2% compared with 95.0% for Binet stage C participants. The difference between the OS curves for Binet stage was non-significant (log-rank: $\chi^2 = 0.030$; $p = 0.863$).

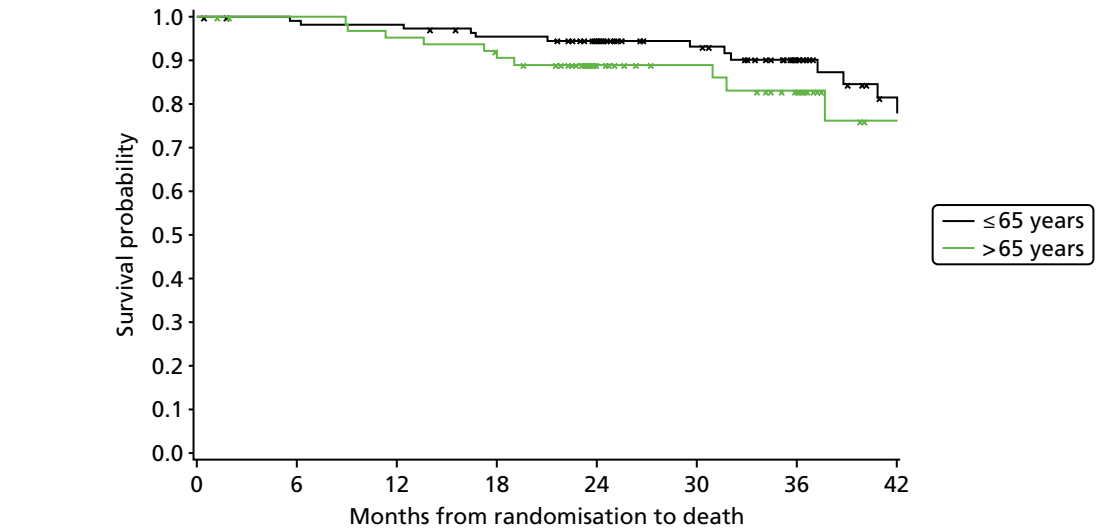
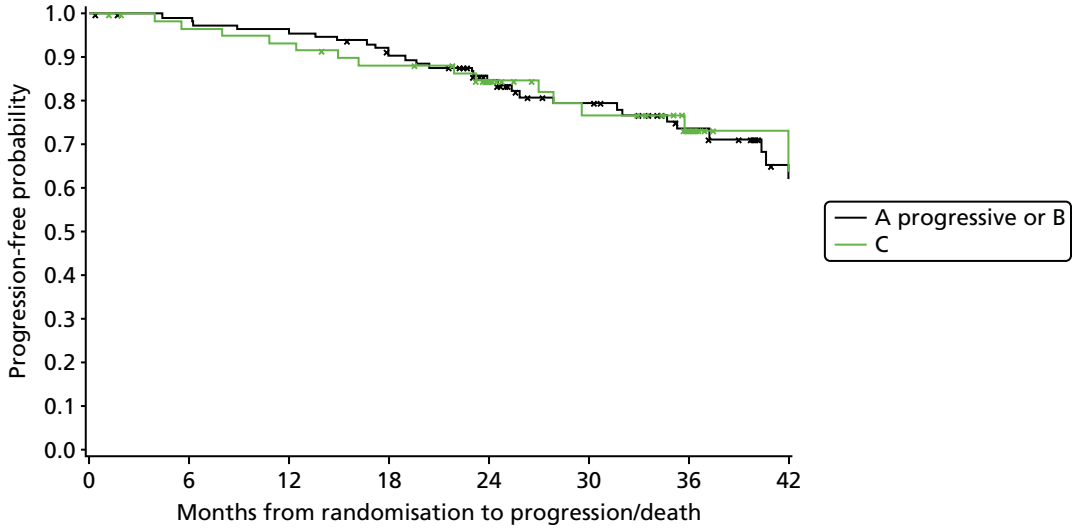
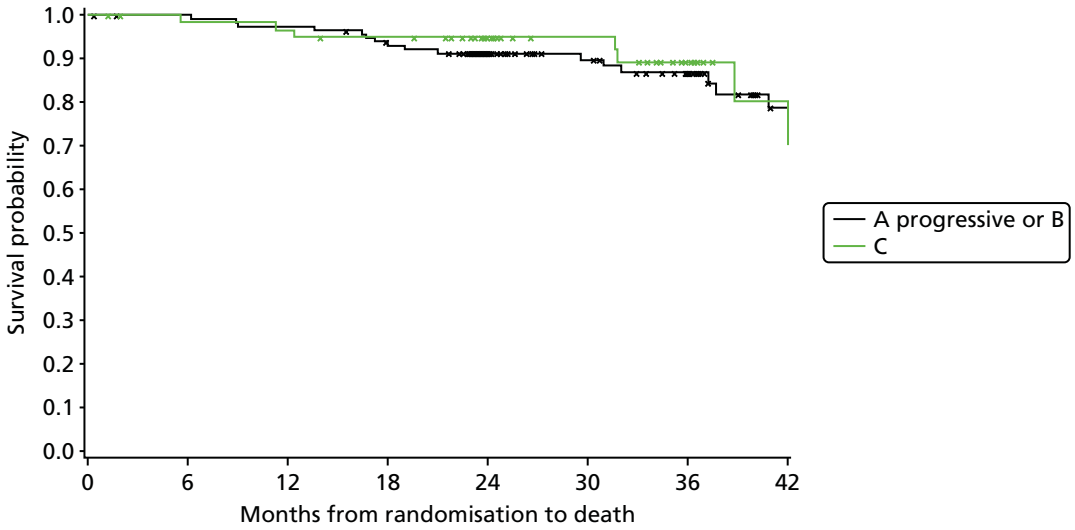


FIGURE 18 Kaplan–Meier plot of OS by age group.



Number at risk								
A progressive or B	116	114	110	102	75	58	49	21
C	61	58	56	52	39	29	16	9

FIGURE 19 Kaplan–Meier plot of time to progression by Binet stage.



Number at risk								
A progressive or B	118	115	112	105	80	63	48	25
C	61	59	58	56	41	33	19	9

FIGURE 20 Kaplan–Meier plot of OS by Binet stage.

Progression-free survival and overall survival by treatment received

Figure 21 presents the Kaplan–Meier curves for time to progression by number of treatment cycles received (three or fewer, more than three). At the time of analysis, of the 31 participants who received three cycles or fewer, 16 (51.6%) had reported an event (i.e. progression or death) compared with 30/148 (20.3%) participants who received more than three cycles of treatment.

The curves show clear divergence from the end of treatment with an overall trend towards an improvement in PFS for participants who received more than three cycles of treatment. At 24 months post randomisation, the PFS probability for participants receiving more than three cycles of treatment was 92.3% compared with 43.9% for those receiving three or less. The overall difference between the PFS curves was significant at the 5% level (log-rank: $\chi^2 = 51.629$; $p < 0.0001$).

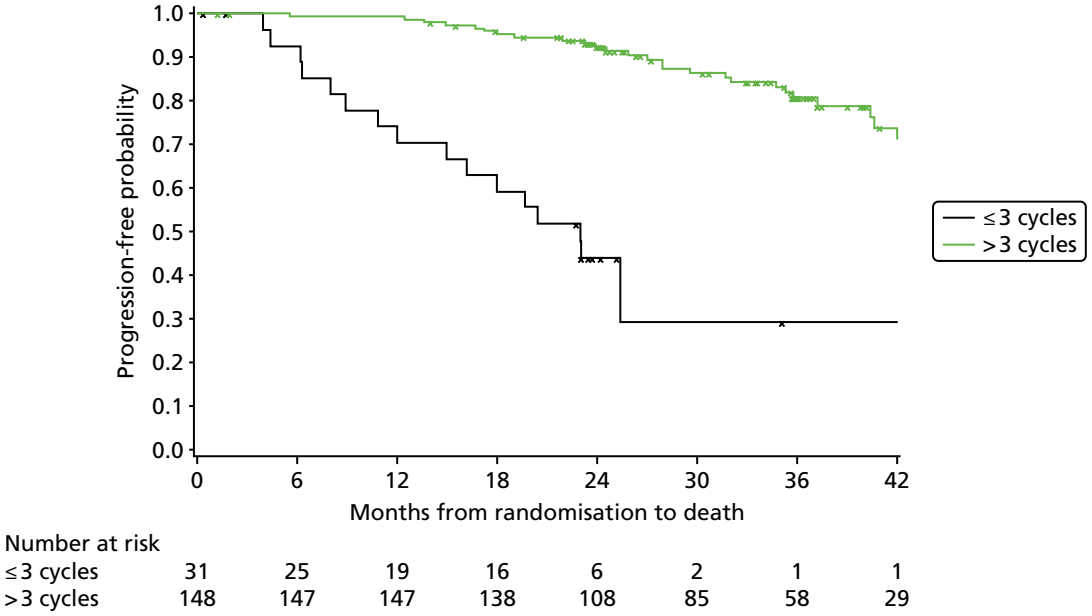


FIGURE 21 Kaplan–Meier plot of PFS by number of treatment cycles received.

Figure 22 presents the Kaplan–Meier curves for OS by number of treatment cycles received (three or fewer, more than three). At the time of analysis, of the 31 participants who received three cycles or less, 8 (25.8%) had died compared with 15/148 (10.1%) participants who received more than three cycles of treatment.

The curves show clear divergence from the end of treatment with an overall trend towards a worse OS for participants who received three or fewer cycles of treatment. At 24 months post randomisation, the OS probability for participants receiving more than three cycles of treatment was 95.9% compared with 74.1% for those receiving three or fewer. The overall difference between the OS curves was significant at the 5% level (log-rank: $\chi^2 = 14.167$; $p = 0.0002$).

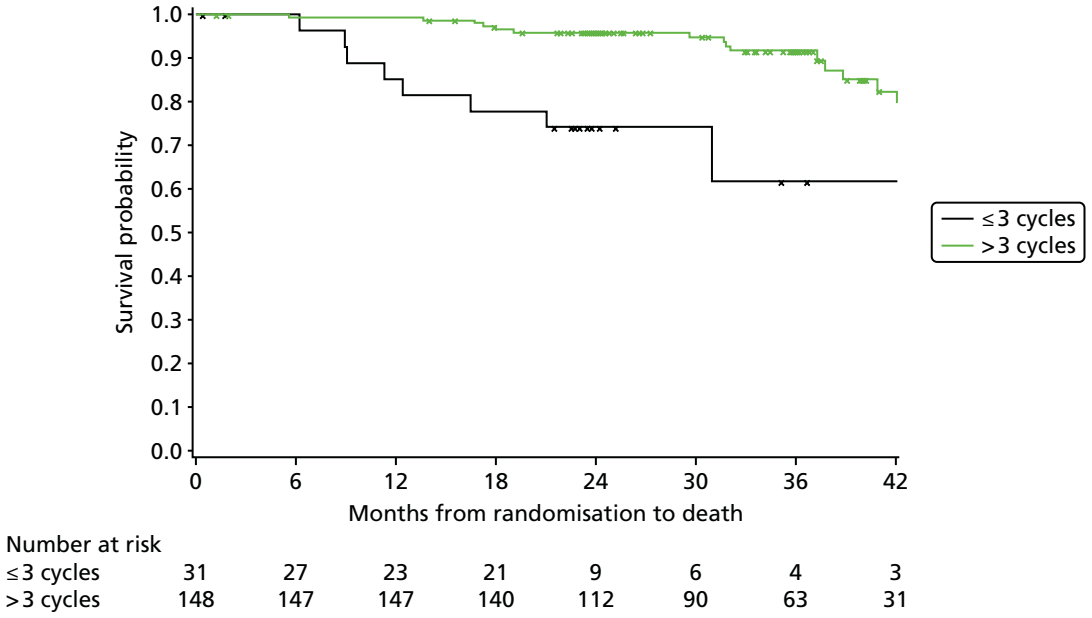


FIGURE 22 Kaplan–Meier plot of OS by number of treatment cycles received.

Progression-free survival and overall survival by granulocyte-colony stimulating factor usage

Figure 23 presents the Kaplan–Meier curves for time to progression by GSCF usage during treatment. At the time of analysis, of the 82 participants who had received GCSF at some stage during their treatment, 21 (25.6%) had reported an event (i.e. progression or death) compared with 23/87 (26.4%) participants who had not received any GSCF.

At 24 months post randomisation, the PFS probability for participants who had received GCSF at some stage during their treatment was 87.6% compared with 83.3% for participants who had not received any GCSF. The difference between the PFS curves for GCSF usage was non-significant (log-rank: $\chi^2 = 0.249$; $p = 0.618$).

Figure 24 presents the Kaplan–Meier curves for OS by GCSF usage during treatment. At the time of analysis, of the 82 participants who had received GCSF at some stage during their treatment, 11 (13.4%) had died compared with 12/87 (13.8%) participants who had not received any GSCF.

At 24 months post randomisation, the OS probability for participants who had received GCSF at some stage during their treatment was 95.1% compared with 89.5% for participants who had not. The difference between the OS curves for GCSF usage was non-significant (log-rank: $\chi^2 = 0.067$; $p = 0.796$).

Progression-free survival and overall survival by genetic risk factors: 17p and 11q

Given that there were only five participants with 17p deletion this analysis was not felt to be appropriate.

Figure 25 presents the Kaplan–Meier curves for time to progression by whether or not participants were 11q deleted. At the time of analysis, of the 26 participants who had an 11q deletion, six (23.1%) had reported an event (i.e. progression or death) compared with 37/142 (26.1%) participants who reported no event.

At 24 months post randomisation, the PFS probability for participants who were 11q deleted was 79.8% compared with 84.5% for participants who were not. The difference between the PFS curves was non-significant (log-rank: $\chi^2 = 0.032$; $p = 0.858$).

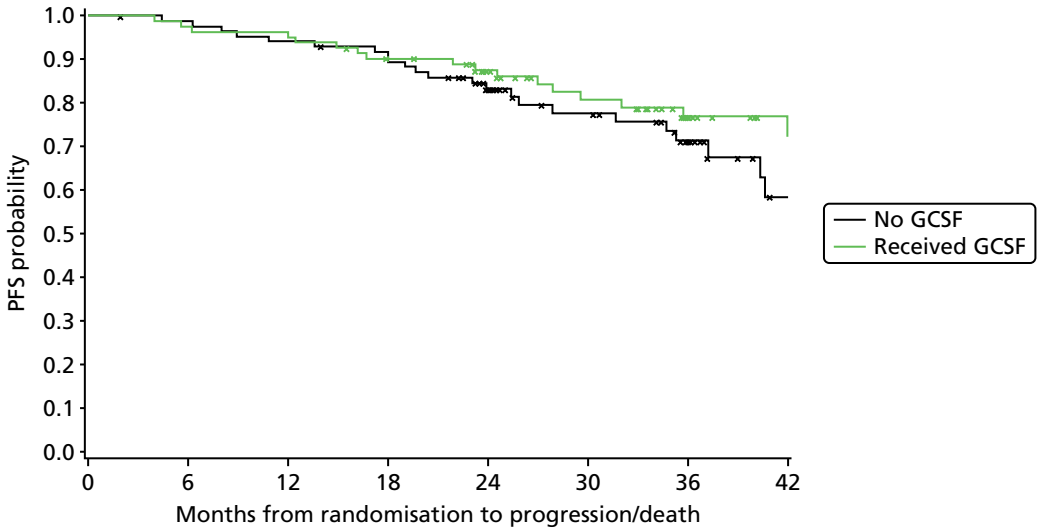


FIGURE 23 Kaplan–Meier plot of PFS by GCSF usage.

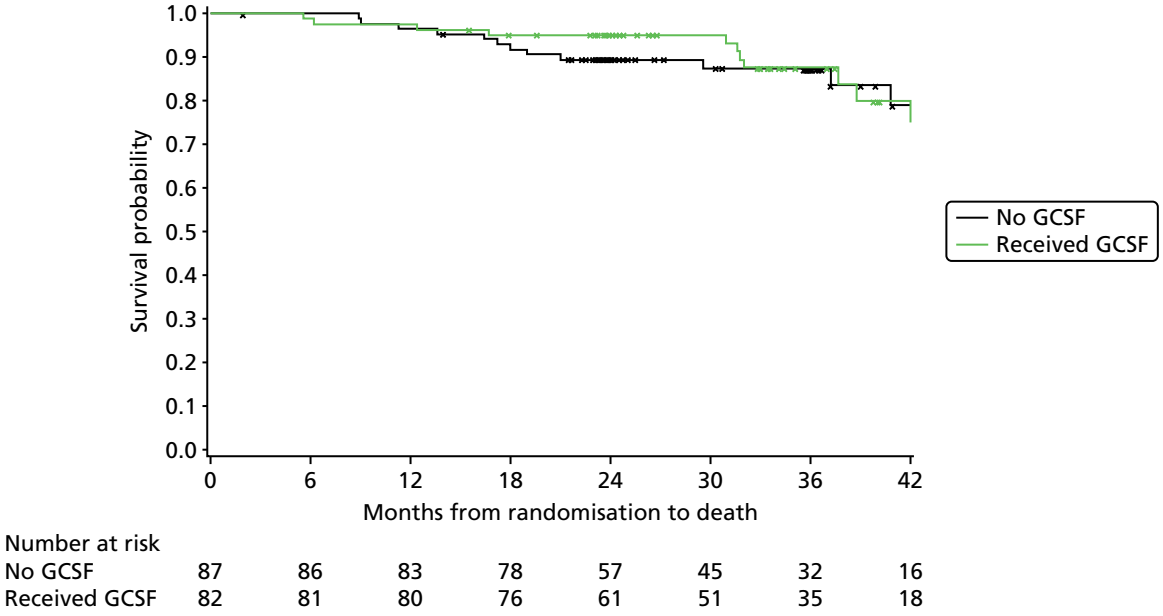


FIGURE 24 Kaplan–Meier plot of OS by GCSF usage.

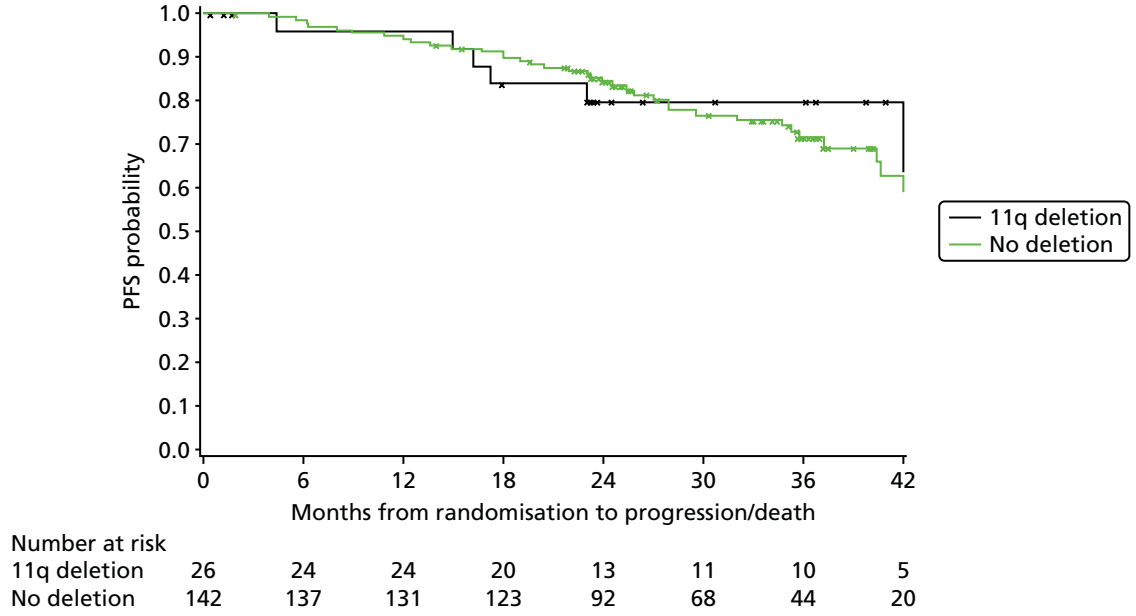
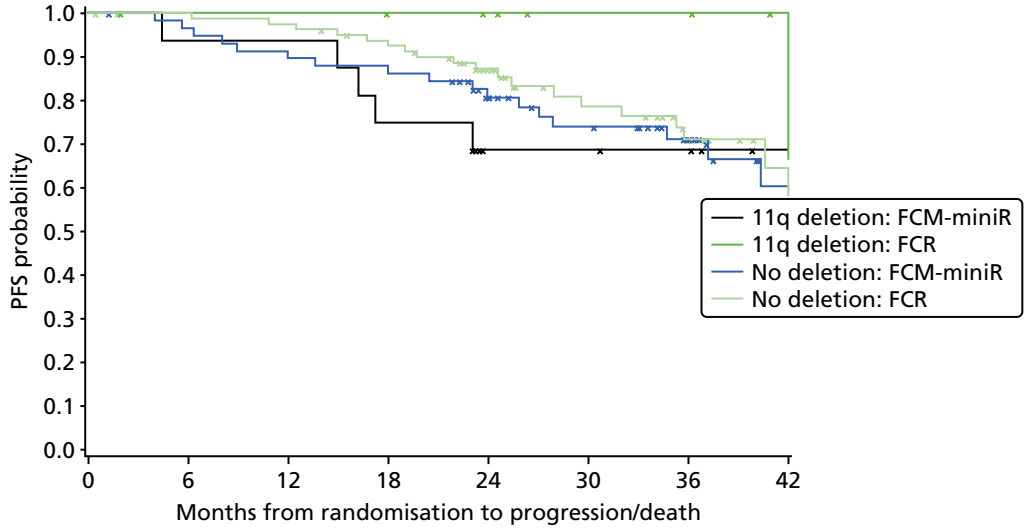


FIGURE 25 Kaplan–Meier plot of PFS by 11q deletion.

Figure 26 presents the Kaplan–Meier curves for PFS by whether or not participants were 11q deleted and by treatment group. The numbers are small, with only 10 and 16 participants in the FCR and FCM-miniR groups, respectively; however, it can be seen that only one of the FCR patients with 11q deletion progressed after over 3 years, compared with 5/16 (31.3%) of 11q-deleted patients on FCM-miniR. Excluding these 11q-deleted patients from the PFS curves brings the FCR and FCM-miniR curves closer together than those in *Figure 5*, although it can be seen that there is still a trend towards a PFS advantage with FCR over FCM-miniR.

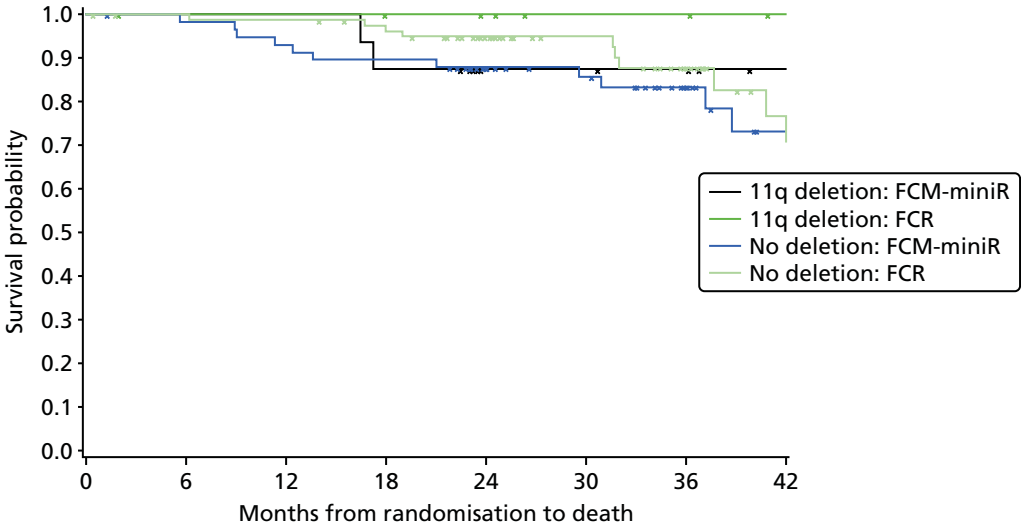
Figure 27 presents the Kaplan–Meier curves for OS by whether or not participants were 11q deleted and by treatment group. The numbers are small, with only 10 and 16 participants in the FCR and FCM-miniR groups, respectively. No FCR patients with 11q deletion died, compared with 2/16 (12.5%) of 11q-deleted patients on FCM-miniR. After excluding these 11q-deleted patients from the OS curves, there is still a trend towards a survival advantage in the FCR group.



Number at risk

11q deletion: FCM-miniR	16	15	15	12	6	6	5	2
11q deletion: FCR	10	9	9	8	7	5	5	3
No deletion: FCM-miniR	59	56	52	50	41	33	24	10
No deletion: FCR	83	81	79	73	51	35	20	10

FIGURE 26 Kaplan–Meier plot of PFS by 11q deletion and treatment group.



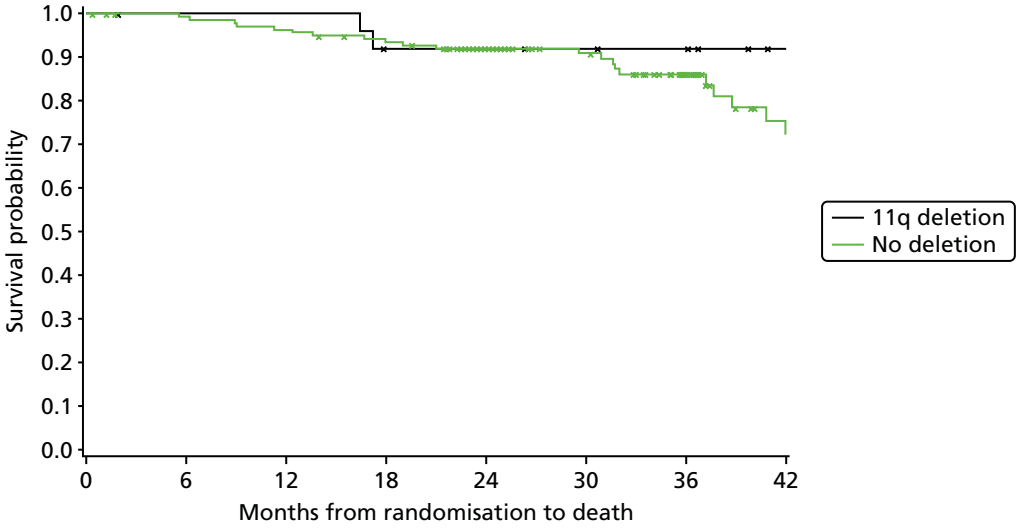
Number at risk

11q deletion: FCM-miniR	16	16	16	14	6	6	5	2
11q deletion: FCR	10	9	9	8	7	5	5	2
No deletion: FCM-miniR	59	57	54	52	44	38	27	12
No deletion: FCR	83	81	80	76	55	40	25	13

FIGURE 27 Kaplan–Meier plot of OS by 11q deletion and treatment group.

Figure 28 presents the Kaplan–Meier curves for OS by whether or not participants were 11q deleted. At the time of analysis, of the 26 participants who had an 11q deletion, 2 (7.7%) had died compared with 21/142 (14.8%) participants who had not.

At 24 months post randomisation, the OS probability was the same for participants who were 11q deleted and those who were not (92.0%). The difference between the OS curves was non-significant (log-rank: $\chi^2 = 0.648$; $p = 0.421$).



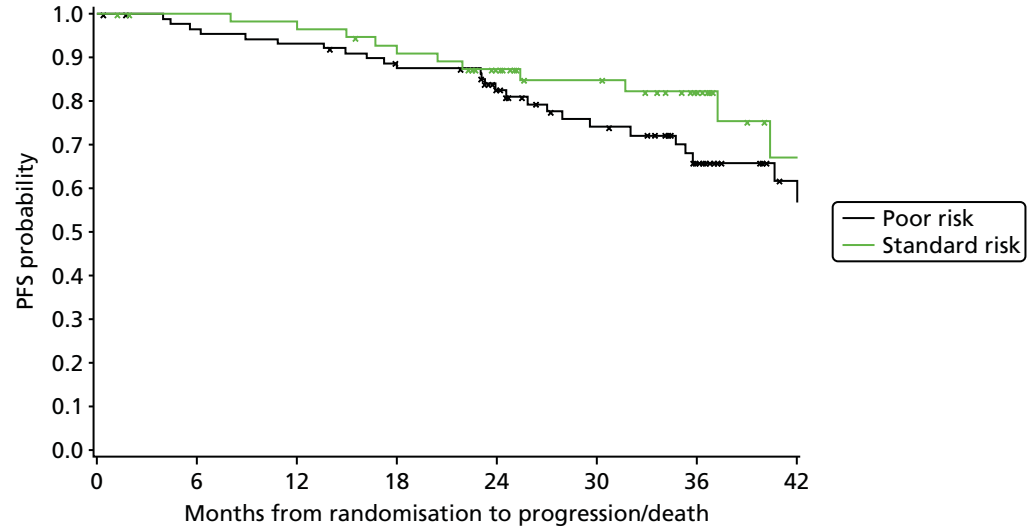
Number at risk								
11q deletion	26	25	25	22	13	11	10	4
No deletion	142	138	134	128	99	78	52	25

FIGURE 28 Kaplan–Meier plot of OS by 11q deletion.

Progression-free survival and overall survival by genetic risk factors: VH mutation risk

Figure 29 presents the Kaplan–Meier curves for time to progression by VH mutation risk, where standard risk indicates that the participant had a VH mutation not involving the VH3–21 gene and poor risk indicates that the participant did not have a VH mutation, or that the VH3–21 gene was involved. At the time of analysis, of the 91 participants with a poor VH mutation risk, 27 (29.7%) had reported an event (i.e. progression or death) whereas 11/58 (18.0%) participants with a standard VH mutation risk had reported an event.

At 24 months post randomisation, the PFS probability for the poor risk group was 82.6% compared with 87.4% for the standard-risk group. Although there appears to be a slight trend in favour of standard-risk participants performing better in terms of PFS, the difference between the PFS curves was non-significant (log-rank: $\chi^2 = 1.672$; $p = 0.1960$).



Number at risk								
Poor risk	91	86	83	76	56	42	29	14
Standard risk	58	56	54	50	42	33	20	8

FIGURE 29 Kaplan–Meier plot of PFS by VH mutation risk.

Figure 30 presents the Kaplan–Meier curves for OS by VH mutation risk. At the time of analysis, of the 91 participants with a poor VH mutation risk, 16 (17.6%) had died whereas 5/58 (8.6%) participants with a standard VH mutation risk had died.

At 24 months post randomisation, the OS probability was 91.0% for the poor-risk group compared with 94.6% for the standard-risk group. The difference between the OS curves was non-significant (log-rank: $\chi^2 = 2.172$; $p = 0.141$), although there is a suggested trend for standard-risk participants performing better in terms of OS.

Safety and toxicity

Safety summaries are based on the safety population, which includes 198 participants, 100 who received FCR, 79 who received FCM-miniR and 19 who received FCM-miniR followed by FCR. The FCR arm excludes two participants randomised to FCR who did not receive any protocol treatment and includes two FCM-miniR participants who received FCR from their first treatment cycle, as planned and documented in *Chapter 2*, *Analysis populations*.

Serious adverse events

A total of 183 SAEs [80 (43.7%) FCR; 81 (44.3%) FCM-miniR; 22 (12.0%) FCM-miniR/FCR] have been reported from 104 (52.5%) participants. In the FCR arm, 49/100 (49.0%) participants reported at least one SAE compared with 46/79 (58.2%) receiving FCM-miniR and 9/22 (47.4%) receiving FCM-miniR followed by FCR (*Table 50*). Of the participants experiencing at least one SAE, the mean number of SAEs reported was 1.8, with a similar number for the FCR (mean = 1.6) and FCM-miniR (mean = 1.8) arms, as for rates for all participants.

Of the 183 SAEs reported, 145 (79.2%) were suspected to be related to protocol treatment (SARs), with a slightly higher proportion in the FCM-miniR arm ($n = 67$, 82.7%) than in the FCR arm ($n = 62$, 77.5%) (*Table 51*). SARs were reported from 89 participants (44.9%), with a higher proportion of SARs reported from participants receiving FCM-miniR ($n = 39$, 49.4%), compared with FCR ($n = 41$, 41.0%), and from nine participants (47.4%) receiving FCM-miniR followed by FCR. There was one SUSAR reported in the trial, from a participant in the FCR arm. This SUSAR was reported to the regulatory authorities (Medicines and Healthcare products Regulatory Agency), sponsor and the main REC within the required timelines for

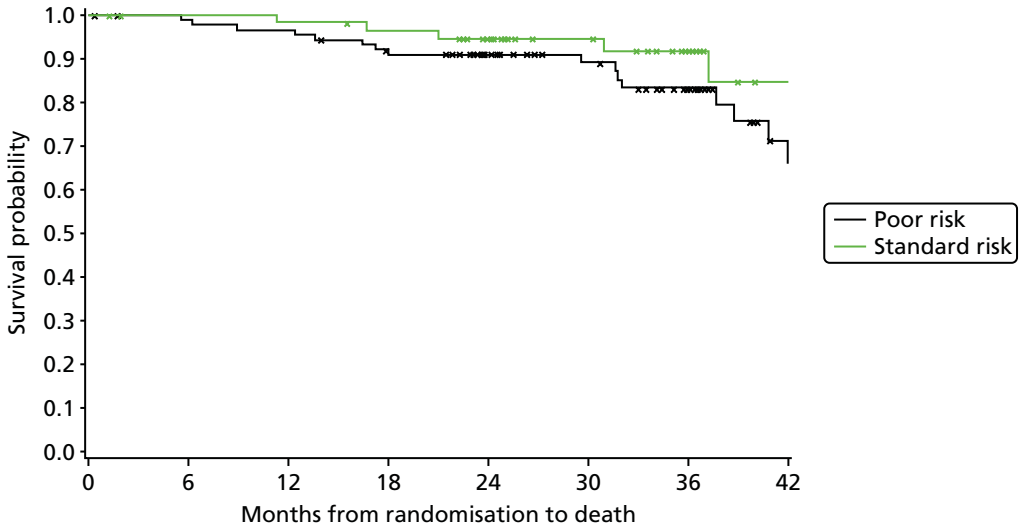


FIGURE 30 Kaplan–Meier plot of OS by VH mutation risk.

TABLE 50 Total number of SAEs reported overall and per participant (safety population)

SAEs	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 19$)	Total ($n = 198$)
Number of participants experiencing at least one SAE, *n* (%)	49 (49.0)	46 (58.2)	9 (47.4)	104 (52.5)
Total number of SAEs reported	80	81	22	183
Number of SAEs per participant who had at least one event				
Mean (SD)	1.6 (1.0)	1.8 (1.2)	2.4 (1.3)	1.8 (1.1)
Median (range)	1 (1–5)	1 (1–5)	2 (1–4)	1 (1–5)
N	49	46	9	104
Number of SAEs per participant (all participants)				
Mean (SD)	0.8 (1.1)	1.0 (1.2)	1.2 (1.5)	0.9 (1.2)
Median (range)	0 (0–5)	1 (0–5)	0 (0–4)	1 (0–5)
N	100	79	19	198

TABLE 51 Relationship with experimental treatment (safety population)

Relationship to experimental treatment	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Suspected, unexpected	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Suspected, expected	61 (76.3)	67 (82.7)	16 (72.7)	144 (78.7)
Not suspected	18 (22.5)	14 (17.3)	6 (27.3)	38 (20.8)
Total	80 (100)	81 (100)	22 (100)	183 (100)
Suspected to be related to				
Fludarabine	2 (3.2)	6 (9.0)	1 (6.3)	9 (6.2)
Cyclophosphamide	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)
Rituximab	7 (11.3)	0 (0.0)	0 (0.0)	7 (4.8)
Low-dose rituximab	0 (0.0)	5 (7.5)	2 (12.5)	7 (4.8)
Fludarabine and cyclophosphamide	21 (33.9)	0 (0.0)	4 (25.0)	25 (17.2)
Fludarabine and mitoxantrone	0 (0.0)	2 (3.0)	0 (0.0)	2 (1.4)
Fludarabine and rituximab	0 (0.0)	0 (0.0)	1 (6.3)	1 (0.7)
Mitoxantrone and low-dose rituximab	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)
FCM	0 (0.0)	21 (31.3)	1 (6.3)	22 (15.2)
FCR	32 (51.6)	0 (0.0)	2 (12.5)	34 (23.4)
Fludarabine, cyclophosphamide and low-dose rituximab	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)
FCM-miniR	0 (0.0)	30 (44.8)	5 (31.3)	35 (24.1)
Total	62 (100)	67 (100)	16 (100)	145 (100)

expedited reporting. The participant received all six cycles of treatment and was diagnosed with a 'squamous cell carcinoma' approximately 4 months after their last cycle of treatment. The event was felt by the Principal Investigator at the site to be related to trial treatment (FCR) and unexpected. Further details on this event, and all SAEs, are provided in *Appendix 1*.

Of the 145 SAEs suspected to be related to protocol treatment, in the FCR arm the majority (51.6%) were suspected to be related to all three IMPs, F, C and R, with 33.9% suspected to be related to just

F and C, and 11.3% suspected to be related to rituximab only. In the FCM-miniR arm, SAEs were most commonly (44.8%) suspected to be related to all four IMPs, F, C, M and reduced-dose rituximab (miniR) with 31.3% suspected to be related to F, C and M.

The majority of SAEs required (prolonged) hospitalisation (89.1%), with 92.5% coming from the FCR arm and 84.0% from the FCM-miniR arm (*Table 52*).

Six SAEs in the FCM-miniR arm were deemed to be life-threatening or resulted in death, compared with three in the FCR arm. In the FCR arm, one participant died as a result of an 'infection' which was suspected to be related to trial treatment within 5 months of their last course of treatment. This participant received two cycles of treatment. In the FCM-miniR arm, one participant died as a result of a 'Bilateral pneumonia' which was suspected to be related to trial treatment within 9 months of their last course of treatment. The participant received all six cycles of treatment. A further FCM-miniR participant died as a result of 'Neutropenic sepsis and infected shoulder', which was not suspected to be related to trial treatment, within 3 months of their last course of treatment. This participant received four cycles of treatment. Further information on the SAEs that resulted in death are provided in *Appendix 1*.

All but three SAEs had recovered at the time of reporting.

The majority of SARs required (or prolonged) hospitalisation (90.3%) (93.5% in the FCR arm compared with 86.6% in the FCM-miniR arm). All but three SARs had recovered at the time of reporting (*Table 53*).

Of the 198 participants in the safety population, 96 (48.5%) required hospitalisation during the trial as a result of an SAE, with a higher proportion in the FCM-miniR arm ($n = 41$, 51.9%) than the FCR arm ($n = 46$, 46.0%) (*Table 54*).

Of the 180 SAEs that were not ongoing, the median duration of an event was 5 days (range: < 1–303 days) with a similar duration in each of the treatment groups (*Table 55*). The median duration of SARs that were suspected to be related to protocol treatment was the same, although there was variability in the mean durations between the treatment arms.

TABLE 52 Seriousness criteria and outcome of each SAE (safety population)

Seriousness criteria and outcome	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Seriousness criteria				
Participant died	1 (1.3)	2 (2.5)	0 (0.0)	3 (1.6)
Life-threatening	2 (2.5)	4 (4.9)	0 (0.0)	6 (3.3)
Required/prolonged hospitalisation	74 (92.5)	68 (84.0)	21 (95.5)	163 (89.1)
Persistent or significant disability/incapacity	2 (2.5)	0 (0.0)	0 (0.0)	2 (1.1)
Jeopardised participant/required intervention to prevent one of the above	10 (12.5)	14 (17.3)	1 (4.5%)	25 (13.7%)
Outcome				
Recovered	72 (90.0)	71 (87.7)	19 (86.4)	162 (88.5)
Recovered with sequelae	5 (6.3)	7 (8.6)	3 (13.6)	15 (8.2)
Condition improving	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)
Condition still present and unchanged	1 (1.3)	1 (1.2)	0 (0.0)	2 (1.1)
Death	1 (1.3)	2 (2.5)	0 (0.0)	3 (1.6)
Total	80 (100)	81 (100)	22 (100)	183 (100)

TABLE 53 Seriousness criteria and outcome of each SAR (safety population)

Seriousness criteria and outcome	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Seriousness criteria				
Participant died	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.3)
Life-threatening	2 (3.2)	4 (6.0)	0 (0.0)	6 (4.1)
Required/prolonged hospitalisation	58 (93.5)	58 (86.6)	15 (93.8)	131 (90.3)
Persistent or significant disability/incapacity	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.3)
Jeopardised participant/required intervention to prevent one of the above	8 (12.9)	11 (16.4)	1 (6.3)	20 (13.8)
Outcome				
Recovered	58 (93.5)	60 (89.6)	15 (93.8)	133 (91.7)
Recovered with sequelae	1 (1.6)	5 (7.5)	1 (6.3)	7 (4.8)
Condition improving	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
Condition still present and unchanged	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.4)
Death	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.4)
Total	62 (100)	67 (100)	16 (100)	145 (100)

TABLE 54 Total number of participants requiring hospitalisation for an SAE (safety population)

Required hospitalisation for an SAE	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 19$)	Total ($n = 198$)
Yes, *n* (%)	46 (46.0)	41 (51.9)	9 (47.4)	96 (48.5)
No, *n* (%)	54 (54.0)	38 (48.1)	10 (52.6)	102 (51.5)

TABLE 55 Duration of SAEs and SARs (safety population)

Duration	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Duration of SAE (days from when SAE became serious to recovery/death)				
Mean (SD)	15.9 (40.9)	15.3 (41.2)	15.9 (53.3)	15.6 (42.5)
Median (range)	4.0 (< 1–280.0)	5.0 (< 1–303.0)	4.5 (< 1–254.0)	5.0 (< 1–303.0)
N	78	80	22	180
Missing	2	1	0	3
Duration of SAR (days from when SAR became serious to recovery/death)				
Mean (SD)	11.7 (22.8)	15.2 (44.5)	19.9 (62.5)	14.2 (39.4)
Median (range)	5.0 (< 1–144.0)	5.0 (< 1–303.0)	4.5 (< 1–254.0)	5.0 (< 1–303.0)
N	60	66	16	142
Missing	2	1	0	3

Of the 145 SAEs suspected to be related to protocol treatment (SARs), the majority ($n = 90$, 62.1%) were classed as 'infections and infestations' according to the MedDRA System Organ Class system (*Table 56*). A higher proportion of events reported in the FCR arm were classed as 'general disorders and administration site conditions' than those reported in the FCM-miniR arm [10 (16.1%) FCR; 6 (9.0%) FCM-miniR].

Adverse events

A total of 2163 AEs have been reported from 192 (97.0%) participants. A total of 1117 events have been reported from 96 participants receiving FCR, 863 events from 77 participants receiving FCM-miniR and 183 from 19 participants who received FCM-miniR followed by FCR. The mean number of AEs reported was similar for the FCR and FCM-miniR treatment groups for the population of participants experiencing at least one event (*Table 57*). Line listings of all AEs by treatment received are presented in *Appendix 2*, *Adverse event listings*.

TABLE 56 MedDRA system organ class for SAEs suspected to be related to trial treatment (SARs) (safety population)

MedDRA system organ class	FCR, *n* (%)	FCM-miniR, *n* (%)	FCM-miniR/FCR, *n* (%)	Total, *n* (%)
Blood and lymphatic system disorders	8 (12.9)	8 (11.9)	0 (0.0)	16 (11.0)
Gastrointestinal disorders	4 (6.5)	4 (6.0)	2 (12.5)	10 (6.9)
General disorders and administration site conditions	10 (16.1)	6 (9.0)	3 (18.8)	19 (13.1)
Immune system disorders	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)
Infections and infestations	36 (58.1)	43 (64.2)	11 (68.8)	90 (62.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.4)
Psychiatric disorders	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.7)
Renal and urinary disorders	0 (0.0)	2 (3.0)	0 (0.0)	2 (1.4)
Skin and subcutaneous tissue disorders	2 (3.2)	1 (1.5)	0 (0.0)	3 (2.1)
Total	62 (100)	67 (100)	16 (100)	145 (100)

TABLE 57 Total number of AEs reported overall and per participant (safety population)

AEs	FCR ($n = 100$)	FCM-miniR ($n = 79$)	FCM-miniR/FCR ($n = 19$)	Total ($n = 198$)
Number of participants experiencing at least one AE, *n* (%)	96 (96.0)	77 (97.5%)	19 (100%)	192 (97.0%)
Number of AEs reported	1117	863	183	2163
Number of AEs per participant who had at least one event				
Mean (SD)	11.6 (7.1)	11.2 (6.9)	9.6 (5.7)	11.3 (6.9)
Median (range)	11 (1–38)	10 (1–36)	8 (1–19)	10 (1–38)
N	96	77	19	192
Number of AEs per participant (overall)				
Mean (SD)	11.2 (7.3)	10.9 (7.0)	9.6 (5.7)	10.9 (7.1)
Median (range)	11 (0–38)	10 (0–36)	8 (1–19)	10 (0–38)
N	100	79	19	198

New AEs most commonly occurred during the first treatment cycle, with the number of new AEs occurring gradually declining with the more treatment cycles received, although this trend will be influenced by the declining number of participants receiving each treatment cycle (*Table 58*). The proportion of new AEs occurring at each treatment cycle appears to be reasonably well balanced between FCR and FCM-miniR.

Table 59 presents the maximum CTCAE grade experienced for each AE by treatment received. The majority of AEs were reported as a maximum CTC grade 1 (50.5%). A higher percentage of CTC grade 3/4 AEs were experienced in the FCM-miniR arm ($n = 193$, 22.4%) than the FCR ($n = 168$, 15.0%) and FCM-miniR/FCR arms ($n = 27$, 14.6%).

Treatment-related mortalities within 3 months of ending protocol treatment

There were no treatment-related mortalities within 3 months of the protocol treatment ending.

One trial participant, receiving FCM-miniR, died within 3 months of discontinuing the protocol treatment but the cause was not suspected to be related to trial treatment. This participant discontinued treatment after their fourth cycle owing to 'Disease progression, requiring further treatment'. After discontinuing treatment, and prior to death, they reported a SAE of 'Neutropenic sepsis and infected shoulder', which was not suspected to be related to the trial treatment. The participant gradually deteriorated and died within 3 months of ending protocol treatment. The primary cause of death was given as 'Infection due to CLL' and the participant's disease status at the time of death was recorded as 'stable disease'.

Secondary cancers

The following tables summarise the secondary cancers that were reported at follow-up.

Table 60 shows that the incidence of secondary cancers was similar across the trial arms, with 11.1% of patients reporting a secondary cancer. The most common types of secondary cancer were skin- and haematological-related cancers.

TABLE 58 Treatment cycle where an AE first occurred (safety population)

Treatment cycle AE first occurred	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
1	280 (25.1)	237 (27.5)	51 (27.9)	568 (26.3)
2	217 (19.4)	156 (18.1)	45 (24.6)	418 (19.3)
3	185 (16.6)	144 (16.7)	22 (12.0)	351 (16.2)
4	164 (14.7)	114 (13.2)	26 (14.2)	304 (14.1)
5	142 (12.7)	99 (11.5)	24 (13.1)	265 (12.3)
6	129 (11.5)	113 (13.1)	15 (8.2)	257 (11.9)
Total	1117 (100)	863 (100)	183 (100)	2163 (100)

TABLE 59 Maximum CTCAE grade (safety population)

Maximum CTCAE grade	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
1	589 (52.7)	405 (46.9)	99 (54.1)	1093 (50.5)
2	354 (31.7)	262 (30.4)	57 (31.1)	673 (31.1)
3	107 (9.6)	118 (13.7)	17 (9.3)	242 (11.2)
4	61 (5.5)	75 (8.7)	10 (5.5)	146 (6.7)
Missing	6 (0.5)	3 (0.3)	0 (0.0)	9 (0.4)
Total	1117 (100)	863 (100)	183 (100)	2163 (100)

TABLE 60 Incidence and type of secondary cancer

Incidence and type of secondary cancer	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Has the participant reported a secondary cancer?				
Yes	11 (11.0)	10 (12.7)	1 (5.3)	22 (11.1)
No	89 (89.0)	69 (87.3)	18 (94.7)	176 (88.9)
Total	100 (100)	79 (100)	19 (100)	198 (100)
Secondary cancer type				
Haematological (lymphoma)	2 (16.7)	2 (18.2)	0 (0.0)	4 (16.7)
Haematological (AML/MDS)	3 (25.0)	2 (18.2)	0 (0.0)	5 (20.8)
Skin (non-melanoma)	2 (16.7)	7 (63.6)	1 (100)	10 (41.7)
Skin (melanoma)	1 (8.3)	0 (0.0)	0 (0.0)	1 (4.2)
Non-haematological (solid tumours)	4 (33.3)	0 (0.0)	0 (0.0)	4 (16.7)
Total	12 (100)	11 (100)	1 (100)	24 (100)

AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome.

Table 61 further summarises the type of secondary cancer reported. Note that the results are not mutually exclusive, as one patient was diagnosed with basal cell carcinoma twice, and another with both squamous cell carcinoma and melanoma.

Table 62 shows the mean, median and ranges of when the secondary cancers were diagnosed from randomisation and from end of treatment.

Summary of statistical results

There is strong evidence to suggest that FCM-miniR is not non-inferior to FCR in terms of CR at 3 months post treatment.

TABLE 61 Further detail on type of secondary cancer

Secondary cancer type	FCR, *N* (%)	FCM-miniR, *N* (%)	FCM-miniR/FCR, *N* (%)	Total, *N* (%)
Lymphoma (other)	2 (16.7)	2 (18.2)	0 (0.0)	4 (16.7)
Myelodysplastic syndrome	2 (16.7)	2 (18.2)	0 (0.0)	4 (16.7)
Acute myeloid leukaemia	1 (8.3)	0 (0.0)	0 (0.0)	1 (4.2)
Basal cell carcinoma	0 (0.0)	3 (27.3)	0 (0.0)	3 (12.5)
Squamous cell carcinoma	2 (16.7)	4 (36.4)	1 (100)	7 (29.2)
Melanoma	1 (8.3)	0 (0.0)	0 (0.0)	1 (4.2)
Lung	1 (8.3)	0 (0.0)	0 (0.0)	1 (4.2)
Hepatobiliary	1 (8.3)	0 (0.0)	0 (0.0)	1 (4.2)
Urological (prostate)	2 (16.7)	0 (0.0)	0 (0.0)	2 (8.3)
Total	12 (100)	11 (100)	1 (100)	24 (100)

TABLE 62 Timing of secondary cancer

Timing of secondary cancer	FCR	FCM-miniR	FCM-miniR/FCR	Total
Months from randomisation to diagnosis				
Mean (SD)	23.9 (14.9)	18.7 (9.4)	24.3	21.5 (12.3)
Median (range)	25.4 (1.6–46.5)	20.0 (6.4–31.6)	24.3 (24.3–24.3)	22.3 (1.6–46.5)
n	12	11	1	24
Months from end of treatment to diagnosis				
Mean (SD)	19.9 (14.3)	13.2 (8.7)	19.2	16.8 (11.9)
Median (range)	21.7 (0.3–41.5)	14.6 (1.7–25.7)	19.2 (19.2–19.2)	16.1 (0.3–41.5)
n	12	11	1	24

From December 2009 to September 2012, 200 of a planned 206 patients were recruited from 34 centres across the UK. A good proportion of participants ($n = 141$, 70.5%) completed the recommended six cycles of treatment, with a slightly higher proportion in the FCR arm than in the FCM-miniR arm (70% vs. 64.6%), and the majority of participants who discontinued treatment early doing so for reasons of toxicity. A similar proportion of participants in each of the treatment arms experienced at least one dose modification to their protocol-defined dose of treatment, and just under half (47.0%) received treatment with GCSF at some stage during their treatment period.

At the interim analysis, carried out on the first half of patients randomised to the trial ($n = 103$), of those with available data, 82.9% of participants achieved a CR in the FCR arm compared with 61.4% in the FCM-miniR arm. The difference in proportions (FCM-miniR – FCR) was –21.6% (99.5% CI –48.0% to 4.8%), which was not statistically significant at the 0.5% ($p = 0.005$) level, although the experimental treatment had the worst performance. This was confirmed by the adjusted analysis (OR 0.32, 99.5% CI 0.07 to 1.48; $p = 0.037$). The primary aim of the interim analysis was to be able to release information of any potential large differences in efficacy between the treatment arms and inform the continued treatment of trial participants earlier than would have been the case with the final analysis. As the results were approaching significance in favour of the control group, and there was evidence of additional toxicity in the FCM-miniR arm, the trial was closed early at the recommendation of the DMEC and participants still receiving FCM-miniR were recommended to transfer to treatment with FCR for the remainder of their treatment cycles.

At the final analysis of the primary end point (at 3 months post treatment), 76.1% of participants in the FCR arm achieved a CR compared with 54.7% in the FCM-miniR arm. The difference in proportions (FCM-miniR – FCR) was –21.4% (95% CI –35.8% to –7.0%) and the adjusted analysis gave an OR of 0.37 for the treatment effect (95% CI 0.19 to 0.73), indicating that participants in the FCM-miniR were significantly less likely to achieve a CR. As the lower limit of the 95% CI and the mean OR were < 0.61 (equivalent to a difference in proportions of 10% based on the observed control rate) and the upper limit of the 95% CI was also below 1, there was very strong evidence that FCM-miniR is not non-inferior to FCR in terms of CR rates at 3 months post treatment, and that it is in fact inferior. The analysis of the PP population and the sensitivity analyses agreed with this conclusion. The exploratory subgroup analyses indicated that there was a significant trend towards participants who received more than three cycles of treatment, and those who did not have a 17p deletion, performing better in terms of response.

The ORR was high at 92.6% with 7.5% fewer participants achieving at least a PR in the FCM-miniR arm compared with the FCR arm (95% CI –15.6% to 0.6%). The difference in the ORR proportions was not statistically significant, although it is approaching significance.

At 3 months post treatment, 53.0% of participants were MRD negative, a higher percentage of participants in the FCR arm (57.0%) than in the FCM-miniR arm (46.4%). The difference in proportions (FCM-miniR – FCR) was –10.6% (95% CI –26.1% to 4.9%) and the adjusted analysis gave an OR of 0.63 for the treatment effect (95% CI 0.34 to 1.20) which was not statistically significant ($\chi^2 = 1.97$; $p = 0.160$), although it was approaching significance.

There was no conclusion of a significant difference between the treatment arms with respect to time to progression (log-rank test, $p = 0.2790$; Wilcoxon rank-sum test, $p = 0.1081$), confirmed by the adjusted Cox regression analysis (HR 1.39, 95% CI 0.77 to 2.49; $p = 0.2771$). There was also no conclusion of a significant difference between the treatment arms with respect to OS (log-rank test, $p = 0.2779$; Wilcoxon rank-sum test, $p = 0.1013$), confirmed by the adjusted Cox regression analysis (HR 1.57, 95% CI 0.68 to 3.58; $p = 0.2876$). However, there was a non-significant trend towards the FCM-miniR participants performing worse. At 24 months from randomisation, 89.4% of the FCR participants remained progression-free compared with 79.1% of the FCM-miniR participants. In terms of OS at 24 months, 95.8% of the FCR participants remained alive compared with 88.5% of the FCM-miniR participants. In the exploratory subgroup analyses, PFS and OS were significantly improved for participants who were MRD negative or had achieved a CR at 3 months post treatment, or who received more than three cycles of treatment. In addition, of those participants who were MRD positive, OS was worse in participants who received FCM-miniR than in those who received FCR, suggesting that after progression the participants initially treated with FCM-miniR responded worse to salvage therapies or died before further treatment was possible. Longer follow-up data are required to be able to assess reliably the time-to-event outcomes, and these will be updated in future.

More participants experienced an SAE in the FCM-miniR arm than the FCR arm (58.2% vs. 49.0%), as well as an SAR (49.4% vs. 41.0%). One SUSAR ('squamous cell carcinoma') was reported during the trial in the FCR arm. More participants in the FCM-miniR arm were hospitalised for an SAE during the trial (51.9% vs. 46.0%) and six SAEs were deemed to be life-threatening or resulted in death compared with three in the FCR arm. A similar proportion of participants experienced an AE in each treatment arm, but a higher proportion of CTCAE grade 3 and 4 AEs were reported in the FCM-miniR arm (22.4% vs. 15.0%). There were no treatment-related mortalities within 3 months of completing protocol treatment.

Throughout the duration of the trial there were nine withdrawals (4.5%), with a similar number of participants coming from each treatment arm.

Chapter 4 Economic evaluation

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The health economics analysis was designed to provide an economic evaluation of previously untreated patients with CLL to compare FCR and FCM-miniR. The aim was to assess the cost-effectiveness of FCR compared with FCM-miniR from a UK NHS and PSS perspective.

Unit cost data

Unit cost of resource use

Individual-level resource use was combined with unit costs to calculate the total health-care use cost for each participant in the trial. In order to convert resource usage figures into costs, unit cost figures were assigned from national sources such as the PSSRU Unit Costs of Health and Social Care 2013.[33] *Table 63* presents the summary of unit costs.

TABLE 63 Summary of participant-reported health-care use and associated unit costs

Resource item	Face-to face-visits, £	Phone call, £	Source
GP surgery visit	45.00	27.00	PSSRU (2013) p. 191: including direct care staff costs with qualification; per participant contact lasting 11.7 minutes
GP out of office hours visit	114.00	27.00	PSSRU (2013) p. 191: including direct care staff costs with qualification (we consider it as out of surgery visit lasting 23.4 minutes)
District nurse	70.00	N/A	PSSRU (2013) p. 183: per hour of home visit including qualification
Health visitor	71.00	N/A	PSSRU (2013) p. 185: per hour of home visit including qualification
Occupational therapist	44.00	N/A	PSSRU (2013) p. 201: per hour participant contact (costs including training)
Physiotherapist	34.00	N/A	PSSRU (2013) p. 175: per hour participant contact (costs including qualification)
Counsellor	58.00	N/A	PSSRU (2013) p. 54: cost per consultation
Home help or care worker	24.00	N/A	PSSRU (2013) p. 202: cost per hour weekday. Each home visit lasting 30 minutes
Psychiatrist	362.00	N/A	PSSRU (2013) p. 247: per face-to-face contact
Psychologist	134.00	N/A	PSSRU (2013) p. 179: per hour participant contact
Hospital inpatient stay	598.00		PSSRU (2013) p. 107: national average non-elective short stay
	2581.00		PSSRU (2013) p. 107: national average non-elective long stay
Hospital day centre	697.00	N/A	PSSRU (2013) p. 107: day cases Healthcare Resource Group data
Hospital outpatient clinic	135.00	N/A	PSSRU (2013) p. 107: weighted average of all outpatient procedures
Hospital A&E department	131.00	N/A	PSSRU (2010) p. 119: national average A&E treatments leading to admitted (not admitted) [not updated in the latest publication]
Nursing home	750.00	N/A	PSSRU (2013) p. 37: establishment cost per permanent resident week

A&E, accident and emergency; N/A, not applicable.

Unit cost of medications

Participants were randomised to receive six cycles of either FCR or FCM-miniR. Each cycle was 28 days. Participants were evaluated after three cycles of chemotherapy and if no response or disease progression was observed they were stopped from receiving further therapy. These participants would still attend follow-up assessments until 24 months after randomisation. Unit costs for medications were obtained from the BNF 67th edition of September 2013.[34] Details for medication dosages given within the six treatment cycles were collected. The total medication costs using the dosage and the frequency provided by the participant were calculated. If the dose of the drug was not recorded, it was assumed that the participant received the same dosage as other participants who were given the same treatment. If the quantity was not recorded, the average quantity for that drug as reported in the data was applied. *Table 64* shows all the unit costs for the drugs that were reported in the trial.

Treatment costs

In addition to the cost of medications used during chemotherapy, an additional cost was identified which was the cost of administering the drug. The costs are shown in *Table 65*.

TABLE 64 Summary of participant-reported medication use and associated unit costs

Drug name	Description	Price (*BNF*) August 2014
Cyclophosphamide		
Tablets	Cyclophosphamide monohydrate BP 53.0 mg equivalent to 50 mg anhydrous cyclophosphamide	Tablets, s/c, cyclophosphamide (anhydrous) 50 mg, net price 100 = £70.70. Label: 25, 27
Solution	Cyclophosphamide monohydrate powder for solution injection or infusion	Injection, powder for reconstitution, cyclophosphamide, net price 500-mg vial = £9.20; 1-g vial = £17.06
Fludarabine		
Tablets	Fludarabine phosphate 50 mg	Tablets, f/c, pink, fludarabine phosphate 10 mg, net price 15-tab pack = £302.48, 20-tab pack = £403.31
Solution	Fludarabine phosphate 50 mg	Injection, powder for reconstitution, fludarabine phosphate, net price 50-mg vial = £147.07
Mitoxantrone		
Solution	Each millilitre of concentrate contains 2 mg mitoxantrone (as hydrochloride) Each 10-ml vial contains 20 mg mitoxantrone as hydrochloride	Concentrate for intravenous infusion, mitoxantrone (as hydrochloride) 2 mg/ml, net price 10-ml vial = £121.85
Rituximab (MabThera)		
Solution	MabThera solution for infusion Composition rituximab 100 mg/10 ml or 500 mg/50 ml	Concentrate for intravenous infusion, rituximab 10 mg/ml, net price 10-ml vial = £174.63, 50-ml vial = £873.15

f/c, film coated; s/c, sugar coated.

TABLE 65 Costs of administering the drug

Drug name[a]	Cost per cycle, £	Source
Rituximab (i.v. administration)	430	NICE, *Rituximab for the first-line treatment of chronic lymphocytic leukaemia*, 2009[48]
FC	230	NICE, *Rituximab for the first-line treatment of chronic lymphocytic leukaemia*, 2009[48]

a As mitoxantrone is also administered as an i.v. infusion and is delivered with rituximab, it is assumed that there is no extra cost to administer mitoxantrone in this instance.

Utility and quality-adjusted life-years

Participant health-related quality of life was assessed using EQ-5D,[28] which was included along with the participant resource-use questionnaires. Changes in EQ-5D scores at baseline, 3 months after treatment ends, and at 12, 18 and 24 months post randomisation were evaluated using two-sample *t*-tests to explore any important differences in these end points within the time frame of the trial.

In line with the NICE reference case[27] the primary health outcome for the economic evaluation was QALYs measured using the EQ-5D questionnaire. Participant responses to the EQ-5D questionnaire at each time point were converted to utilities using the standard UK tariff values[28] and the 'area under the curve' approach. QALYs were calculated by multiplying these values with the time spent in each state, with quality of life linearly interpolated for the periods between the four observations provided in the trial data. Average QALYs between adjacent time points were calculated to generate smoothed estimates between the time points. A sensitivity analysis was conducted using the SF-12 trial questionnaire responses (instead of the EQ-5D) to calculate QALYs.

Missing data

The mean total cost per participant was calculated for NHS and PSS perspectives by adding the costs of inpatient stay, outpatient visit, consultations, medication, treatment and applicable interventions for all participants where response data were available. Missing QALY data were predicted in terms of baseline EQ-5D, visual analogue scale of health-related quality of life, treatment received, age, sex and resource use for that time period. From the overall sample, missing data represented 33.98%. Importantly, the health economics criteria for inclusion were slightly more restrictive than those for the statistical analysis; for those cases in which either resource usage or quality of life data were unavailable, these figures cannot be calculated. The complete data analysis was based on 136 participants. We addressed missingness using multiple imputations via chained equations[35,36] to complete missing data assuming missing at random and using Stata 13 (StataCorp LP, College Station, TX, USA). A total of 10 imputations were created to stabilise the result. Following multiple imputations, data for 162 participants were accounted for. The reported cost-effectiveness results were synthesised based on all imputed data sets.

Within-trial cost-effectiveness analysis

Cost-effectiveness results: base case

Resource use and QALY data were available for 162 participants, with 92 participants being treated with FCR and 70 participants with FCM-miniR.

Health-care resource use

The total costs associated with resource use during the trial are shown in *Tables 66* and *67*. The mean total NHS and PSS resource use costs during therapy are £15,492 for FCR and £9049 for FCM-miniR. Costs were significantly higher for FCR (+£6444; $p = 0.00$). In the 18 months following the therapy period, the difference in resource use costs between the two arms diminished, with a mean total cost of £1756 for FCR and £1570 for FCM-miniR ($p = 0.71$). There were no significant differences in NHS and PSS resource use costs between the treatment arms following the end of therapy according to the *t*-tests.

Health outcomes

Table 68 presents the EQ-5D scores at baseline, 3 months after therapy ended, and 12, 18 and 24 months post randomisation with missing values imputed. Both treatment groups showed increasing EQ-5D scores from baseline up to 3 months after the end of therapy, with a slight dip at 12 months and 18 months post randomisation in both arms before increasing again.

TABLE 66 Costs of resources used in relation to CLL by treatment arms (not imputed) during therapy

Cost type		FCR ($n = 92$), £	FCM-miniR ($n = 70$), £	Difference: p-value of t-test
Cycles 1–3 (medication and treatment)	Mean (SD)	6152 (1811)	2763 (901)	0.0000
Cycles 4–6 (medication and treatment)	Mean (SD)	5701 (2769)	2916 (1411)	0.0000
Health and social services use[a]	Mean (SD)	218 (448)	254 (417)	0.5779
Hospital-based care services	Mean (SD)	3421 (3989)	3116 (4261)	0.6198
Total	Mean (SD)	15,492 (6478)	9049 (5516)	0.0000

SD, standard deviation.
a These costs do not include the cost of the intervention.

TABLE 67 Costs of resources used in relation to CLL by treatment arms (not imputed) from end of therapy to 24 months

Cost type		FCR ($n = 92$), £	FCM-miniR ($n = 70$), £	Difference: p-value of t-test
Health and social services use[a]	Mean (SD)	269 (381)	265 (306)	0.5780
Hospital-based care services	Mean (SD)	1487 (2285)	1472 (4075)	0.9757
Total resource use	Mean (SD)	1756 (2402)	1570 (3720)	0.7133

a The costs do not include the cost of the intervention.

TABLE 68 European Quality of Life-5 Dimensions index scores at the baseline and follow-ups, and QALYs of CLL participants by treatment arm (imputed data)

Parameter		FCR ($n = 92$)	FCM-miniR ($n = 70$)	Difference: p-value of t-test
Baseline	Mean (SD)	0.829 (0.200)	0.774 (0.275)	0.169
	Median (min.–max.)	0.814 (–0.016–1.00)	0.812 (–0.0.16–1.00)	
3 months after end of therapy	Mean (SD)	0.852 (0.141)	0.868 (0.194)	0.546
	Median (min.–max.)	0.858 (0.378–1.00)	0.870 (–0.239–1.00)	
12 months post randomisation	Mean (SD)	0.838 (0.177)	0.863 (0.218)	0.434
	Median (min.–max.)	0.883 (0.189–1.00)	0.934 (–0.74–1.00)	
18 months post randomisation	Mean (SD)	0.833 (0.180)	0.851 (0.184)	0.517
	Median (min.–max.)	0.927 (0.145–1.00)	0.937 (–0.003–0.965)	
24 months post randomisation	Mean (SD)	0.852 (0.161)	0.871 (0.097)	0.383
	Median (min.–max.)	0.895 (–0.071–0.965)	0.876 (0.498–0.965)	
Total QALYs	Mean (SD)	1.610 (0.329)	1.552 (0.414)	0.316
	Median (min.–max.)	1.714 (0.418–2.00)	1.722 (0.049–1.974)	

Max., maximum; min., minimum; SD, standard deviation.

On average, the difference between arms was marginal. Independent sample *t*-tests indicated that the changes in EQ-5D score over time were not statistically significant. The average total QALYs gained over the 24 months was marginally higher in the FCR arm (1.61) than in the FCM-miniR arm (1.55) ($p = 0.40$).

Cost-effectiveness results within the NHS and Personal Social Services perspectives

Table 69 shows the total costs and EQ-5D-generated QALYs for each of the treatment arms. Differences in QALYs between groups were minimal and suggested marginal health decrements in the FCM-miniR arm compared with the FCR arm. The FCR group had the highest EQ-5D-generated QALYs over the trial period. The mean total cost was significantly higher for the FCR group. The high standard deviation (SD) for the deterministic cost estimates indicates the presence of a few outlying individuals who incurred significant health service costs.

Table 70 below provides the probabilistic cost-effectiveness results, showing the incremental costs and benefits as well as the ICER. The results suggest that FCM-miniR is associated with an incremental cost saving of £6619 and an incremental QALY loss of 0.059. Note that, owing to the fact that FCM-miniR is associated with both negative cost and QALY increments, the ICER result cannot be interpreted in the usual way as the cost per additional QALY associated with FCM-miniR; the ICER instead represents the cost saved per QALY lost. That is, if the NHS adopts FCM-miniR, it could expect to save £112,193 per QALY lost. As this cost saving outweighs the value of a lost QALY based on a WTP of £20,000 per QALY, the overall net benefit associated with FCM-miniR is positive (£5349) and FCM-miniR is therefore expected to be cost-effective over a 24-month time horizon.

The uncertainty around the cost-effectiveness estimate is represented graphically on the cost-effectiveness plane (*Figure 31*) using bootstrapping with 10,000 iterations. This method samples at random with replacement from each of the 10 imputed data sets, producing 10,000 incremental cost and incremental QALY estimates.

Figure 31 shows that all the points were below the *x*-axis, indicating that FCM-miniR is cost-saving compared with FCR, and most points were to the left of the *y*-axis, indicating that FCM-miniR produces fewer QALYs than FCR. The majority of points lie below the £20,000/QALY threshold line, indicating that FCM-miniR is cost-effective.

TABLE 69 Total costs and QALYs (EQ-5D) by treatment arm (NHS and PSS perspectives, deterministic)

Total costs and QALYs	FCR	FCM-miniR
n	92	70
Total QALYs (SD)	1.610 (0.329)	1.552 (0.412)
Total cost, £ (SD)	17,248 (7156)	10,619 (7312)

TABLE 70 Cost-effectiveness results (NHS and PSS perspectives, probabilistic)

Strategy	Total cost, £ (SD)	Total QALY (based on EQ-5D) (SD)	Incremental cost, £ (SD)	Incremental QALY (SD)	ICER, £	Incremental NB, £ (SD)
FCR	17,241 (745)	1.610 (0.04)				
FCM-miniR	10,622 (758)	1.551 (0.05)	–6619 (1061)	–0.059(0.06)	112,193[a]	5439 (1546)

a Pounds saved per QALY lost.

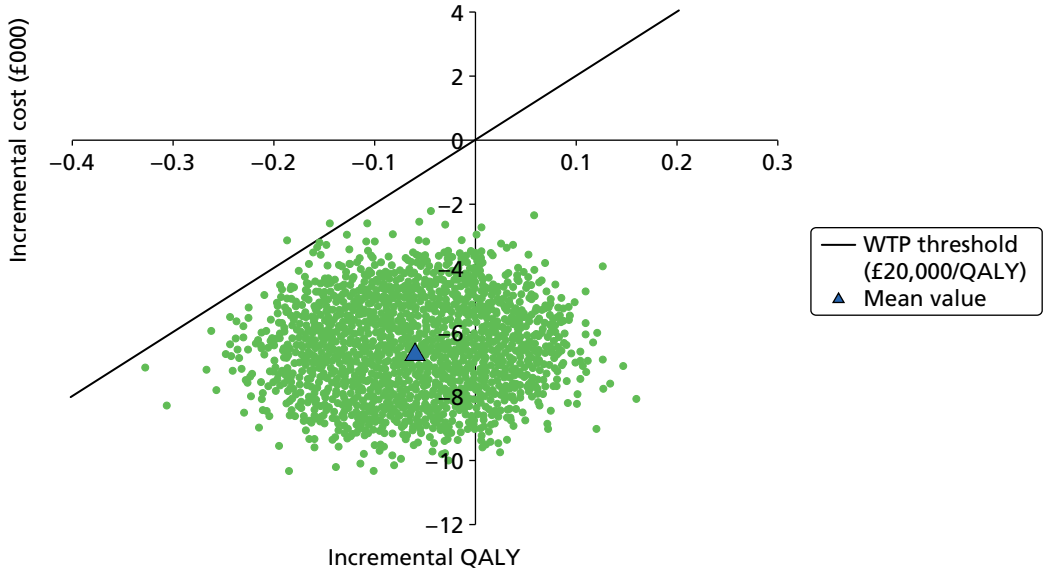

FIGURE 31 Cost-effectiveness plane showing the incremental costs and QALYs for FCM-miniR compared with FCR from the bootstrap analysis of the within-trial results over 24 months (EQ-5D, NHS and PSS perspectives).

The CEAC showing the probability that FCR is cost-effective is presented below in *Figure 32* with a range of cost-effectiveness WTP thresholds values. The probability that FCM-miniR is cost-effective is high and remains above 60% up to a threshold value of £100,000 per QALY.

Sensitivity analyses within trial in the NHS and Personal Social Services perspective

In order to test the robustness of the within-trial analysis a number of different cost-effectiveness analyses were completed.

Sensitivity analysis of health utility measurement

A similar cost-effectiveness analysis was completed using SF-6D-generated QALYs. When the equivalent SF-6D figures were analysed, a different pattern was observed. There was a decrease in mean SF-6D values between baseline and 3 months post randomisation, with fluctuations in either direction at the follow-up time points. The average total QALYs gained were slightly higher in the FCM-miniR arm (1.211) than the FCR arm (1.195) ($p = 0.81$), in contrast to the EQ-5D analysis in which FCR produced a higher overall QALY value. A statistically significant difference in the SF-6D utility values was observed at the 24 months post randomisation time point only (*Table 71*).

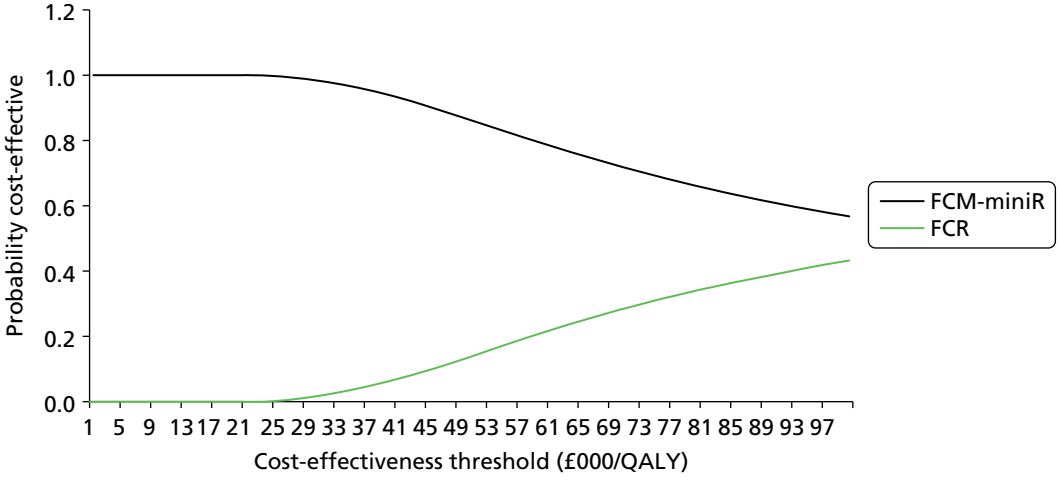

FIGURE 32 Cost-effectiveness acceptability curves at 12 months (NHS and PSS perspectives, using EQ-5D generated QALYs).

TABLE 71 Short Form questionnaire-6 Dimensions index scores at baseline and follow-ups, and QALYs of CLL participants by treatment arm (imputed data)

Parameter		FCR ($n = 92$)	FCM-miniR ($n = 89$)	Difference: p-value of t-test
Baseline	Mean (SD)	0.651 (0.290)	0.670 (0.269)	0.713
	Median (min.–max.)	0.723 (–0.01–1.00)	0.723 (–0.128–1.00)	
3 months after end of therapy	Mean (SD)	0.606 (0.261)	0.593 (0.242)	0.645
	Median (min.–max.)	0.6592 (–0.024–1.00)	0.634 (–0.074–1.00)	
12 months post randomisation	Mean (SD)	0.715 (0.238)	0.706 (0.237)	0.814
	Median (min.–max.)	0.770 (–0.127–1.00)	0.770 (–0.060–1.00)	
18 months post randomisation	Mean (SD)	0.670 (0.239)	0.722 (0.219)	0.157
	Median (min.–max.)	0.711 (–0.075–0.965)	0.777 (–0.071–0.965)	
24 months post randomisation	Mean (SD)	0.612 (0.289)	0.763 (0.170)	0.000[a]
	Median (min.–max.)	0.704 (–0.059–1.00)	0.808 (–0.014–0.965)	
Total QALYs	Mean (SD)	1.195 (0.414)	1.211 (0.412)	0.812
	Median (min.–max.)	1.242 (0.038–1.850)	1.305 (0.126–1.820)	

Max., maximum; min., minimum.
a Statistically significant at the 95% confidence level.

Table 72 below shows the total costs and SF-6D-generated QALYs for each of the treatment arms. FCM-miniR is associated with an incremental cost saving of £6492 and an incremental QALY gain of 0.016 compared with FCR; FCM-miniR therefore dominates FCR, being more effective and less costly, with a positive INB of £6805.

Using the NICE WTP threshold of £20,000, FCM-miniR is expected to be 100% cost-effective over a 24-month time horizon. This is illustrated in *Figure 33* by the fact that all of the simulated points in the probabilistic sensitivity analysis lie under the WTP threshold.

Impact of crossover participants

To assess the impact of removing the 21 participants who crossed over from the FCM-miniR arm to FCR in the base-case analysis, two further sensitivity analyses were conducted:

1. ITT, whereby any transfer of participants from one arm to another is ignored and participants who crossed over from FCM-miniR to FCR are retained in the analysis of the FCM-miniR arm
2. participants who were transferred are deemed to have been in the FCR treatment arm from randomisation.

The results of these analyses can be seen in *Table 73*. The results show consistency in the trend of costs and QALYs in both types of analyses (i.e. using EQ-5D- or SF-6D-generated QALYs).

TABLE 72 Cost-effectiveness results (NHS and PSS perspectives, deterministic)

Strategy	Total cost, £	Total QALY (based on SF-6D)	Incremental cost, £	Incremental QALY	ICER	INB, £
FCR	17,248	1.1949				
FCM-miniR	10,756	1.2105	–£6492	0.016	FCM-miniR dominates	6805

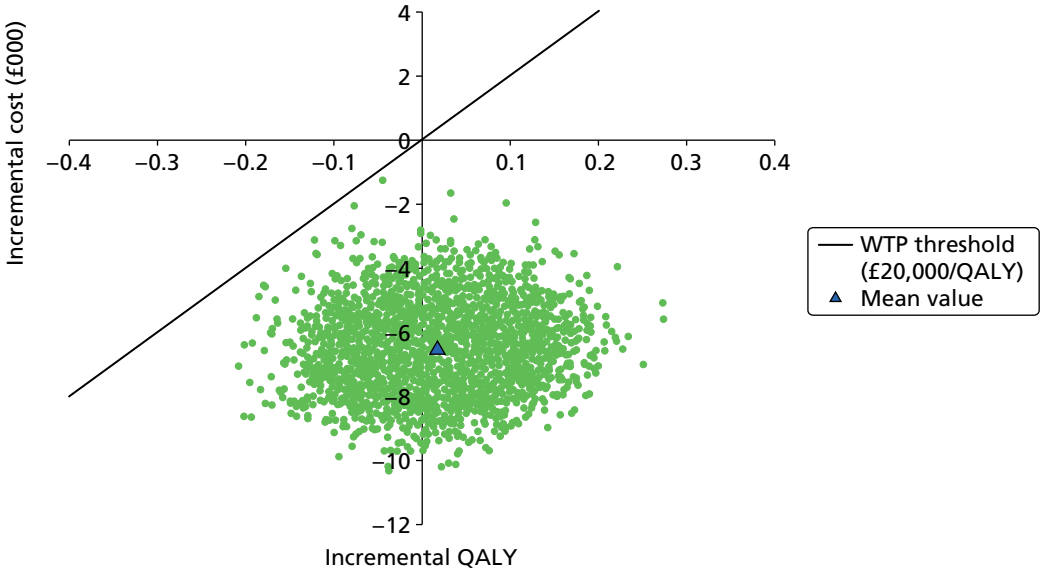

FIGURE 33 Cost-effectiveness plane generated from bootstrapped mean cost and SF-6D-generated QALY differences over 24 months (NHS and PSS perspectives).

TABLE 73 Analyses accounting for interim change

EQ-5D	Incremental cost, £	Incremental QALY gain	ICER, £	INB, £
Base case				
FCM-miniR vs. FCR	–6619	–0.0590	112,193[a]	5439
ITT				
FCM-miniR vs. FCR	–5761	–0.0467	123,298[a]	4826
Transferred from baseline				
FCM-miniR vs. FCR	–6000	–0.0523	114,657[a]	4954
SF-6D				
Base case				
FCM-miniR vs. FCR	–6456	0.0176	FCM-miniR dominates	6807
ITT				
FCM-miniR vs. FCR	–5674	0.0305	FCM-miniR dominates	6284
Transferred from baseline				
FCM-miniR vs. FCR	–6031	0.0138	FCM-miniR dominates	6308

a £ saved/QALY lost.

Summary of within-trial cost-effectiveness analysis

Using the EQ-5D to generate QALYs, the results showed that participants with CLL, treated in the FCM-miniR arm, did not show a higher QALY gain when compared with participants in the FCR arm (1.552 vs. 1.610). However, FCM-miniR presented negative incremental costs (£6443), indicating that treatment with FCM-miniR would lead to cost savings. This difference was driven by the higher cost of delivery of FCR, with cost differences stemming from treatment costs during the six cycles of chemotherapy.

Based on imputed data, the analysis found the incremental QALY gain to favour FCR, despite the difference being minimal at 0.059 (roughly equivalent to 21.5 days of full health). This result is robust to sensitivity analysis and stochastic bootstrapping.

However, using SF-6D to generate QALYs, the results showed that participants with CLL treated with FCM-miniR showed a slightly higher QALY gain than participants in the FCR arm (1.211 vs. 1.195). This gain, together with the incremental cost saving of £6805, suggests that FCM-miniR dominates FCR and is cost-effective at a £20,000 WTP threshold. Despite this difference in QALY findings between the two quality-of-life measures, FCM-miniR was found to be cost-effective in both analyses.

The within-trial analysis is conducted on data collected over a 24-month time period. The majority of CLL participants go on to live much longer than this; therefore, the within-trial analysis is unlikely to capture all of the relevant differences in long-term costs and health outcomes between the two participant groups. Hence, there is a need for decision model analysis to extrapolate these results to lifetime horizons.

Lifetime cost-effectiveness analysis

A de novo decision analytic model was developed to estimate the lifetime cost-effectiveness of FCM-miniR compared with FCR. The base-case analysis was conducted using QALYs derived from participant EQ-5D questionnaire responses in the trial, and it was assumed that any difference between the two treatments in terms of rate of disease progression was contained within the first 2 years from treatment initiation (i.e. within the trial period). The analysis was conducted from an NHS and PSS perspective and adhered to current NICE reference case standards.[27] For the base-case model, probabilistic analysis (using 10,000 Monte-Carlo simulations) was conducted in order to account for uncertainty around the model parameter input values. In addition, deterministic one-way sensitivity analyses were conducted to assess the influence of changes to individual model parameters and key model assumptions on the results. A value of information analysis was conducted to determine the potential value to the NHS of conducting additional research on the cost-effectiveness of FCM-miniR compared with FCR.

Base-case model results

Results of the base-case analyses are presented in *Table 74* (deterministic results) and *Table 75* (probabilistic results). Taking into account uncertainty around the model parameters (i.e. using the

TABLE 74 Deterministic model lifetime cost-effectiveness results

Strategy	Total cost, £	Total QALY	Incremental cost, £	Incremental QALY	ICER, £	Net benefit, £	Incremental net benefit, £
FCR	31,176	6.12				91,324	
FCM- miniR	23,468	5.46	–7708	–0.67	11,576[a]	85,715	–5609

a Pounds gained per QALY lost.

TABLE 75 Probabilistic model lifetime cost-effectiveness results

Strategy	Total cost, £ (SD)	Total QALY (SD)	Incremental cost, £ (SD)	Incremental QALY (SD)	ICER, £	Net benefit, £ (SD)	Incremental net benefit, £ (SD)
FCR	31,314 (7237)	7.76 (0.26)				123,917 (8447)	
FCM-miniR	23,590 (6997)	7.04 (0.36)	–7723 (3281)	–0.73 (0.42)	10,651[a]	117,137 (9449)	–6780 (7907)

a Pounds gained per QALY lost.

probabilistic results), FCM-miniR is associated with an expected lifetime cost saving of £7723 and a lifetime QALY loss of 0.73 compared with FCR; an incremental loss of over two-thirds of a healthy life-year. As the incremental cost and QALYs are both negative, the ICER does not represent the incremental cost per additional QALY, but rather represents the cost saved per QALY lost associated with adoption of FCM-miniR. The ICER therefore indicates that one QALY will be lost for every £10,624 saved by adopting FCM-miniR. As the amount saved is less than the societal WTP for a QALY (£20,000), the overall expected INB of FCM-miniR is negative. This indicates that adoption of FCM-miniR would lead to a lifetime loss of benefit for the NHS and PSS, and FCM-miniR is therefore not expected to be cost-effective. The expected lost net benefit associated with FCM-miniR is –£6780, which is equivalent to a net health loss of 0.34 QALYs (assuming that QALYs are valued at £20,000 per QALY). There is significant uncertainty around this result, as can be seen by the large SD value for the INB (SD = 7907).

The results of the probabilistic analysis are presented in *Figure 34*. Each point on the graph represents the result of one probabilistic simulation of the model and indicates a potential incremental cost and QALY for FCM-miniR compared with FCR. The diagonal line represents the currently accepted WTP per QALY threshold of £20,000 per QALY. Points that lie below the threshold line are considered cost-effective; points above the threshold line are not considered to be cost-effective. In this analysis, the points are widely distributed, with many points lying in both cost-effective and non-cost-effective regions. This indicates that there is significant uncertainty around the cost-effectiveness of FCM-miniR compared with FCR over a lifetime horizon. The mean of the simulated values lies above the threshold line, indicating that, on average, FCM-miniR is not expected to be cost-effective.

The CEAC shows the proportion of model simulation points that lie under the cost-effectiveness threshold plane across different threshold values, which indicates the probability that each treatment is cost-effective at given WTP values. The CEAC for FCM-miniR versus FCR is presented in *Figure 35*. At low cost per additional QALY thresholds, FCM-miniR is associated with a high probability of being cost-effective. However, as the threshold value increases the probability of FCM-miniR being cost-effective rapidly diminishes, and FCR is associated with an increasing probability of cost-effectiveness. At a threshold value of £20,000 per QALY, FCM-miniR is associated with 19% probability of being cost-effective; increasing the threshold value to £30,000 per QALY results in a drop to a 12% probability of being cost-effective.

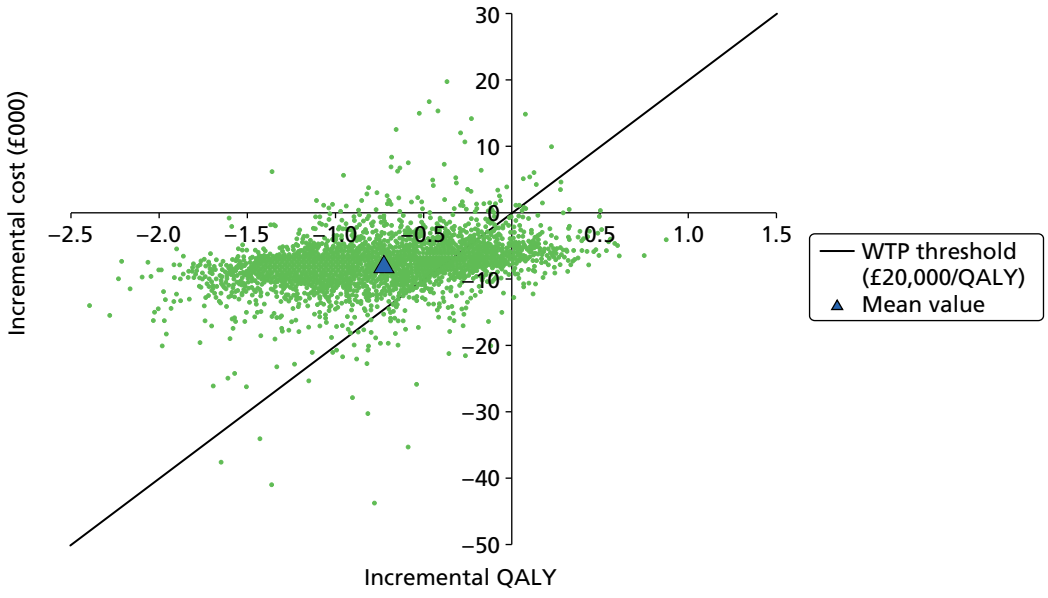

FIGURE 34 Scatterplot of model lifetime cost-effectiveness results for FCM-miniR vs. FCR.

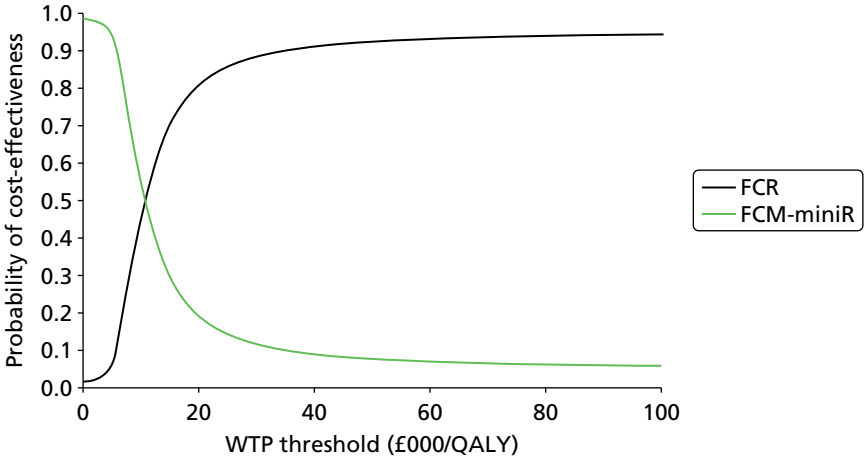

FIGURE 35 Cost-effectiveness acceptability curve for model lifetime analysis.

Sensitivity analyses

One-way deterministic sensitivity analysis

Results of the one-way deterministic sensitivity analysis are presented in *Figure 36*. The vertical line indicates the base-case deterministic INB value for FCM-miniR versus FCR (–£5609). The horizontal bars indicate the extent to which this base-case value is altered when individual model parameter values are increased or decreased by 25% of their base-case value. From the diagram it appears that altering the discount rate and utility of the progression-free state results in the greatest change to the cost-effectiveness result. However, FCM-miniR is associated with a negative INB in all of the analyses considered, indicating that FCM-miniR is

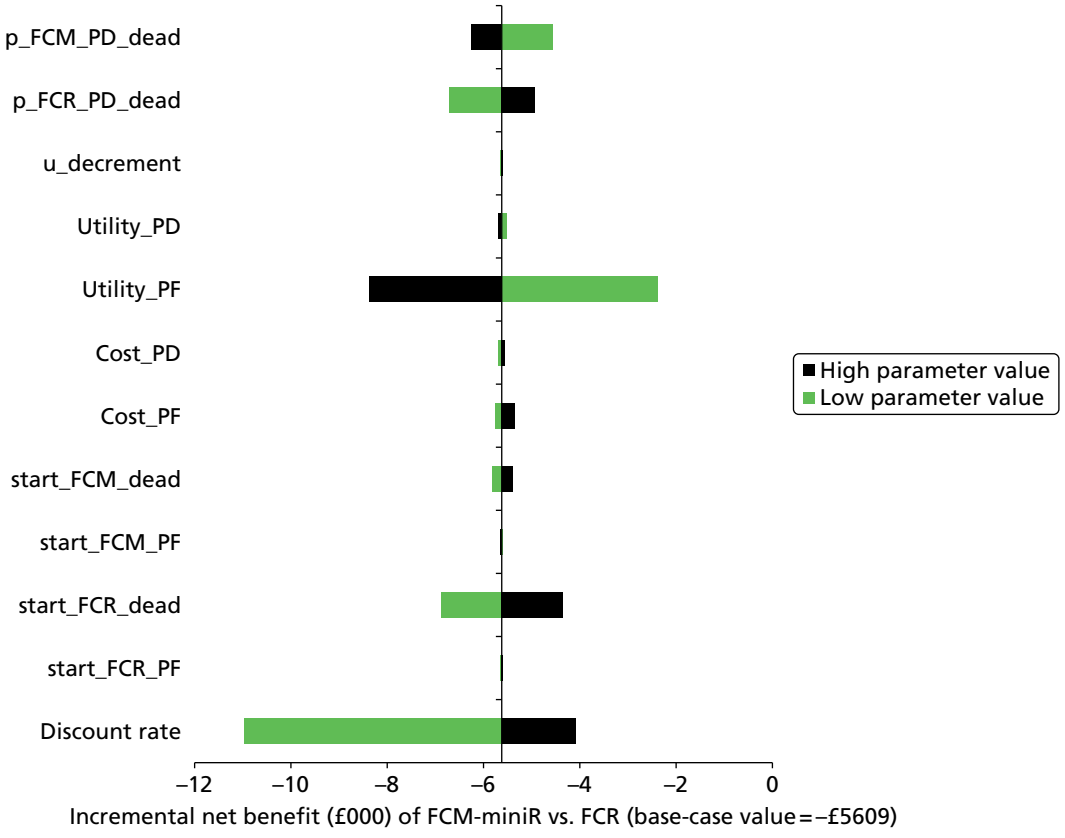

FIGURE 36 Tornado plot of one-way deterministic sensitivity analysis results.

not expected to be cost-effective in any of the analyses. Changes in the input parameters therefore have no effect on the overall result of the analysis.

Intention-to-treat analysis (including participants who crossed over from fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab to fludarabine, cyclophosphamide and mitoxantrone)

Results of the sensitivity analysis using the ITT population are shown in *Table 76*. Compared with the base-case analysis in which participants who crossed over from FCM-miniR to FCR were excluded from the analysis, the incremental cost saving associated with FCM-miniR compared with FCR is slightly reduced (–£7708 vs. –£6593), and the incremental QALY loss is reduced (–0.67 vs. –0.56). Nevertheless, FCM-miniR remains non-cost-effective, with a negative INB value (–£4591 compared with the base-case deterministic value of –£5609). This indicates that the exclusion of the participants who crossed over from FCM-miniR to FCM has no effect on the overall cost-effectiveness result.

Short Form questionnaire-6 Dimensions

Results of the sensitivity analysis using QALYs derived from participant-reported SF-12 forms (converted to SF-6D utilities) are shown in *Table 77*. As for the base-case analysis using EQ-5D-derived utilities, FCM-miniR is associated with a negative incremental cost and utility value, indicating that FCM-miniR is expected to be cost saving but less effective than FCR. Compared with the EQ-5D analysis, using SF-6D utilities leads to a smaller QALY loss associated with FCM-miniR (–0.55 compared with –0.67); however, this QALY decrement still outweighs the expected cost saving, resulting in a negative INB value. FCM-miniR is therefore still expected to be non-cost-effective over a lifetime horizon, as in the base-case analysis.

Treatment effect

Results of the sensitivity analysis extending the differential rates of progression observed between FCR and FCM-miniR in the trial beyond the trial period are shown in *Table 78*. Owing to the fact that in the trial period participants in the FCR arm progressed at a slower rate than participants in the FCM-miniR arm, extending this effect beyond the trial period by applying the observed HR in the trial benefits the FCR arm. The expected net benefit associated with FCM-miniR therefore decreases as the HR is applied over longer time periods, with FCM-miniR becoming increasingly non-cost-effective as the treatment effect is extended. The expected INB falls from –£5609 in the base case to –£9750 when the differential rates of progression are applied over a lifetime horizon. FCM-miniR therefore remains non-cost-effective across all the analyses.

TABLE 76 Model sensitivity analysis using ITT population

Strategy	Total cost, £	Total QALY	Incremental cost, £	Incremental QALY	ICER, £	NB, £	Incremental NB, £
FCR	30,741	7.63				121,924	
FCM-miniR	24,148	7.07	–6593	–0.56	11,790[a]	117,333	–4591

a Pounds gained per QALY lost.

TABLE 77 Model sensitivity analysis using QALYs derived from the SF-12 form

Strategy	Total cost, £	Total QALY	Incremental cost, £	Incremental QALY	ICER, £	NB, £	Incremental NB, £
FCR	31,437	6.41				96,678	
FCM-miniR	23,842	5.85	–7595	–0.55	13,721[a]	93,203	–3475

a Pounds gained per QALY lost.

TABLE 78 Sensitivity analysis extending observed differential rate of progression in trial over different time horizons (deterministic results)

Outcome	Base case (differential effect in 2-year trial period)	3-year time horizon (HR applied up to year 3)	5-year time horizon	10-year time horizon	Lifetime time horizon
Incremental cost, £	–7708	–7717	–7720	–7716	–7705
Incremental QALY	–0.67	–0.76	–0.84	–0.86	–0.87
FCR-miniR incremental NB, £	–5609	–7549	–9198	–9520	–9750

Value of information analysis

Results of the population EVPI analysis are shown in *Figure 37*. The EVPI value represents the absolute maximum that the NHS should be willing to spend on further research on the cost-effectiveness of FCM-miniR versus FCR. At a £20,000 per QALY threshold, and assuming a 10-year effective time horizon for the new treatment, the expected value of information is £21M. The maximum EVPI value (£43M) is reached at a £10,600/QALY threshold value (equivalent to the ICER value for FCM-miniR), as this is the point at which uncertainty around parameter estimates in the model has the greatest influence on the decision of whether or not to adopt the new treatment.

Results of the EVPPI analysis are shown in *Figure 38*. Uncertainty around the starting distributions of the model (i.e. the proportion of participants who begin the model with progressed disease as opposed to being disease free) is found to be the most influential factor, with the associated EVPPI values for these parameters being substantial. These parameters are directly related to the efficacy of each of the treatments in terms of delaying disease progression, so it is unsurprising that these have a large impact on the model results.

The value of information results suggest that there is the potential for further research into the cost-effectiveness of FCM-miniR compared with FCR to be of value to the NHS. However, the EVPI and EVPPI values provide only a necessary (but not sufficient) condition for the decision to fund further research (i.e. a positive EVPI/EVPPI value indicates that there may be value in conducting further research). The decision of whether or not to invest in further research and what design that research should take requires further analysis of the cost of research and the value of particular trial designs.

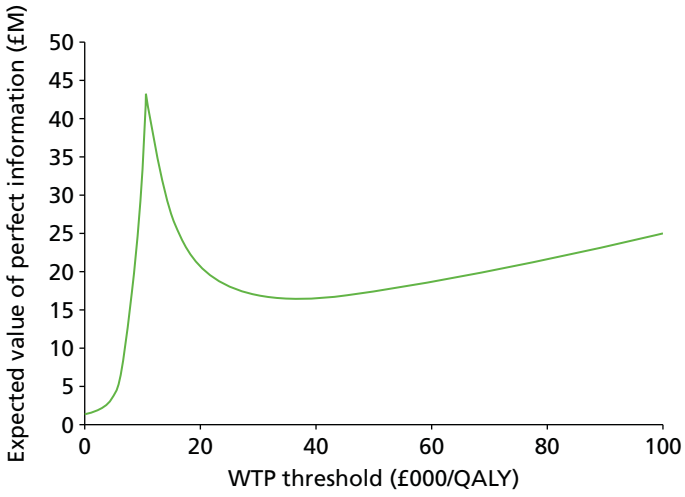

FIGURE 37 Population EVPI.

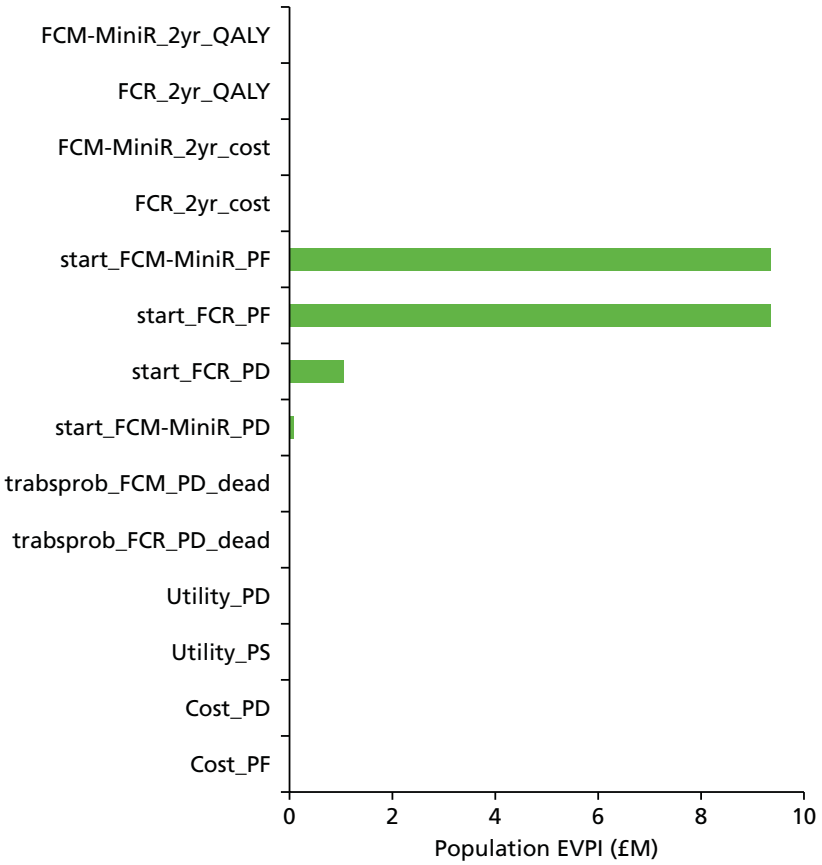

FIGURE 38 Population EVPPI for base-case model (£20,000/QALY threshold, 10-year effective lifetime and annual incidence of 2943).

Predicted overall survival

The predicted OS curves simulated by the base-case model are presented in *Figure 39*. The difference in OS between the two arms is greatest at the beginning of the model simulation; this is attributable to the fact that the model begins from the end of the trial 24-month period, and the proportion of participants surviving in each arm was taken directly from the trial follow-up data which showed the given discrepancy between the two arms. Subsequently in the model, however, it is assumed that the risk of mortality in both the progression-free and progressed disease states is the same in both arms. In the future, validation of the model could be achieved by comparing the predicted OS with real-world data; currently these data are unavailable and we therefore show the OS curves for illustrative purposes only.

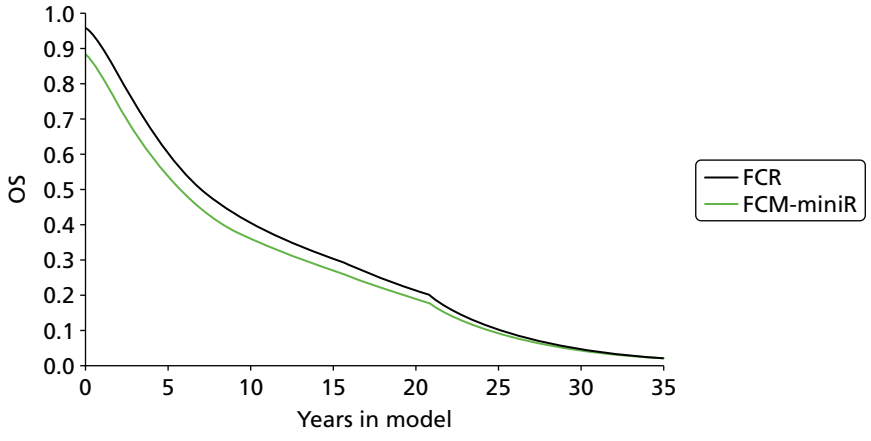

FIGURE 39 Overall survival curves simulated from the lifetime decision analytic model.

Summary of decision model lifetime cost-effectiveness analysis

The results of the decision analytic model indicate that FCM-miniR is not expected to be cost-effective over a lifetime horizon. Compared with FCR, FCM-miniR is associated with an average lifetime cost saving of £7723 per patient, and a lifetime QALY loss of 0.73. The resulting expected INB associated with FCM-miniR is –£6780 (equivalent to a net health loss of –0.34 QALYs), indicating that if FCM-miniR were to be adopted instead of FCR the NHS would be worse off as a whole.

Results of the deterministic sensitivity analyses found that the results were robust to changes in individual model parameters, with FCM-miniR remaining non-cost-effective in all of the analyses conducted. However, when joint parameter uncertainty is considered (using probabilistic sensitivity analysis), there is some uncertainty around the results: at a £20,000 per QALY threshold, there is a 19% chance that FCM-miniR is cost-effective. The expected value of information analysis indicates that there is potential benefit to conducting further research into the cost-effectiveness of FCM-miniR; however, additional considerations (such as the cost of research and specific research design) would need to be considered before a definitive recommendation for further research could be made.

Summary of the economic evaluation

An economic evaluation was conducted to assess the cost-effectiveness of FCM-miniR compared with FCR from a UK NHS and PSS perspective. The evaluation consisted of two components: a within-trial analysis, in which cost-effectiveness was assessed within the 24-month trial period using individual participant data collected in the trial; and a decision analytic model analysis, in which cost-effectiveness was assessed over a lifetime horizon using standard modelling techniques to extrapolate the trial analysis to a lifetime horizon.

The results of the within-trial analysis indicate that FCM-miniR is cost-effective compared with FCR over a 24-month time horizon, although it should be noted that cost-effectiveness in this instance is achieved only by virtue of the fact that the cost savings associated with FCM-miniR in the short term outweigh the associated QALY losses. In the base-case analysis, FCM-miniR was associated with a mean cost saving of £6619 and a mean QALY loss of –0.059 compared with FCR. The corresponding ICER was £112,193, indicating that for every £112,193 saved by adopting FCM-miniR, one QALY would be lost. Assuming that one QALY is valued at £20,000 (the threshold currently adopted by NICE), FCM-miniR is therefore associated with a positive INB of £5439, indicating that it is cost-effective compared with FCR. In a sensitivity analysis using SF-6D QALYs derived from the SF-12 questionnaire (instead of EQ-5D as in the base case), FCM-miniR was estimated to result in an overall QALY increase (+0.016) compared with FCR, resulting in FCM-miniR dominating FCR (being more effective and less costly). Altering the analysis to include participants who crossed over from FCM-miniR to FCR had minimal effect on the results. The base-case probabilistic analysis found that at a £20,000 per QALY threshold, there is a 100% probability that FCM-miniR is cost-effective compared with FCR over a 24-month time horizon.

However, the cost-effectiveness of FCM-miniR was not sustained in the long-term analysis. Results of the economic decision model indicate that FCM-miniR is not expected to be cost-effective over a lifetime horizon. The base-case analysis indicates that over a lifetime horizon FCM-miniR is expected to result in a mean cost saving of £7723 and a mean QALY loss of 0.73 QALYs. The associated ICER is £10,651, indicating that, for every £10,651 saved by adopting FCM-miniR, one QALY would be lost. In contrast to the within-trial analysis, the cost saving associated with FCM-miniR is no longer sufficient to outweigh the QALY loss, and FCM-miniR is no longer cost-effective, with an incremental net loss of –£6780. However, lack of available data regarding long-term outcomes means that there is uncertainty around this result; at a £20,000 per QALY threshold there is a 19% chance that FCM-miniR is cost-effective. Owing to this uncertainty, the value of information analysis found that there is potential value in conducting further research on the cost-effectiveness of FCM-miniR. Nevertheless, the cost of further research and the likely value of specific research designs would need to be considered before making a definitive recommendation regarding the value of further research.

Chapter 5 Discussion

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Interpretation

The ARCTIC trial demonstrated that the combination of FCM-miniR was not non-inferior to FCR for the primary end point of CR. However, the CR rates observed in the trial were very high compared with previous studies involving FCR in both Europe[4,5] and the USA.[2,3] It appears that the addition of mitoxantrone to the regime created more toxicity, limiting the dose and/or duration of therapy compared with the FCR arm. There is no sign that low-dose rituximab is as effective as the full dose when given with chemoimmunotherapy. The trial also confirmed that patients who respond well, achieving either a CR and/or the eradication of detectable MRD, have a better outcome than those with worse responses.

The ARCTIC trial protocolised the use of haematopoietic growth factors, namely GCSF, to support the blood counts if they were low and delaying further courses of therapy. It appears that this planned use of GCSF as secondary prophylaxis (given only to patients whose neutropenia was delaying subsequent cycles of treatment) allows more patients to complete their planned therapy and that this leads to a similar outcome when compared with those patients who do not require GCSF.

The reason for the very high response rates and the favourable PFS and OS in ARCTIC is unclear. The reasons for this, compared with international trials with similar entry criteria, are probably multifactorial, and there are at least five possible factors that could account for this: (1) FC were given by the oral route in ARCTIC rather than intravenously as in previous studies; (2) the exposure for each cycle of treatment was 5 days rather than the 3 days over which FCR is given intravenously – this might be important as when alkylating agents are used alone they appear to be more effective when given over a few days; (3) patients in ARCTIC received primary prophylaxis against PCP with co-trimoxazole or equivalent and aciclovir prophylaxis to prevent herpes zoster virus reactivation; (4) the use of GCSF as secondary prophylaxis allowed the optimisation of therapy in patients who were struggling to complete the full six cycles of treatment; (5) the centres in the UK that recruited patients are generally large cancer centres and the patients are cared for by haematologists rather than by small community practices.

The ARCTIC trial confirmed some important factors regarding the outcome of therapy in CLL. In particular, patients who achieved a CR had a better outcome, with 93.4% of CR patients being progression-free at 24 months, compared with 65.4% of patients who did not achieve a CR. In addition, patients who achieved the eradication of detectable MRD from their bone marrow 3 months after completing therapy had a 96.4% probability of being progression-free after 24 months, compared with 79.2% for patients not achieving a MRD-negative response. A somewhat surprising finding was that the PFS was similar for patients aged over 65 years and those under 65 years of age, suggesting that the selection of patients for therapy by fitness rather than age is effective. This justifies the selection of patients for FCR and the inclusion of certain groups of patients such as those with renal dysfunction, who also fared reasonably well in ARCTIC and who in most previous series have been excluded from FCR-like therapies. In comparison with historical series of FC given prior to the advent of rituximab, it does appear that the addition of low-dose rituximab to FC with mitoxantrone (FCM-miniR) is better than FC in terms of response and PFS, although it is inferior to FCR. This indicates that low-dose rituximab is clinically active but probably less so than the full conventional dose.

Economic evaluation discussion

In both the within-trial and the decision model analyses, FCM-miniR was found to be associated with negative incremental costs and benefits compared with FCR. Care needs to be taken when interpreting the results of both analyses, given that ICERs have a different meaning when both cost and benefit increments are negative. Typically, a new intervention is found to be more expensive and more effective than the standard-care treatment (with results of probabilistic analyses lying in the north-east quadrant of the cost-effectiveness plane). In such cases, the ICER represents the additional cost required to be spent on the new treatment in order to gain an additional QALY compared with the standard-care treatment. However, in the case of new treatment that is less costly and less effective than the comparator treatment (with results of probabilistic analyses lying in the south-west quadrant of the cost-effectiveness plane), the ICER instead represents the incremental cost saved per QALY lost compared with the standard-care treatment. For example, in the economic analysis FCM-miniR is associated with an ICER of £10,651, indicating that for every £10,651 saved by adopting FCM-miniR, one QALY will be lost compared with FCR. Assuming a WTP of £20,000 per QALY, this means that FCM-miniR is not cost-effective, which may not be immediately clear from the ICER result. For this reason, it is preferable to look at the INB results rather than the ICERs, as interpretation of net benefit results does not depend on the direction of the incremental cost and QALYs. If the INB associated with a new treatment is positive, then that treatment is cost-effective, whereas if it is negative the treatment is not cost-effective. Thus, for the case of the decision model analysis, FCM-miniR is associated with an INB of –£6780, indicating that FCM-miniR is not cost-effective over a lifetime horizon.

Treatments that are both cost- and QALY-decreasing can still be cost-effective because the cost saved can be spent on treatments or interventions elsewhere in the NHS in order to gain additional QALYs, which may outweigh the QALY loss associated with the given intervention. That is, the overall INB of the new treatment compared with the standard-care treatment may be positive (indicating cost-effectiveness) if the cost saving associated with the new treatment is sufficient to outweigh the QALY loss. In the case of the within-trial analysis, FCM-miniR was associated with a mean cost saving of £6619 and a mean QALY loss of –0.056. In this case, the cost saved outweighs the QALYs lost, resulting in a positive INB. However, for the decision model analysis, the cost saving associated with FCM-miniR (£7723) was unable to outweigh the QALY loss (–0.73), resulting in a negative INB (i.e. $-0.735 \times 20{,}000 + 7723 = -£6780$; equivalent to a net health loss of $-0.735 + 7723/20{,}000 = -0.34$ QALYs).

The discrepancy in the short- and long-term cost-effectiveness analyses results (i.e. the fact that FCM-miniR is found to be cost-effective in the within-trial analysis but not in the model lifetime analysis) is attributable to the fact that all cost-savings associated with FCM-miniR occur in the short term (i.e. when therapy costs are incurred). In the model it is assumed that costs in the progression-free and progressed disease states are the same for both treatments, so the benefit of FCM-miniR in terms of reducing treatment costs is contained in the initial trial 24-month period of the model. Over the lifetime analysis, the cost savings associated with FCM-miniR are, therefore, diluted and are no longer sufficient to outweigh the QALY losses associated with the new treatment.

For the within-trial analysis, the results of QALY calculations were not consistent across health utility measures. The base-case EQ-5D analysis found FCM-miniR to be inferior to FCR in terms of QALY production (resulting in a –0.059 QALY decrement), whereas the SF-6D analysis found FCM-miniR to be superior to FCR (resulting in a +0.016 QALY increment). The reason for this discrepancy is unclear. The SF-12 questionnaire used to derive the SF-6D QALYs asks more detailed questions regarding patients' emotional states, and *t*-test results showed significant differences using SF-6D at 24 months post randomisation, whereas no significant differences between arms were shown using EQ-5D. This could suggest that the SF-12 form is more sensitive to changes in health states for this population. Nevertheless, despite the difference in expected QALY values between the EQ-5D and SF-6D analyses, both analyses indicate that FCM-miniR is associated with a positive INB value and therefore represents a cost-effective investment for the NHS. Overall, there is some uncertainty around the model results (see *Generalisability*) which will not have been captured in the deterministic or probabilistic sensitivity analyses. It is unclear in

which direction this uncertainty is likely to impact on the results; therefore, some caution should be maintained when drawing conclusions from the model results.

Summary

In summary, we have shown that FCM-miniR does not have a non-inferior CR rate compared with FCR for the frontline therapy of CLL and that, over the lifetime of the patients, FCM-miniR was not found to be cost-effective compared with FCR. Therefore, there is no evidence against FCR remaining the gold-standard treatment for patients with CLL who require therapy and are considered fit for fludarabine-based combinations.

Generalisability

The ARCTIC trial was a randomised Phase IIB rather than a Phase III trial, but it was large and well-powered to show non-inferiority in terms of CR rates. The primary end point CR is associated with outcome in many other studies and was rigorously assessed by three independent assessors who were blinded to the treatment that patients received. In addition, the secondary end points, such as the eradication of MRD, are supportive, which is strongly associated with outcome; and the follow-up of the study, with a median of 35.6 months since randomisation, is mature enough to allow some interpretation of both PFS and OS. The efficacy outcome was consistent across the primary and secondary end points, which validates the conclusions of the trial.

In terms of the health economic assessment, there are some limitations to the analysis. The decision analytic model has several important limitations that should be considered when interpreting the results. These are highlighted below:

(a) The model structure is unlikely to be sufficiently detailed to capture all the relevant differences between the two treatments in terms of costs and benefits. In particular, the progression-free state aggregates information on several distinct disease stages that each treatment may impact differently on and, once in the progressed disease state, patients were not permitted to return to the progression-free state, as does occur temporarily in practice.
(b) The rate of progression in each arm for a given time point was set to the value given by the calibrated RDM model; each value in time was therefore fixed and this variable was not included in the probabilistic analysis or in the value of information analysis. The results are, therefore, likely to underestimate the uncertainty around the cost-effectiveness results and the associated value of additional information to resolve that uncertainty.
(c) The cost and utility values for the progressed disease state are unlikely to be accurate estimates. Owing to a lack of available data, the cost and utility values for the progressed disease state were sourced from the literature; although care was taken to identify the most relevant estimates available, these values are still unlikely to reflect accurately the true cost of progressed disease for CLL patients. In addition, it may be that the cost of progressed disease is not the same across the two arms; however, without any evidence to the contrary the cost of progressed disease was assumed equivalent.

In addition for the within-trial analysis, previous 3-month costs at baseline would have allowed for adjustment in case of higher (or lower) initial costs for patients at the beginning of the study; however, these costs were not collected and were instead assumed to be equivalent between arms.

The question of the value of adding mitoxantrone to FCR has been answered clearly. It also appears that the question of whether lower doses of rituximab are as effective has been answered, although one of the limitations of the trial is that the toxicity of adding mitoxantrone could have confounded the interpretation of the low-dose rituximab question.

A real strength of ARCTIC is that it is the first randomised trial in which FC were given orally in the FCR combination. This has demonstrated that the outcomes for oral FCR appear to be superior to the historical control series where all the drugs were given intravenously.

The patients recruited into ARCTIC were entered at 34 centres throughout the UK. Given the large number of patients recruited and the geographical distribution of the patients, the trial population is very similar to fit patients in the UK generally, and thus the outcome of the trial is generalisable to the whole UK CLL patient population.

We have managed to address the key questions without the need for a larger Phase III trial. A weakness of the trial is that over the past few years, since the design of the trial, there has been an extremely rapid increase in the number of therapies for CLL and this has meant that the interest in chemoimmunotherapy, such as FCR, has weakened in favour of the novel targeted treatments.

Overall evidence

In summary, the ARCTIC trial showed that the combination of FCM-miniR was not non-inferior to FCR and, in fact, that FCM-miniR was significantly inferior in terms of CR. Even though FCM-miniR was less expensive, it was not cost-effective in the long term to use FCM-miniR rather than FCR. Therefore, there is no evidence against FCR remaining the gold-standard therapy for CLL in patients considered fit for fludarabine-based therapy.

Chapter 6 Conclusions

Implications for health care

- There is no evidence against FCR remaining the gold-standard therapy for CLL.
- Oral FC and intense supportive care (primary antibiotic prophylaxis, secondary GCSF support, etc.) optimise the delivery of FCR-like therapies.
- Improved responses (both CR and MRD negativity) are associated with better outcomes, justifying the planned use of MRD negativity by the European Medicines Agency as a surrogate end point for drug approval in CLL.
- In countries in which the cost of 'conventional' dose rituximab is prohibitive, it appears that low-dose rituximab (100 mg per cycle) is active and may be worth testing further.

Recommendations for research

Fludarabine, cyclophosphamide and rituximab remains the gold-standard therapy for frontline CLL and should be used as the 'standard' arm in subsequent trials. It is acceptable, maybe even advisable, to allow the use of oral FC in future trials. The surrogate end point of the eradication of MRD is a good prognostic marker for PFS and therefore acceptable in future Phase II CLL trials.

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Anna Chalmers (Head of Trial Management, Leeds Institute for Clinical Trials Research at the University of Leeds) oversaw and co-ordinated the running of the trial, acquisition of data, trial monitoring, safety reporting and GCP requirements.

Dena Howard and **Peter Hillmen** (Consultant Haematologist, Leeds Institute of Cancer and Pathology at the University of Leeds), along with **Walter M Gregory** (Professor of Statistical Methodology in Clinical Trials and Cancer Division Director, Leeds Institute for Clinical Trials Research at the University of Leeds), designed the randomised controlled trial and were involved in obtaining funding.

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The ARCTIC trial was conceived by **Peter Hillmen**, who had overall responsibility for the trial.

Publications

Hillmen P, Milligan D, Schuh A, McParland L, Chalmers A, Munir T, *et al.* Results of the randomised phase II NCRI ARCTIC (Attenuated dose Rituximab with ChemoTherapy In CLL) trial of low dose rituximab in previously untreated CLL). Presented at the 55th ASH Annual Meeting and Exposition, New Orleans, LA, December 2013.

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Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Serious adverse event listings

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Blood and lymphatic system disorders	N00014/ 00028/002	Neutropenia	UK	67	Male	Neutropenia	Required/prolonged hospitalisation
FCR	Blood and lymphatic system disorders	N00076/ 00187/001	Platelet count decreased	UK	65	Male	Platelets already low prior to starting treatment on trial (Professor Hillmen aware) but further decrease has prompted a halt to chemotherapy. Also halved owing to Coombs-negative haemolytic anaemia. F-Up 30 September 14 ?ITP ?chemotherapy-induced hypoplasia continues to be observed	Jeopardised patient/required intervention to prevent one of the above
FCR	Blood and lymphatic system disorders	N00080/ 00032/001	Infection	UK	55	Male	Anaemic and very tired and nauseated, poor oral intake. Admitted for 3-unit blood transfusion and i.v. antiemetics and fluids. Hb post 3 units of blood = 8; 1 day later Hb was 7.9. Follow-up report: prolonged hospital admission to ITU. Recurrent sepsis requiring ionotropes and invasive ventilation. Followed by fungal liver abscess; died despite appropriate fungal treatment	Required/prolonged hospitalisation/patient died/ life-threatening/persistent or significant disability/incapacity
FCR	Blood and lymphatic system disorders	N00098/ 00017/001	Extremely low Hb	UK	50	Female	Came for end-of-therapy visit at day 23 of cycle 6. Looked extremely pale, slightly yellow, felt faint with effort of walking. Breathless, BP 98/P134. Hb found to be 3.9 g/dl. Results awaited	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above
FCR	Blood and lymphatic system disorders	N00098/ 00017/002	Low Hb: 5.9 g/dl on Pentra	UK	50	Female	Pale, breathless on exertion, Hb of 7.5 g/dl on main lab. Plan: to transpose 3 units of blood	Required/prolonged hospitalisation
FCR	Blood and lymphatic system disorders	N00114/ 00088/001	Persistent neutropenia related to chemotherapy	UK	72	Male	Patient has had five cycles. He has had persistent neutropenia. Upon discussion with Chief Investigator, final course to be omitted. D/W Professor Hillmen 1 November 2011 decision to stop treatment	Jeopardised patient/required intervention to prevent one of the above

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Blood and lymphatic system disorders	N00175/ 00155/001	Anaemia	UK	61	Female	Admitted for a planned hospital visit for a 4-unit blood transfusion. Additional information: not reported at time of event as only admitted to ward; no day case space available	Required/prolonged hospitalisation
FCR	Blood and lymphatic system disorders	N00230/ 00033/002	Myelodysplasia: RAES	UK	61	Female	Anaemia and thrombocytopenia	Persistent or significant disability/incapacity/ jeopardised patient/required intervention to prevent one of the above
FCR	Gastrointestinal disorders	N00050/ 00120/001	Diarrhoea and vomiting	UK	65	Male	Admitted with diarrhoea and vomiting. Plan for patient to stay overnight. Outcome not known yet	Required/prolonged hospitalisation
FCR	Gastrointestinal disorders	N00098/ 00060/002	Nausea and vomiting	UK	52	Male	Admitted with nausea and vomiting post chemotherapy	Required/prolonged hospitalisation
FCR	Gastrointestinal disorders	N00114/ 00088/003	Gastroenteritis	UK	72	Male	Diarrhoea and vomiting, abdominal pain. Stool isolated *C. diff* (non-toxin variety). Discharged 2 April 2012	Required/prolonged hospitalisation
FCR	Gastrointestinal disorders	N00349/ 00035/001	Nausea	UK	66	Female	Presented with uncontrolled nausea. Reduced intake of oral fluids and difficulty taking oral medication. Follow-up report: discharged from hospital 17 March 2011	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00014/ 00028/004	Infection/anaemia	UK	67	Male	General weakness, lethargy, headache, sweating, sore throat, cough (expectorating). Follow-up report: confirmed swine flu on 7 January 2011	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00014/ 00028/005	Anaemia grade 4	UK	67	Male	General weakness/fatigue, lethargy, anaemia, cough (expectoration). Follow-up report – Hb of 4.6. Discharged 10 February 2011 with Hb of 10.8 g/dl (grade 1)	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00014/ 00029/001	Rigors	UK	53	Female	High temperature and shaking	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	General disorders and administration site conditions	N00098/ 00019/001	Pyrexial 38.2 post first dose of rituximab	UK	67	Male	Reacted to rituximab with vomiting and cold sweat. Given hydrocortisone, piriton and ondansetron. Recovered. One infusion finished, vomited again and had rigor. Settled again but then spiked temperature of 38.2 °C and was admitted for observation, i.v. fluids, i.v. antibiotics. Note: this was day 1, cycle 1 of split rituximab. This was day 1, cycle 1 for the patient, who is having first dose of rituximab split over 2 days (has commenced second rituximab day today). Therefore received on 100 mg rituximab	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00114/ 00055/001	Fever and rigors	UK	65	Male	Fever, increased CRP, probable delayed rituximab reaction, no evidence of sepsis. Chest radiograph normal, urine microbiology negative. Follow-up report: admitted to hospital 13 January 2011, treated with prophylactic i.v. antibiotics and i.v. hydrocortisone. Discharged: 18 January 2011	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00173/ 00011/001	Hypoxia	UK	72	Female	Developed breathlessness 15 April 2010 during rituximab infusion. Symptoms improved with oxygen therapy. Oxygen saturations are 84% on room air. Awaiting V/Q scan and chest radiography ?Chest infection ?Pulmonary embolism. CTPA 21 April 2010 showed no evidence of pulmonary	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00173/ 00137/001	Vomiting	UK	59	Female	Post chemotherapy nausea and vomiting requiring admission for antiemetics and i.v. fluids	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00218/ 00168/001	Fever and non-specifically unwell	UK	63	Male	See above: admitted for antibiotics and assessment, no evidence of TLS. Dramatic reduction in WBC? All chemotherapy-related – probably	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	General disorders and administration site conditions	N00319/ 00125/001	Allergic reaction	UK	61	Female	Pyrexia. Rigor. Hypotension	Required/prolonged hospitalisation
FCR	General disorders and administration site conditions	N00391/ 00194/002	Probable rituximab reaction	UK	74	Male	Emergency admission with fever, cough and vomiting one day after chemotherapy on 9 January 2013. (See attached discharge summary.) Required emergency medical admission with fever, cough and vomiting. Had similar episode following fourth cycle of chemotherapy on 13 December 2012 and treatment was terminated at that time. On this occasion, received pre-medication with hydrocortisone, piriton and paracetamol prior to receiving rituximab and commencing oral FC. On admission looked reasonably well with a good colour and well perfused. Temperature 39.4 °C. Pulse 106 per minute. BP 119/60. Respiratory rate 20 per minute. Saturations 93% breathing room air. Had no lymphadenopathy. Heart sounds were normal and there were a few crackles at both lung bases. The abdomen was soft and non-tender and no organs or masses felt. Hb 12.7 g/dl, WBC 4.9 × 109/l, platelets 163 × 109/l. CRP < 5 mg/l, lactate 2.6 mmol/l, routine biochemistry otherwise normal. Chest radiograph from 9 January 2013 was thought to be clear but the clinical report has suggested minor patchy change around the upper pole of the right hilum possibly representing early infection. Blood culture was negative. Was treated as according to sepsis six protocol with i.v. fluids and antibiotics consisting of Co-Amoxiclav	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
							and Clarithromycin. Developed hypotension and SIRS score increased from 1 to 2. With i.v. fluids blood pressure recovered and SIRS score fell to 0. Was well enough to be discharged home on the following medication: Aciclovir 400 mgs twice daily, paracetamol 1 g as required. Chemotherapy was discontinued. We have decided to avoid any further rituximab in the future. We plan one further final course of chemotherapy with oral FC plus oral Mesna to protect against possible chemotherapy-induced cystitis. Remains on Pentamidine inhalations on a monthly basis as prophylaxis against PCP and this will continue for up to 6 months after last dose of fludarabine	
FCR	Infections and infestations	N00014/00028/003	Febrile neutropenia	UK	67	Male	Neutropenia grade 4, pyrexia 38 °C	Required/prolonged hospitalisation
FCR	Infections and infestations	N00014/00112/001	Shingles	UK	62	Male	Itchy painful rash	Required/prolonged hospitalisation
FCR	Infections and infestations	N00040/00056/001	Neutropenic sepsis	UK	59	Male	Admitted 22 February 2011. Neutrophils 0.09 10/l on 24 February 2011. Discharged 28 February 2011; neutrophils 1.10 10/l	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00046/ 00185/001	Infection with grade 4 neutrophils	UK	63	Male	Pyrexial with cough and signs of infection, last few days at home. Attended 74 day ward for routine i.v. immunoglobulins today. Neutropenic and septic therefore admitted for tazocin and gentamicin. Blood cultures, viral screen and chest radiograph taken – results pending. Additional information: neutrophils 0.0 × 10^9/l, Hb 11.1 g/dl, phs 174. 31 December 2012. Follow-up SAE viral screen, chest radiography, blood cultures – negative. Given i.v. tazocin + gentamicin for 5 days. Neutropenic so given × 4 days G-GP, GP; CSF after this plus 7 days of oral antibiotics. Discharged 4 January 2013	Required/prolonged hospitalisation
FCR	Infections and infestations	N00050/ 00041/001	Febrile neutropenia	UK	69	Female	Pyrexia, feeling unwell. Follow-up report: neutrophil counts recovered on 14 December 2010. However, patient remained hospitalised for respiratory infection	Required/prolonged hospitalisation
FCR	Infections and infestations	N00098/ 00001/001	Neutropenic sepsis	UK	41	Male	Patient felt shivery. Temperature checked at home – 38 °C. Rang ward and was admitted. Neutrophils 0.28	Required/prolonged hospitalisation
FCR	Infections and infestations	N00098/ 00060/001	Fever – no focus identified	UK	52	Male	Patient admitted feeling hot and cold, decreased eating and drinking. Generally unwell for 4/7	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00098/ 00060/003	Probable late PCP/PJP	UK	52	Male	Admitted with shortness of breath on exertion and cough. Also vomiting and nausea. Patient noted to be lymphopenic with lymphocyte count of 0.74. CT scan was suggestive of PCP or atypical infection. Information on cause and outcome to follow. Additional information CT scan on 2 June 2012 stated that appearances were felt to be pneumocystis. Clinically appeared to be PCP and all other microbiology performed showed no other organism. Patient commenced on co-trimoxazole prophylactically	Required/prolonged hospitalisation
FCR	Infections and infestations	N00099/ 00084/001	Pyrexia ?neutropenic sepsis	UK	59	Female	Pyrexia, patient feeling unwell	Required/prolonged hospitalisation
FCR	Infections and infestations	N00099/ 00105/001	Neutropenic sepsis	UK	68	Male	Admitted 2 days after the chemotherapy with sudden drop of WBCs and neutrophils. He is on broad spectrum antibiotics	Required/prolonged hospitalisation
FCR	Infections and infestations	N00106/ 00130/001	Neutropenic sepsis	UK	70	Male	Fever/rigors. Now apyrexial, on tazocin + gentamicin: gentamicin now stopped. Completed 5 days tazocin, now on oral ciprofloxacin and GCSF – discharged home	Life-threatening/required/ prolonged hospitalisation
FCR	Infections and infestations	N00106/ 00130/002	Neutropenic sepsis	UK	70	Male	Presented with fever + neutropenia – responded to i.v. antibiotics. Neutrophils 0.3 on 27 April 2012 – recovered to 1.5 1 May 2012 – Discharged home	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00106/ 00179/001	Pyrexial, neutropenic	UK	68	Female	Nausea and vomiting. ?chest infection. Additional information received by fax 6 August 2012: rituximab 600 mg given i.v. statutory dose on 26 July 2012. NB: patient had rituximab given over 2 days = 700 mg in total. Follow-up report: Neutrophils recovered to 1.1 on 7 August 2012. Chest radiograph showed Lt base atelectasis – no growth in urine/stool or blood	Required/prolonged hospitalisation
FCR	Infections and infestations	N00106/ 00179/003	Neutropenic sepsis	UK	68	Female	Neutropenic sepsis. Drug reaction, facial swelling and itchy rash. Fever 40 °C. Follow-up report. Neutropenic sepsis. 0.0 on 23 October 2012 – recovered to 0.9 on 27 October 2012. No sepsis found. Drug reaction – itchy rash and pyrexia. Resolved by 27 October 2012. Patient discharged 27 October 2012	Required/prolonged hospitalisation
FCR	Infections and infestations	N00114/ 00067/001	Neutropenic sepsis	UK	61	Female	Increasingly unwell for 4 days prior to admission with high temperature. Temperature on admission: 38 °C. Neutrophils 1.2 CRP 13. Follow-up report: increasingly unwell. Temperature 38 °C, neutrophils 0.2 CRP 13	Required/prolonged hospitalisation
FCR	Infections and infestations	N00114/ 00067/002	Neutropenic sepsis? cause	UK	61	Female	Febrile 38.1 on 17 July 2011. Nausea/ vomited × 2 in 24 hours. Decreased appetite	Required/prolonged hospitalisation
FCR	Infections and infestations	N00114/ 00067/003	?Neutropenic sepsis	UK	61	Female	Temperature 38.1 °C, nausea and vomiting, decreased appetite	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00114/ 00067/004	Neutropenic sepsis	UK	61	Female	Neutropenic sepsis. Recently noticed infection under arm. GP prescribed Flucloxacillin. Not neutropenic + pyrexial. Admitted to hospital 23 January 2012 for i.v. antibiotics. Follow-up report received: admitted 23 January 2012 with febrile neutropenia (having been on Flucloxacillin for 3 days for axillary gland infection). Treated with i.v. tazocin + GCSF. Subsequent rise in neutrophils. Discharged home 27 January 2012 on oral antibiotics	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above
FCR	Infections and infestations	N00114/ 00088/002	Neutropenic sepsis	UK	72	Male	4-day history of dysuria and left loin pain. Follow-up report: admitted following 4-day history of dysuria, loin pain and haematuria. Found to be neutropenic. Discharged home 3 January 2011	Required/prolonged hospitalisation
FCR	Infections and infestations	N00153/ 00026/001	Infection	UK	53	Male	Patient admitted with fever 37.8 °C, feeling generally unwell. Not neutropenic. Treated for 24 hours with i.v. antibiotics, then discharged home	Required/prolonged hospitalisation
FCR	Infections and infestations	N00153/ 00050/001	Chest infection	UK	53	Male	Seen in triage unit on 24 February 2011 with SOB, commenced on oral antibiotics. Symptoms worsened. Admitted on 27 February 2011 with pyrexia, productive cough, commenced i.v. antibiotics. Follow-up report: patient admitted via triage unit with shortness of breath, productive cough, treated on i.v. antibiotics	Required/prolonged hospitalisation
FCR	Infections and infestations	N00173/ 00011/003	Lower respiratory tract inf.	UK	72	Female	Cough and pyrexia, not neutropenic	Required/prolonged hospitalisation
FCR	Infections and infestations	N00218/ 00168/002	Neutropenic sepsis	UK	63	Male	Admitted neutropenic sepsis. Temperature: 38.4 °C. Neutropenic. Painful area around anus. Awaiting surgical review. Started imipenem	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00230/ 00033/001	Neutropenic sepsis	UK	61	Female	Temperature: 38.8 °C. Loose stools, decreased appetite. Follow-up report: allergic reaction to meropenum/Tazocin (penicillin)	Required/prolonged hospitalisation
FCR	Infections and infestations	N00231/ 00174/001	Febrile, rigors, ?septic. Episodes of diarrhoea for 2 days	UK	67	Male	22 August 2012, 19.50, arrived in A&E complaining of feeling unwell and high temperature 38.1 °C. Triage assessment BP 134/80, Temperature 36.6 °C, O_2 sats 97%. Admitted to acute medical unit. i.v. antibiotics started. No obvious focus of sepsis identified. Discharged on 26 August 2012 with oral Ciprofloxacin	Required/prolonged hospitalisation
FCR	Infections and infestations	N00231/ 00174/002	Febrile illness (pyrexia, rigors)	UK	67	Male	Admitted via A&E 27/8/12. Complained of feeling unwell, malaise, T 37.9 °C. Treated with i.v. teicoplanin (Targocid, Sanofi). Follow-up report: CRP remains high, unwell and malaise, no site of infection. i.v. antibiotics changed to meropenam. CT – NAD. Diabetes unstable blood sugars. Now discharged on insulin, 80 mg Glucazide, Novami × 30 14/g units. See attached CRP report	Required/prolonged hospitalisation
FCR	Infections and infestations	N00231/ 00174/003	Neutropenic sepsis	UK	67	Male	Pyrexia, neutropenic (0.9). Presumed neutropenic sepsis, site of infection unknown. CRP 19.7. Pyrexia at home 38.9 °C on arrival to A&E 37.8 °C. Treated with Tazocin and Gentamicin and Meropenem i.v. Discharged from hospital to home 18 October 2012	Required/prolonged hospitalisation
FCR	Infections and infestations	N00255/ 00138/001	Neutropenic sepsis	UK	61	Female	Patient was admitted to hospital with chief complaint of headache and temperature of 39.1 °C. Developed neutropenic sepsis and low haemoglobin. Commenced on i.v. antibiotics and received 4 units of blood. Day 20 post chemotherapy	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00255/ 00166/001	Febrile neutropenia	UK	66	Female	Admitted with left earache, fevers, rigors and feeling unwell	Required/prolonged hospitalisation
FCR	Infections and infestations	N00255/ 00166/002	Neutropenic sepsis	UK	66	Female	Temperature 39.6 °C, rigors, neutrophils 0.1, haemoptysis	Required/prolonged hospitalisation
FCR	Infections and infestations	N00280/ 00008/001	Neutropenic sepsis	UK	60	Male	Persistent pyrexia, feeling generally unwell – admitted 31 May 2010 – i.v. antibiotics given. Blood culture – negative after 5 days' incubation	Required/prolonged hospitalisation
FCR	Infections and infestations	N00319/ 00125/002	Febrile neutropenia	UK	61	Female	Temperature at home 38.8° C, admitted to hospital, on admission neutrophils 0.04. Noted rash at home improved on admission	Required/prolonged hospitalisation
FCR	Infections and infestations	N00361/ 00123/002	Neutropenic sepsis	UK	67	Female	Pyrexial (39.5 at home)? Source. Full infection screen completed – all specimens negative. Commenced i.v. Meropenem 1 g TDS. Pyrexia settled 7 July 2012 at 0.2 onwards. Patient remains apyrexial at present. Still no cause identified	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00391/ 00111/001	Neutropenic sepsis	UK	75	Male	GP referral. 2-day history of feeling unwell, dizzy, breathless, rash over back and arms. Temperature 38.5 °C on admission. Neutrophils 0.8. Commenced i.v. antibiotics and GCSF. Follow-up report received: please see attached discharge summary to up-date SAE information. Treated with Gentamicin and Tazocin, and Co-trimoxazole was discontinued as the most likely culprit for rash. Also received Filgrastim to stimulate neutrophil recovery. Fever and rash settled then rash appeared to worsen on legs. Were set to send home on 9 November 2011 but developed unexplained fever which settled the following day. By this time was switched to oral Ciprofloxacin. Neutrophils on discharge had improved to 2.0 × 10/l. Plan to keep off Co-trimoxazole and considering rechallenging when rash is fully settled. Will give prophylactic Pegfilgrastim to try to prevent further admissions with neutropenic sepsis	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00391/ 00194/001	?Neutropenic sepsis. ?Viral infection. ?Drug-induced gastritis	UK	74	Male	Admitted via A&E with 1-day history of nausea/vomiting and sore throat. Neutrophils on 12 December 2012 1.1. Temperature 37.3 °C at home but increased to 40.0 °C on admission. Shaking limbs and sore head. Follow-up report: admitted 13 December 2012. Fever of unknown origin. He has already shown clinical remission to three cycles of treatment. Discharged 15/12/12. On admission he was febrile (38.3 °C) with pulse 95 per minute, BP 135/70, saturations 94% breathing air. SIRS score 0. There was no evidence of any oral thrush and no lymphadenopathy. Heart sounds normal, chest clear, abdomen soft and non-tender with no organs or masses felt. Haemoglobin on admission 12.4 g/dl, WBC 3.3×10^9/l, neutrophils 2.8×10^9/l, platelets 139×10^9/l. Routine biochemistry was normal other than a minor rise in his creatinine to 129 µmol/l. Cultures of blood/urine negative. Treated with i.v. fluids and received single dose of paracetamol. Temperature settled nicely and did not require antibiotics. Cause for fever uncertain but possibly reaction to 4th cycle of chemotherapy which was discontinued after just 24 hours. Discharged home taking maintenance acyclovir 400 mg twice daily. Will be reviewed at Macmillan Centre on 24/12/12 with an up-to-date blood test. Hope to resume the chemotherapy as planned providing this is tolerated	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00698/ 00198/001	Febrile neutropenia	UK	71	Male	Neutrophils – 0.1 on admission to local hospital, commenced on i.v. antibiotics. Pyrexial on admission. Follow-up: SAE G4 febrile neutropenia – admitted to local hospital on 1 January 2013. Treated successfully i.v. antibiotics. No source of infection found but urinalysis positive for nitrates	Jeopardised patient/required intervention to prevent one of the above/required/ prolonged hospitalisation
FCR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N00098/ 00002/001	Squamous cell carcinoma – two lesions: lower back and central chest	UK	63	Male	Central chest lesion seen 20 August 2010 and initially thought to be Giant Molluscum. Increased in size over next few weeks. Patient went to GP – referred to dermatologist. Biopsy done and also lesion on back noted and excised. Biopsy revealed both to be SCC	Jeopardised patient/required intervention to prevent one of the above
FCR	Psychiatric disorders	N00349/ 00104/002	Psychotic episode	UK	69	Male	Catatonic. Follow up received 24 February 2012 – Discharged from hospital 10 January 2012 on diazepam. 24 February 2012 no longer on medication for his anxiety	Required/prolonged hospitalisation
FCR	Skin and subcutaneous tissue disorders	N00349/ 00070/001	Rash	UK	63	Male	Reaction to Rituximab infusion	Required/prolonged hospitalisation
FCR	Skin and subcutaneous tissue disorders	N00353/ 00122/001	Erythemous rash grade 3	UK	72	Male	Rash covering all of body and face. Skin red, inflamed and hot to touch.	Required/prolonged hospitalisation
FCM-miniR	Blood and lymphatic system disorders	N00009/ 00127/001	Pleural effusion and pulmonary embolism	UK	57	Male	Increased shortness of breath since day 7 of cycle 1 of FCM treatment. No improvement despite increasing asthma inhalers. Became very breathless and admitted on 31 December 2011. CTPA on 3 January 2012 confirmed huge bilateral pleural effusion and pulmonary embolisms in right upper lobe artery	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/001	Neutropenic sepsis	UK	65	Female	Patient admitted with a low-grade pyrexia and neutropenic at 0.2. Discharged from hospital but remains severely neutropenic (sequelae)	Required/prolonged hospitalisation
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/002	Neutropenic sepsis	UK	65	Female	Patient admitted with feeling unwell for a few days. Feeling hot and cold and shaky. Diarrhoea for past few days. Neutrophil count 0.1 × 10/l. Was previously discharged with neutropenia (sequelae) – readmitted on 17 October 2010	Required/prolonged hospitalisation
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/003	DCT negative autoimmune haemolysis	UK	46	Male	Probably owing to fludarabine. Discussed with Chief Investigator – to omit cycle 6 and treat ATHA as needed. Professor Hillmen 1 November 11 agreed action	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/004	Pulmonary embolism	UK	46	Male	Following post-treatment CT scan. Patient noted to have pulmonary embolism. Commenced on Clexane/Warfarin. Possibly attributable to haemolytic anaemia. Follow-up report: following post-treatment CT scan, patient noted to have pulmonary embolism. Commenced on Clexane and Warfarin	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Blood and lymphatic system disorders	N00153/ 00010/001	Neutropenia	UK	58	Male	Patient neutrophils grade 4 – 0.37 10/l. Follow-up report: neutrophils grade 4. Dose reduction of 25% and ratiograstim with each cycle	Jeopardised patient/required intervention to prevent one of the above

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Blood and lymphatic system disorders	N00391/ 00144/001	Marked pancytopenia post chemotherapy. Cough and short of breath	UK	57	Female	Reason for admission: (1) marked pancytopenia following chemotherapy with low HB, leucopenia and thrombocytopenia; (2) shortness of breath and slight cough. This 57-year-old lady was admitted to the medical ward under the care of the physician on 6 November 2012. She had a temperature of 37.5 °C but she was feeling very tired and also had a cough. At the time of her admission her full blood count was as follows: HB 5.9 g/dl, white cell count 0.9×10^9/l, neutrophils 0.2×10^9/l, platelets 72×10^9/l. She was comfortable but looked very pale. Heart sounds were normal and there were no audible murmurs. There was no oedema. Chest was clear. Abdomen was soft, there was no hepatosplenomegaly. Central nervous system was grossly normal. She was transfused with 4 units of red cells. She was also given Pentamidine 300 mg by nebuliser route on 8 November 2012. NB: Research Nurse only aware of this on 14 December 2012? If needs reported as 43 days past end of chemotherapy	Required/prolonged hospitalisation
FCM-miniR	Blood and lymphatic system disorders	N01527/ 00030/001	Anaemia	UK	49	Male	Headaches, dizziness, shortness of breath since Sunday. GI bleeding does not seem to be cause. DAT-positive haemolysts	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N00050/ 00083/001	Vomiting	UK	54	Male	Nausea and vomiting – medication taken with no effect. Admitted to ward 96	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/001	Vomiting	UK	62	Female	Patient admitted with vomiting, unresolved with oral antiemetics. Last day of oral chemotherapy. Given i.v. fluids and further antiemetic. Normal renal function and FBC	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/002	Nausea and vomiting	UK	62	Female	Patient admitted with nausea and vomiting during cycle 2 FMC-miniR. Given i.v. fluids and i.v. antiemetics	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N01527/ 00184/001	Vomiting	UK	63	Female	Patient admitted to MAU 4 October 2012 at Royal Blackburn Hospital with vomiting post chemotherapy. Last cycle 27 September 2012. Observations: BP 138/80, HR 79, temperature 36.6 °C, RR12, sats 99% RA. Blood reports attached. Chest radiograph – clear	Required/prolonged hospitalisation
FCM-miniR	General disorders and administration site conditions	N00040/ 00180/001	Serious Rituximab reaction	UK	65	Male	Patient became unresponsive, BP unrecordable, HR 34, sats 94% on air. Patient lost output – IM adrenaline given – swift recovery post adrenaline. Hypotension. CTCAE grade 4 hypotension	Life-threatening/required/ prolonged hospitalisation
FCM-miniR	General disorders and administration site conditions	N00098/ 00004/001	High-grade fever	UK	60	Male	Developed high-grade fever during first cycle of FCM-miniR. Temperature maximum 39.1 °C at 16.20 and not reducing with paracetamol. Decision by medical team to admit to ward. i.v. fluids	Required/prolonged hospitalisation
FCM-miniR	General disorders and administration site conditions	N00098/ 00005/003	Anaphylaxis	UK	56	Male	Acute anaphylaxis, leading to collapse, loss of consciousness, generalised seizure, associated bronchospasm	Life-threatening/jeopardised patient/required intervention to prevent one of the above
FCM-miniR	General disorders and administration site conditions	N00098/ 00099/001	Vasovagal episode with first dose of rituximab	UK	61	Male	Patient became diapheretic, hypotensive and lost consciousness for approx. 1 minute. Bradycardic on recovery. BP and pulse recovered back to baseline within 3–4 minutes. Second episode of collapse after mitoxantrone, recovered very quickly	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	General disorders and administration site conditions	N00099/ 00036/001	Reaction to Rituximab	UK	61	Male	During rituximab infusion suddenly felt unwell, light headed and sweaty. Required oxygen. Later in the day felt sick, had slight rigors and lost consciousness for approx. 10–20 seconds. Oxygen reapplied. Rituximab stopped	Life-threatening
FCM-miniR	General disorders and administration site conditions	N00153/ 00156/001	Infusion reaction	UK	58	Male	Patient had a reaction to the rituximab infusion, BP dropped to 70/40, HR 41, momentary loss of consciousness, < 1 minute. i.v. hydration given and additional i.v. hydrocortisone. Rituximab infusion was omitted – patient recovered. WCC = 434	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Immune system disorders	N00361/ 00109/001	Haemolytic anaemia	UK	66	Female	Patient was due second cycle of FCM-miniR on 17 November 2011. Hb reduced to 79, bilirubin increased to 22. Reviewed by doctor – Heamolysing. Doctor completed haemolysis screen, given 2 units red cell concentrate (blood) and commenced Prednisolone 50 mgs. Reviewed 18 November 2011: Hb 95, bilirubin 16	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Infections and infestations	N00014/ 00054/001	Sepsis	UK	52	Male	Possible viral infection?? Swine flu with grade 3 neutropenia	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00040/ 00108/001	Neutropenic sepsis	UK	56	Male	Fever 39.4 °C. Lethargy	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00040/ 00108/002	Pyrexia	UK	56	Male	Previous admission for neutropenic sepsis – discharged home. Re-admitted with pyrexia, antibiotics given i.v., no cause for pyrexia found as yet. Follow-up report: 1 November 2011, discharged 18 October 2011 and recommenced treatment on 20 October 2010	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00040/ 00108/004	Neutropenic sepsis	UK	56	Male	Pyrexia. Feeling generally unwell. Developed rash following dose of co-amoxiclav. Treatment changed. No new drugs on discharge	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00050/ 00095/001	Neutropenic sepsis	UK	60	Male	Admitted with neutropenic sepsis (with haematura). Generally cytopenic. Results on 01 January 12, Hb 7.7, WBC 0.50, neutrophils 0.13, Platelets 59	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00080/ 00058/001	Infection with grade 4 neutrophils	UK	51	Female	Cough with yellow sputum, chest tightness, pyrexial	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00080/ 00058/002	Chest infection/febrile neutropenia	UK	51	Female	Started feeling unwell on the 14 October 2011 came to clinic. No temperature and chest clear. On the 27 October 2011 increased temperature and feeling unwell with productive cough	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00098/ 00005/001	Pyrexia and rigors	UK	56	Male	Possible neutropenic sepsis, spiking temperatures. i.v. antibiotics given, no source identified. Neutrophils > 1.0 × 10/l	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00098/ 00005/002	Pyrexia and diarrhoea	UK	56	Male	Recurrent fever 38.8 °C, episodes of diarrhoea, flushing, readmitted. No source identified – i.v. antibiotics. Neutrophils > 1.0 × 10/l	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00098/ 00005/004	Neutropenic sepsis	UK	56	Male	Felt hot and cold. Temperature 38.6 °C. Admitted. Commenced i.v. antibiotics (finished chemotherapy tablets for this cycle 4 days previously)	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00098/ 00005/005	Fever, unknown origin, nausea	UK	56	Male	Spike temperature of 38 °C evening of 18 May 2010. Very nauseated and vomiting. Temperature resolved, but up again this morning. Reviewed by haem doctor. Decision to admit	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00098/ 00115/001	Urinary tract infection	UK	69	Male	Admitted with chills + rigors + lower abdominal pain + dysuria and dark urine. Apyrexial. Not neutropenic CRP 236. Given i.v. antibiotics + discharged 7 May 2012 on 7 days' oral antibiotics. For USS urinary tract. Treatment already stopped as end of 6 cycles	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00099/ 00027/003	Neutropenic sepsis	UK	65	Female	High temperature, neutrophils 0.3, platelets 130. Follow-up report: patient also presented with diarrhoea which settled prior to discharge	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00099/ 00036/002	Neutropenic sepsis	UK	61	Male	Patient admitted to hospital with pyrexia and feeling unwell. Symptoms included increased fatigue and dysuria. Temperature 37.8 °C. Neutrophil count 0.6 × 10/l	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00099/ 00045/001	Neutropenic sepsis	UK	73	Male	Patient admitted with sore throat and fever. Clinically septic with tachycardia, fever (temperature 39 °C), neutrophils 0.10 × 10/l. Treatment – i.v. fluids, i.v. antibiotics	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00106/ 00075/001	URTI (not neutropenic) and anaemia	UK	63	Male	Admitted with fever, non-productive cough, shortness of breath at rest, sore throat. Oral ciprofloxacin given 4/7 days prior to admission. Treated as per hospital protocol with i.v. antibiotics. Transfused 4 units of RBC. Condition improved. Likely to be viral	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00106/ 00075/003	Neutropenic sepsis	UK	63	Male	Admitted on 30 April 2011 with febrile neutropenia. Treated with i.v. Gentamicin and Tazocin and discharged home on 2 May 2011. He was then readmitted on the same day with rigor, pyrexia, oedema of the face, hands and feet with rash. Likely to be a drug reaction, not yet determined. Treated with Clarithromycin and Ciprofloxacin. E-mail text from Hazel Wynn, Research Nurse – 'In response to our telephone call I can confirm that pt 75, MD has had an adverse event form sent on 26 April 11 and 4 May 2011 and that after discussing with Dr Eagleton, Dr Pushkarran and Dr Pattison these two SAEs are to be counted as 1 ongoing adverse event. Note therefore that this SAE is linked with SAE 00106/ 00075/02, additional information received recorded here in order to be able to capture on database'	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00111/ 00132/001	Pyrexia neutropenia	UK	73	Male	Increasingly unwell, urinary symptoms, confusion, pyrexia, admitted to hospital – neutropenic	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00111/ 00132/003	Opportunistic infection associated with > grade 2 lymphopenia	UK	73	Male	Began feeling not right in head on 15 February 2013, frequency of urine. Started on i.v. antibiotics. PCP diagnosed (likely), diagnosed 22 February 2013. Septrim commenced	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00114/ 00006/002	Infection	UK	70	Male	Productive cough for 5 days. Headache. Pyrexia (38.1 °C). Associated rigors. Admitted to hospital 22 February 2012, diagnosed influenza A. Treated with oseltamivir and GCSF. Discharged home 27 February 2012	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00114/ 00023/001	Bilateral pneumonia	UK	69	Female	Admitted to hospital 8 July 2011 with shortness of breath. Diagnosed with bilateral pneumonia. Admitted to intensive care unit on 25 July 2011 with worsening pneumonia. Intubated 28 July 2011. Patient deteriorated and died 26 August 2011. Cause of death: (1) pneumonia; (2) CLL. Event likely to have been caused by immunosuppression from disease and treatment. Queried with trials office at time of admission whether this needed reporting as SAE. Informed that as it was more than 30 days post treatment SAE not required. However, have since been informed that SAE was required	Patient died/required/ prolonged hospitalisation
FCM-miniR	Infections and infestations	N00114/ 00086/001	Neutropenic sepsis	UK	46	Male	Rigors. Temperature 38.4 °C (19 August 2011). Spiked temperature 17 August 2011, which settled with paracetamol. Coeyzal symptoms for 2 weeks. Commenced i.v. Tazocin (19 August 2011). Follow-up report: admitted 19 August 2011. i.v. antibiotics	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00114/ 00094/001	Dehydration and diarrhoea, secondary to low haemoglobin	UK	75	Female	Patient collapsed at home prior to pre-booked blood transfusion. Following transfusion patient had episode of loose stool. Follow-up report: admitted 5 September 2011. Discharged 7 September 2011. *Campylobacter* found in stool	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00132/ 00069/001	Neutropenic sepsis	UK	65	Male	Patient admitted with neutropenic fever of 37.7 °C post chemotherapy. Patient received i.v. antibiotics and a sepsis screen and was discharged on oral antibiotics	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00132/ 00069/002	Grade 2 fevers after chemotherapy	UK	65	Male	Admitted with grade 2 fevers, day 5 of cycle 4 chemotherapy with neutrophils of 1.30 × 10/l. No focal localising signs of infection. Placed on broad spectrum antibiotics. Discharged 3 August 2011	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00153/ 00010/002	Febrile neutropenia	UK	58	Male	Patient admitted to hospital febrile and neutropenic, feeling dizzy and light headed. Treated as per neutropenic protocol. Follow-up report: Patient admitted febrile and neutropenic. Treated with i.v. antibiotics and PEG Filgrastim. Temperature settled, patient discharged. Awaiting decision on future chemotherapy treatment. 4 August 2010: bone marrow exam outstanding. 16 August 2010 – ratiograstim stopped, PEG filgrastim given, neutropenia resolved	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00153/ 00016/001	Neutropenic sepsis/ Neutropenic fever	UK	54	Female	Upper respiratory tract infection. Neutropenic fever. Follow-up report: patient admitted to hospital on 31 August 2010 with fever and 5-day history of productive cough. Treated with i.v. antibiotics; blood cultures negative. Discharged on oral antibiotics for 5 days	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Infections and infestations	N00153/ 00020/001	Neutropenic sepsis	UK	61	Female	Patient admitted after 2-day history of temperature, FBC shows neutropenia. More detail to follow. Follow-up report: presented to A&E with fever and flu-like symptoms. Treated with i.v. antibiotics as per neutropenic sepsis protocol. GCSF FCVR 4 days. 5 days of oral antibiotics on discharge	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00153/ 00020/002	Neutropenic sepsis	UK	61	Female	Patient admitted with fever and neutropenic count of 0.63×10^9/l. Treated with i.v. antibiotic as per local neutropenic sepsis protocol. To delay next cycle of treatment – due 20 September 2010. Follow-up report: discharged on oral antibiotics with neutrophil count > 2.0 10/l. Cycle 4 FCM-miniR delayed	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00153/ 00156/002	Lower respiratory tract infection	UK	58	Male	Admitted owing to cough/fever – patient's diagnosis at discharge = neutropenic sepsis/lower respiratory tract infection. 5 days of i.v. tazocin + 2 days of i.v. gentamicin was given. Discharged on 10 days of oral antibiotics	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00161/ 00047/001	Neutropenic sepsis	UK	60	Male	Low-grade pyrexia, productive cough, neutrophils 0.06 10/l. Treatment of Tazocin and Gentamycin – i.v. Follow-up report: discharged on 3 December 2010	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00161/ 00047/002	Suspected neutropenic sepsis	UK	60	Male	Temperature of 38.7 °C on admission – increased to 39.5 °C. Also had cough. WBC = 1.8 10/l, neutrophils = 1.3 10/l	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00161/ 00047/003	Chest infection	UK	60	Male	Cough, temperature and shaking. Neutrophils = 1.3	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00280/ 00039/001	Septic/sepsis	UK	72	Female	Temperature 39.1 °C. Diarrhoea, abdominal pain, headache and vomiting. Patient to be admitted. Follow-up: neutrophils 1.0 on admission. Dropped to nadir of 0.5 during admission. Now recovered	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00319/ 00080/001	Neutropenia	UK	63	Male	Temperature 37.6 °C, admitted neutrophils 0.53	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00319/ 00080/002	Temperature 37.8°C	UK	63	Male	Temperature of 37.8 °C, no other signs or symptoms	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00319/ 00080/003	Temperature 37.5°C	UK	63	Male	Temperature 37.7 °C at home, fatigue. (Hospital policy to admit patients with 37.5 °C or above)	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00319/ 00080/004	Fever. Grade 1	UK	63	Male	Non-neutropenic fever. Temperature 38.6 °C. Treated with intravenous antibiotics 2 g Ceftazidime and 280 mg Gentamicin. Chest radiography performed, no findings	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00353/ 00065/001	Fever	UK	57	Male	Constant temperature 38.3 °C	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00391/ 00071/001	Grade 3 anaemia and grade 4 febrile neutropenia	UK	60	Female	Felt cold and shivery for 3 days, chronic cough. Admitted 1 May 2011. Neutrophils = 0.2. Responded to i.v. antibiotics, two doses Filgrastim. 2-unit transfusion	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00391/ 00142/001	Neutropenia and fever and sweats	UK	73	Male	Ongoing neutropenia post cycle 1 chemotherapy on 27 April 2012. Fevers at night up to 38.5 °C. Day 46 post chemotherapy with intermittent GCSF cover. Apyrexial on admission. Neutrophils 0.6 and blood cultures taken. Follow-up report: please see attached discharge summary for full details of event. On admission looked well and was afebrile. Pulse 85 per minute, BP 110/60, sats 99% breathing air. Had significant cervical and predominantly left axillary lymphadenopathy. Heart sounds normal, chest clear, abdomen soft with no organs or masses felt. Commenced i.v. Gentamicin and Tazocin but despite this developed temperature of 39 °C. Received a 2-unit blood transfusion. Temperature fluctuated and SIRS score reached 2 and received i.v. fluids for hypotension. We were not altogether happy with his ongoing fevers of up to 38 °C but in view of neutrophils recovering to 1.1 and RB anxiety to go home we agreed to this early review. Was seen again on 21 June 2012. Had been quite well at home with no fevers during the day but admitted to sweats at night. Neutrophils had recovered to 10×10^9/l so we therefore discontinued figrastim and continues with fluconazole 100 mg daily, co-trimoxazole 960 mg M,W,F and acyclovir 400 mg twice daily	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N01527/ 00081/002	Febrile neutropenia	UK	74	Female	Fever, rigors, generally unwell. ?Neutropenic sepsis	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N01527/ 00081/003	Febrile neutropenia	UK	74	Female	Pyrexia, rigors, neutropenic sepsis. This event is 31 days after last treatment dose but have reported as second episode since last treatment. Follow-up report: a1 onset of first sign has been updated following review of medical notes	Required/prolonged hospitalisation
FCM-miniR	Musculoskeletal and connective tissue disorders	N01527/ 00081/001	Infection with normal ANC ?septic arthritis	UK	74	Female	Right knee/left lower leg swelling, pain, pyrexia, anaemia. No action taken as yet, see section B. However tx may be delayed, next cycle due 9 June 2011. Follow-up report: medical opinion is condition probably gout	Required/prolonged hospitalisation
FCM-miniR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N01527/ 00081/004	EBV – Associated lymphoproliferative disorder	UK	74	Female	Patient presented with cough and was referred for chest radiography by GP. CT scan urgently arranged as well as bronchial biopsy. Verbal notification via PI confirming diagnosis. Additional information: see attached reports. Supplementary report with diagnosis to follow when available. Supplementary report now updated. This is an EBV-driven lymphoproliferative disorder. This is unlikely to be clonally related to the underlying CLL but may have occurred as a consequence of the disease and treatment related immunosuppression. Update: patient received 6 cycles RCHOP (January–May 2013) with a CR	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR	Renal and urinary disorders	N00071/ 00021/001	Acute renal failure – tumour lysis syndrome	UK	56	Female	Nausea and vomiting since chemotherapy 24/6/10. Refused admission 1/7/10 (to GP). Admitted 2/7/10. Na 129, K+ 8.3, Ur –52.5, Cr 853, Ca 1.64, PO_4 –10.46, urate 2.36, WBC count 178.6 on 28/6/10, 6.5 on 2/7/10. Tumour lysis syndrome	Life-threatening

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Renal and urinary disorders	N00353/ 00165/001	Renal failure CTC grade 3	UK	66	Male	Shortness of breath, hypotension, acute tubular necrosis. CRP 9.7 mg/l, urea 25.6 mmol/l, creatinine 258 µmol/l. Bloods on 16 July 2012: potassium 6.3 mmol/l, urea 6.2 mmol/l, creatinine 530 mmol/l. Follow-up report: patient reviewed on 23 July 2013 and clinician happy for treatment to continue	Required/prolonged hospitalisation
FCM-miniR	Skin and subcutaneous tissue disorders	N00106/ 00075/002	Pyrexia/rash – macular/papular	UK	63	Male	Flu-like symptoms. Rash covering entire body. Temperature. E-mail text from Hazel Wynn, Research Nurse – 'In response to our telephone call I can confirm that pt 75, MD has had an adverse event form sent on 26 April 11 and 4 May 11 and that after discussing with Dr Eagleton, Dr Pushkarran and Dr Pattison these two SAEs are to be counted as 1 ongoing adverse event. Note therefore that this SAE is linked with SAE 00106/00075/03, additional information received recorded there in order to be able to capture on database'	Required/prolonged hospitalisation/jeopardised patient/required intervention to prevent one of the above
FCM-miniR/ FCR	Gastrointestinal disorders	N00173/ 00145/001	Nausea and vomiting	UK	72	Male	Nausea + vomiting + unable to eat or drink from day after chemotherapy	Required/prolonged hospitalisation
FCM-miniR/ FCR	Gastrointestinal disorders	N00319/ 00189/001	Vomiting (grade 3)	UK	66	Female	Patient called triage line with vomiting on Day 4 chemotherapy. GP went out. Patient attended clinic Day 5 still experiencing uncontrolled nausea/vomiting. Not able to eat/drink, feeling weak. Admitted from clinic for i.v. fluids/antiemetics	Required/prolonged hospitalisation
FCM-miniR/ FCR	General disorders and administration site conditions	N00137/ 00196/002	Nausea, vomiting, and dehydration	UK	50	Female	Informed today (25 September 2012) that R-T was admitted with nausea, vomiting and dehydration. Given antiemetics and i.v. fluids	Required/prolonged hospitalisation

continued

TABLE 79 Serious adverse events suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/003	Fever (absence neutropenia)	UK	46	Male	Rituximab and mitoxantrone given in clinic. 2 hours post infusion patient started to feel cold and shivery at home. Temperature 38.8 °C and vomited. Admitted to hospital. Infection? Drug reaction?	Required/prolonged hospitalisation
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/004	Cytokine release grade 3	UK	46	Male	Pyrexia, moderate chills, rigor, commencing 12 hours post infusion of rituximab. Severe delayed reaction post #2 course – inpatient admission with fever + hypotension. Intervention given promptly post course 3, therefore reaction not as severe	Jeopardised patient/required intervention to prevent one of the above
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/001	Febrile neutropenia	UK	67	Female	Pyrexia unknown origin	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/002	Febrile	UK	67	Female	Patient reported pyrexia. Follow-up information: 11 December 2012 – Possible viral infection – unknown – nil found on blood cultures	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/003	Neutropenic sepsis	UK	50	Female	Admitted post chemotherapy with nausea and vomiting. Low neutrophils noted. Commenced neutropenic sepsis protocol. Given i.v. fluids then, once settled, oral fluids. Discharged to finish course of oral antibiotics. Mildly raised bilirubin – abdominal ultrasound showed nil liver or gall bladder issues	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/004	Neutropenic sepsis	UK	50	Female	Admitted with sweating and generally unwell. Follow-up report: admitted post chemotherapy with nausea and vomiting. Low neutrophils noted. Commenced neutropenic sepsis protocol. Given i.v. fluids, then once settled oral fluids. Discharged to finish course oral antibiotics. Mildly raised bilirubin. Abdominal ultrasound showed nil liver or gall bladder issues	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR/ FCR	Infections and infestations	N00153/ 00148/001	Febrile neutropenia	UK	54	Female	Patient was admitted into hospital owing to febrile neutropenia, i.v. antibiotics commenced	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00153/ 00177/001	Febrile neutropenia	UK	59	Female	Patient felt unwell/shivery at home. Temperature = 37.9 °C. Neutrophils 0.6. i.v. antibiotics given. Patient was discharged on oral antibiotics	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00153/ 00186/001	Febrile neutropenia	UK	52	Female	Patient was admitted into hospital with neutropenic sepsis, neutrophils = 0.27	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00218/ 00162/001	Neutropenic fever	UK	64	Male	Hospital admission with pyrexia and neutropenia. ?VZV. Fever and intermittent rash at present but suspicious for VZV (was on prophylactic aciclovir). Follow-up report: 4 September 2012 blood culture negative. VZV not diagnosed	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/002	Neutropenic sepsis (febrile neutropenia)	UK	66	Female	Developed a fever at home, 37.5 °C, and felt unwell. Neutrophils 0.30 on admission. Commenced on i.v. antibiotics and i.v. fluids. Additional information: patient had FCM-miniR for first cycle and FCR thereafter	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/003	Febrile neutropenia	UK	66	Female	Developed a fever during hospital visit (clinic appointment). 38.5°C. Neutrophils 0.94 on admission. Commenced i.v. ABs. Additional information: patient had FCM-miniR for cycle 1 then switched to FCR	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/004	Neutropenia with fever 37.8°C	UK	66	Female	Generally feeling unwell; pyrexial, temperature 37.8 °C. Neutrophils 0.54	Required/prolonged hospitalisation

BP, blood pressure; *C. diff.*, *Clostridium difficile*; CRP, C-reactive protein; CT, computerised tomography; CTPA, computerised tomography pulmonary angiography; EBV, Epstein–Barr virus; GI, gastrointestinal; GP, general practitioner; Hb, haemoglobin; HR, heart rate; ITU, intensive therapy unit; i.v., intravenous; NAD, no active disease; PEG, percutaneous endoscopic gastrostomy; PI, principal investigator; PJP, *Pneumocystis jiroveci* pneumonia; SCC, squamous cell carcinoma; SIRS, systemic inflammatory response syndrome; SOB, shortness of breath; TLS, tumour lysis syndrome; URTI, upper respiratory tract infection; WBC, white blood cell.
SAE ID number: centre code/patient ID/SAE number.

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCR	Blood and lymphatic system disorders	N00014/ 00028/002	Neutropenia	Suspected, expected	FCR
FCR	Blood and lymphatic system disorders	N00076/ 00187/001	Platelet count decreased	Suspected, expected	FC
FCR	Blood and lymphatic system disorders	N00080/ 00032/001	Infection	Suspected, expected	FC
FCR	Blood and lymphatic system disorders	N00098/ 00017/001	Extremely low Hb	Suspected, expected	FCR
FCR	Blood and lymphatic system disorders	N00098/ 00017/002	Low Hb 5.9 g/dl on Pentra	Suspected, expected	FCR
FCR	Blood and lymphatic system disorders	N00114/ 00088/001	Persistent neutropenia related to chemotherapy	Suspected, expected	FCR
FCR	Blood and lymphatic system disorders	N00175/ 00155/001	Anaemia	Suspected, expected	FCR
FCR	Blood and lymphatic system disorders	N00230/ 00033/002	Myelodysplasia: RAES	Suspected, expected	FC
FCR	Gastrointestinal disorders	N00050/ 00120/001	Diarrhoea and vomiting	Suspected, expected	FC
FCR	Gastrointestinal disorders	N00098/ 00060/002	Nausea and vomiting	Suspected, expected	FC
FCR	Gastrointestinal disorders	N00114/ 00088/003	Gastroenteritis	Suspected, expected	FCR
FCR	Gastrointestinal disorders	N00349/ 00035/001	Nausea	Suspected, expected	FC
FCR	General disorders and administration site conditions	N00014/ 00028/004	Infection/anaemia	Suspected, expected	FCR
FCR	General disorders and administration site conditions	N00014/ 00028/005	Anaemia grade 4	Suspected, expected	FCR
FCR	General disorders and administration site conditions	N00014/ 00029/001	Rigors	Suspected, expected	Rituximab
FCR	General disorders and administration site conditions	N00098/ 00019/001	Pyrexial 38.2 °C post first dose of Rituximab	Suspected, expected	Rituximab
FCR	General disorders and administration site conditions	N00114/ 00055/001	Fever and rigors	Suspected, expected	Rituximab
FCR	General disorders and administration site conditions	N00173/ 00011/001	Hypoxia	Suspected, expected	Rituximab
FCR	General disorders and administration site conditions	N00173/ 00137/001	Vomiting	Suspected, expected	FC

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
	21 July 2010	27 October 2010	1 November 2010	5	Recovered
CLL	21 August 2012	31 December 2012			Condition still present and unchanged
Other illness: general frailty/ possible GBS	23 August 2010	6 October 2010		144	Death
CLL	30 April 2010	3 November 2010	6 November 2010	3	Recovered with sequelae
	30 April 2010	12 November 2010	13 November 2010	1	Recovered
Concomitant medications	24 May 2011	2 November 2011	2 January 2012	61	Recovered
	30 May 2012	16 October 2012	16 October 2012	0	Recovered
	24 August 2010	6 May 2014		.	Condition improving
	7 November 2011	20 December 2011	21 December 2011	1	Recovered
	24 January 2011	28 April 2011	28 April 2011	0	Recovered
Other: suspect take-away meal	24 May 2011	1 April 2012	2 April 2012	1	Recovered
	10 September 2010	16 March 2011	15 April 2011	30	Recovered
	21 July 2010	4 January 2011	11 February 2011	38	Recovered
	21 July 2010	19 January 2011	10 February 2011	22	Recovered
	4 August 2010	24 August 2010	26 August 2010	2	Recovered
	8 June 2010	17 June 2010	18 June 2010	1	Recovered
CLL	5 January 2011	12 January 2011	18 January 2011	6	Recovered
CLL; asthma	29 March 2010	16 April 2010	21 April 2010	5	Recovered
Other: constipation	5 March 2012	8 April 2012	9 April 2012	1	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCR	General disorders and administration site conditions	N00218/ 00168/001	Fever and non-specifically unwell	Suspected, expected	FCR
FCR	General disorders and administration site conditions	N00319/ 00125/001	Allergic reaction	Suspected, expected	Rituximab
FCR	General disorders and administration site conditions	N00391/ 00194/002	Probable rituximab reaction	Suspected, expected	Rituximab
FCR	Infections and infestations	N00014/ 00028/003	Febrile neutropenia	Suspected, expected	FCR
FCR	Infections and infestations	N00014/ 00112/001	Shingles	Suspected, expected	FCR
FCR	Infections and infestations	N00040/ 00056/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00046/ 00185/001	Infection with grade 4 neutrophils	Suspected, expected	FCR
FCR	Infections and infestations	N00050/ 00041/001	Febrile neutropenia	Suspected, expected	FCR
FCR	Infections and infestations	N00098/ 00001/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00098/ 00060/001	Fever: no focus identified	Suspected, expected	FC
FCR	Infections and infestations	N00098/ 00060/003	Probable late PCP/PJP	Suspected, expected	FCR
FCR	Infections and infestations	N00099/ 00084/001	Pyrexia ?neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00099/ 00105/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00106/ 00130/001	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00106/ 00130/002	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00106/ 00179/001	Pyrexial, neutropenic	Suspected, expected	FCR
FCR	Infections and infestations	N00106/ 00179/003	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00114/ 00067/001	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00114/ 00067/002	Neutropenic sepsis ?cause	Suspected, expected	FC
FCR	Infections and infestations	N00114/ 00067/003	?Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00114/ 00067/004	Neutropenic sepsis	Suspected, expected	FCR

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
Other: ? infection underlying – none proven	4 July 2012	11 July 2012	13 July 2012	2	Recovered
CLL	12 December 2011	2 February 2012	2 February 2012	0	Recovered
	12 September 2012	10 January 2013	14 January 2013	4	Recovered
	21 July 2010	6 December 2010	13 December 2010	7	Recovered
	19 October 2011	8 February 2012	11 February 2012	3	Recovered
	7 January 2011	22 February 2011	28 February 2011	6	Recovered
CLL	13 August 2012	31 December 2012	4 January 2013	4	Recovered
	19 October 2010	11 December 2010	14 December 2010	3	Recovered
	14 December 2009	2 January 2010	5 January 2010	3	Recovered
CLL	24 January 2011	4 March 2011	7 March 2011	3	Recovered
	24 January 2011	30 May 2012	6 June 2012	7	Recovered
	11 May 2011	24 October 2011	27 October 2011	3	Recovered
	26 August 2011	7 September 2011	17 September 2011	10	Recovered
	16 January 2012	24 March 2012	28 March 2012	4	Recovered
	16 January 2012	27 April 2012	1 May 2012	4	Recovered
	17 July 2012	2 August 2012	7 August 2012	5	Recovered
Concomitant medications	17 July 2012	24 October 2012	27 October 2012	3	Recovered
	9 February 2011	23 May 2011	28 May 2011	5	Recovered
	9 September 2011	18 July 2011	25 July 2011	7	Recovered
CLL	9 February 2011	7 October 2011	14 October 2011	7	Recovered
	9 February 2011	23 January 2012	27 January 2012	4	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCR	Infections and infestations	N00114/ 00088/002	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00153/ 00026/001	Infection	Suspected, expected	FCR
FCR	Infections and infestations	N00153/ 00050/001	Chest infection	Suspected, expected	FCR
FCR	Infections and infestations	N00173/ 00011/003	Lower respiratory tract infection	Suspected, expected	FCR
FCR	Infections and infestations	N00218/ 00168/002	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00230/ 00033/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00231/ 00174/001	Febrile, rigors, ?septic. Episodes of diarrhoea for 2 days	Suspected, expected	FC
FCR	Infections and infestations	N00231/ 00174/002	Febrile illness (pyrexia, rigors)	Suspected, expected	FC
FCR	Infections and infestations	N00231/ 00174/003	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00255/ 00138/001	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00255/ 00166/001	Febrile neutropenia	Suspected, expected	FCR
FCR	Infections and infestations	N00255/ 00166/002	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00280/ 00008/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00319/ 00125/002	Febrile neutropenia	Suspected, expected	FCR
FCR	Infections and infestations	N00361/ 00123/002	Neutropenic sepsis	Suspected, expected	FCR
FCR	Infections and infestations	N00391/ 00111/001	Neutropenic sepsis	Suspected, expected	FC
FCR	Infections and infestations	N00391/ 00194/001	?Neutropenic sepsis. ?Viral infection. ?Drug-induced gastritis	Suspected, expected	FC
FCR	Infections and infestations	N00698/ 00198/001	Febrile neutropenia	Suspected, expected	FCR
FCR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N00098/ 00002/001	SCC: two lesions (lower back and central chest)	Suspected, unexpected	FCR
FCR	Psychiatric disorders	N00349/ 00104/002	Psychotic episode	Suspected, expected	Fludarabine

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
CLL	24 May 2011	24 December 2011	3 January 2012	10	Recovered
	20 July 2010	10 August 2010	11 August 2010	1	Recovered
	26 November 2010	27 February 2011	1 March 2011	2	Recovered
CLL	29 March 2010	6 July 2010	12 July 2010	6	Recovered
	4 July 2012	25 September 2012	4 October 2012	9	Recovered
	24 August 2010	26 September 2010	5 October 2010	9	Recovered
Other: infection	9 July 2012	22 August 2012	26 August 2012	4	Recovered
Other: infection	9 July 2012	27 August 2012	10 September 2012	14	Recovered
	9 July 2012	1 October 2012	18 October 2012	17	Recovered
CLL	13 March 2012	7 April 2012	16 April 2012	9	Recovered
	29 June 2012	13 September 2012	18 September 2012	5	Recovered
	29 June 2012	17 March 2013	30 March 2013	13	Recovered
	22 March 2010	31 May 2010	07 June 2010	7	Recovered
CLL	12 December 2011	20 February 2012	24 February 2012	4	Recovered
CLL	21 November 2011	5 July 2012	9 July 2012	4	Recovered
	6 October 2011	4 November 2011	10 November 2011	6	Recovered
	12 September 2012	13 December 2012	15 December 2012	2	Recovered
	19 September 2012	31 December 2012	5 January 2013	5	Recovered
	13 January 2010	6 October 2010	14 December 2010	69	Recovered
Other illness: long history anxiety	25 August 2011	20 December 2011	24 February 2012	66	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCR	Skin and subcutaneous tissue disorders	N00349/ 00070/001	Rash	Suspected, expected	Rituximab
FCR	Skin and subcutaneous tissue disorders	N00353/ 00122/001	Erythemous rash grade 3	Suspected, expected	Fludarabine
FCM-miniR	Blood and lymphatic system disorders	N00009/ 00127/001	Pleural effusion and pulmonary embolism	Suspected, expected	Cyclophosphamide
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/001	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/002	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/003	DCT-negative autoimmune haemolysis	Suspected, expected	Fludarabine
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/004	Pulmonary embolism	Suspected, expected	Fludarabine
FCM-miniR	Blood and lymphatic system disorders	N00153/ 00010/001	Neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR	Blood and lymphatic system disorders	N00391/ 00144/001	Marked pancytopenia post chemotherapy. Cough and SOB	Suspected, expected	FCM
FCM-miniR	Blood and lymphatic system disorders	N01527/ 00030/001	Anaemia	Suspected, expected	Fludarabine
FCM-miniR	Gastrointestinal disorders	N00050/ 00083/001	Vomiting	Suspected, expected	FCM
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/001	Vomiting	Suspected, expected	FCM
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/002	Nausea and vomiting	Suspected, expected	FCM
FCM-miniR	Gastrointestinal disorders	N01527/ 00184/001	Vomiting	Suspected, expected	Fludarabine and mitoxantrone
FCM-miniR	General disorders and administration site conditions	N00040/ 00180/001	Serious Rituximab reaction	Suspected, expected	Low-dose Rituximab
FCM-miniR	General disorders and administration site conditions	N00098/ 00004/001	High-grade fever	Suspected, expected	Mitoxantrone and low-dose Rituximab
FCM-miniR	General disorders and administration site conditions	N00098/ 00005/003	Anaphylaxis	Suspected, expected	Low-dose Rituximab
FCM-miniR	General disorders and administration site conditions	N00098/ 00099/001	Vasovagal episode with first dose of rituximab	Suspected, expected	Low-dose Rituximab
FCM-miniR	General disorders and administration site conditions	N00099/ 00036/001	Reaction to Rituximab	Suspected, expected	Low-dose Rituximab

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
	09 March 2011	12 April 2011	13 April 2011	1	Recovered
Concomitant medications	11 November 2011	19 December 2011	9 January 2012	21	Recovered
	15 December 2011	31 December 2011	11 January 2012	11	Recovered
	20 July 2010	1 October 2010	7 October 2010	6	Recovered with sequelae
	20 July 2010	17 October 2010	25 October 2010	8	Recovered with sequelae
CLL	18 May 2011	02 November 2011			Condition still present and unchanged
CLL; auto-immune haemolytic anaemia	18 May 2011	16 January 2012	14 November 2012	303	Recovered with sequelae
Concomitant medications	25 March 2010	7 April 2010	26 April 2010	19	Recovered
	17 April 2012	6 November 2012	9 November 2012	3	Recovered
	9 August 2010	27 August 2010	31 August 2010	4	Recovered
	6 May 2011	10 September 2011	11 September 2011	1	Recovered
	31 August 2010	21 September 2010	23 September 2010	2	Recovered
	31 August 2010	16 October 2010	19 October 2010	3	Recovered
	06 August 2012	04 October 2012	05 October 2012	1	Recovered
	20 July 2012	30 July 2012	31 July 2012	1	Recovered
	2 February 2010	24 February 2010	25 February 2010	1	Recovered
	15 February 2010	17 February 2010	17 February 2010	0	Recovered
Other: high vagal tone	27 July 2011	10 August 2011	11 August 2011	1	Recovered
	16 September 2010	27 September 2010	27 September 2010	0	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCM-miniR	General disorders and administration site conditions	N00153/ 00156/001	Infusion reaction	Suspected, expected	Low-dose Rituximab
FCM-miniR	Immune system disorders	N00361/ 00109/001	Haemolytic anaemia	Suspected, expected	Fludarabine
FCM-miniR	Infections and infestations	N00014/ 00054/001	Sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00040/ 00108/001	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00040/ 00108/002	Pyrexia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00040/ 00108/004	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00050/ 00095/001	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00080/ 00058/001	Infection with grade 4 neutrophils	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00080/ 00058/002	Chest infection/febrile neutropenia	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00098/ 00005/001	Pyrexia and rigors	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00098/ 00005/002	Pyrexia and diarrhoea	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00098/ 00005/004	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00098/ 00005/005	Fever, unknown origin, nausea	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00098/ 00115/001	Urinary tract infection	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00099/ 00027/003	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00099/ 00036/002	Neutropenic sepsis	Suspected, expected	Fludarabine and mitoxantrone
FCM-miniR	Infections and infestations	N00099/ 00045/001	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00106/ 00075/001	URTI (not neutropenic) and anaemia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00106/ 00075/003	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00111/ 00132/001	Pyrexia neutropenia	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00111/ 00132/003	Opportunistic infection associated with > grade 2 lymphopenia	Suspected, expected	FCM-mini-R

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
	31 May 2012	7 June 2012	7 June 2012	0	Recovered
	5 October 2011	17 November 2011	15 February 2012	90	Recovered
	5 January 2011	4 February 2011	22 February 2011	18	Recovered
	8 September 2011	24 September 2011	2 October 2011	8	Recovered
CLL	8 September 2011	7 October 2011	18 October 2011	11	Recovered
CLL	8 September 2011	7 January 2012	13 January 2012	6	Recovered
	21 July 2011	31 December 2011	4 January 2012	4	Recovered
	17 January 2011	28 April 2011	3 May 2011	5	Recovered
	17 January 2011	28 October 2011	3 November 2011	6	Recovered
	15 February 2010	5 March 2010	8 March 2010	3	Recovered
	15 February 2010	8 March 2010	12 March 2010	4	Recovered
	15 February 2010	22 April 2010	28 April 2010	6	Recovered
Concomitant medications infection	15 February 2010	19 May 2010	21 May 2010	2	Recovered
CLL	27 October 2011	4 May 2012	14 May 2012	10	Recovered
	20 July 2010	22 February 2011	25 February 2011	3	Recovered with sequelae
	16 September 2010	03 November 2010	10 November 2010	7	Recovered with sequelae
	9 November 2010	29 March 2011	3 April 2011	5	Recovered
CLL	21 March 2011	6 April 2011	8 April 2011	2	Recovered
	21 March 2011	2 May 2011	4 May 2011	2	Recovered
CLL	30 January 2012	8 May 2012	14 May 2012	6	Recovered
CLL	30 January 2012	16 February 2013	8 March 2013	20	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCM-miniR	Infections and infestations	N00114/ 00006/002	Infection	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00114/ 00023/001	Bilateral pneumonia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00114/ 00086/001	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00114/ 00094/001	Dehydration and diarrhoea, secondary to low Hb	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00132/ 00069/001	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00132/ 00069/002	Grade 2 fevers after chemotherapy	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00153/ 00010/002	Febrile neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00153/ 00016/001	Neutropenic sepsis/ neutropenic fever	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00153/ 00020/001	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00153/ 00020/002	Neutropenic sepsis	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00153/ 00156/002	Lower respiratory tract infection	Suspected, expected	FC and low-dose R
FCM-miniR	Infections and infestations	N00161/ 00047/001	Neutropenic sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00161/ 00047/002	Suspected neutropenic sepsis	Suspected, expected	Fludarabine
FCM-miniR	Infections and infestations	N00161/ 00047/003	Chest infection	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00280/ 00039/001	Septic/sepsis	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00319/ 00080/001	Neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00319/ 00080/002	Temperature 37.8 °C	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00319/ 00080/003	Temperature 37.5 °C	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00319/ 00080/004	Fever: grade 1	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N00353/ 00065/001	Fever	Suspected, expected	FCM
FCM-miniR	Infections and infestations	N00391/ 00071/001	Grade 3 anaemia and grade 4 febrile neutropenia	Suspected, expected	FCM

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
	22 February 2010	22 February 2012	27 February 2012	5	Recovered
CLL	8 July 2010	8 July 2011		50	Death
Other: in-dwelling Hickman line	18 May 2011	19 August 2011	26 August 2011	7	Recovered
CLL	8 July 2011	5 September 2011	7 September 2011	2	Recovered
	7 March 2011	10 May 2011	12 May 2011	2	Recovered
	7 March 2011	30 July 2011	3 August 2011	4	Recovered
	25 March 2010	3 August 2010	7 August 2010	4	Recovered
	30 April 2010	31 August 2010	8 September 2010	8	Recovered
	16 June 2010	2 September 2010	12 September 2010	10	Recovered
	16 June 2010	14 September 2010	19 September 2010	5	Recovered
	31 May 2012	6 September 2012	10 September 2012	4	Recovered
	12 November 2010	1 December 2010	3 December 2010	2	Recovered
Other illness: lung scarring from previous infection	12 November 2010	12 August 2011	15 August 2011	3	Recovered
CLL	12 November 2010	26 August 2011	30 August 2011	4	Recovered
	13 October 2010	11 February 2011	16 February 2011	5	Recovered
	3 May 2011	5 July 2011	18 July 2011	13	Recovered
CLL	3 May 2011	18 July 2011	18 July 2011	0	Recovered
	3 May 2011	31 August 2011	1 September 2011	1	Recovered
	3 May 2011	1 October 2011	6 October 2011	5	Recovered
	9 February 2011	22 April 2011	23 April 2011	1	Recovered
	11 March 2011	1 May 2011	5 May 2011	4	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCM-miniR	Infections and infestations	N00391/ 00142/001	Neutropenia and fever and sweats	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N01527/ 00081/002	Febrile neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR	Infections and infestations	N01527/ 00081/003	Febrile neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR	Musculoskeletal and connective tissue disorders	N01527/ 00081/001	Infection with normal ANC ?septic arthritis	Suspected, expected	FCM-mini-R
FCM-miniR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N01527/ 00081/004	EBV – associated lymphoproliferative disorder	Suspected, expected	Fludarabine
FCM-miniR	Renal and urinary disorders	N00071/ 00021/001	Acute renal failure: tumour lysis syndrome	Suspected, expected	FCM-mini-R
FCM-miniR	Renal and urinary disorders	N00353/ 00165/001	Renal failure CTCAE grade 3	Suspected, expected	FCM-mini-R
FCM-miniR	Skin and subcutaneous tissue disorders	N00106/ 00075/002	Pyrexia/rash: macular/ papular	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	Gastrointestinal disorders	N00173/ 00145/001	Nausea and vomiting	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	Gastrointestinal disorders	N00319/ 00189/001	Vomiting (grade 3)	Suspected, expected	Fludarabine
FCM-miniR/ FCR	General disorders and administration site conditions	N00137/ 00196/002	Nausea, vomiting and dehydration	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/003	Fever (absence neutropenia)	Suspected, expected	Low-dose Rituximab
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/004	Cytokine release grade 3	Suspected, expected	Low-dose Rituximab
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/001	Febrile neutropenia	Suspected, expected	FC
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/002	Febrile	Suspected, expected	Fludarabine and rituximab
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/003	Neutropenic sepsis	Suspected, expected	FCR
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/004	Neutropenic sepsis	Suspected, expected	FCR

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
CLL	10 April 2012	12 June 2012	18 June 2012	6	Recovered
CLL	5 May 2011	17 August 2011	25 August 2011	8	Recovered
CLL	5 May 2011	30 September 2011	7 October 2011	7	Recovered
Other illness: previous septic arthritis	5 May 2011	6 June 2011	9 June 2011	3	Recovered
	5 May 2011	10 December 2012	20 June 2013	192	Recovered
Other illness: vomiting/ dehydration ?did not take allopurinol (patient stopped taking aciclovir/ septrin/allopurinol when nauseous/ vomiting)	17 June 2010	2 July 2010	20 July 2010	18	Recovered
Other illness: acute tubular necrosis; Hypotension	28 June 2012	13 July 2012	23 July 2012	10	Recovered
Other illness: ?Viral/ bacterial infection	21 March 2011	22 April 2011	01 June 2011	40	Recovered
	30 April 2012	20 June 2012	21 June 2012	1	Recovered
	30 August 2012	11 September 2012	17 September 2012	6	Recovered
	17 September 2012	24 September 2012	27 September 2012	3	Recovered
	28 June 2012	14 August 2012	18 August 2012	4	Recovered
	28 June 2012	19 September 2012	19 September 2012	0	Recovered
	4 July 2012	6 August 2012	13 August 2012	7	Recovered
	4 July 2012	26 November 2012	3 December 2012	7	Recovered
	17 September 2012	16 January 2013	22 January 2013	6	Recovered with sequelae
	17 September 2012	13 February 2013	25 October 2013	254	Recovered

continued

TABLE 80 Serious adverse events suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment	Suspected product(s)
FCM-miniR/ FCR	Infections and infestations	N00153/ 00148/001	Febrile neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	Infections and infestations	N00153/ 00177/001	Febrile neutropenia	Suspected, expected	FCM
FCM-miniR/ FCR	Infections and infestations	N00153/ 00186/001	Febrile neutropenia	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	Infections and infestations	N00218/ 00162/001	Neutropenic fever	Suspected, expected	FCM-mini-R
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/002	Neutropenic sepsis (febrile neutropenia)	Suspected, expected	FC
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/003	Febrile neutropenia	Suspected, expected	FC
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/004	Neutropenia with fever 37.8 °C	Suspected, expected	FC

ANC, absolute neutrophil count; CTC, common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Events; EBV, Epstein–Barr virus; HB, haemoglobin; PJP, *Pneumocystis jiroveci* pneumonia; SCC, squamous cell carcinoma; SOB, shortness of breath; URTI, upper respiratory tract infection.
SAE duration: days from date SAE became serious to date of recovery/death (if known).
SAE ID number: centre code/patient ID/SAE number.

Other causality (in addition to trial medications)	Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Outcome of SAE
	4 May 2012	27 May 2012	31 May 2012	4	Recovered
	13 July 2012	4 August 2012	5 August 2012	1	Recovered
CLL	13 August 2012	30 August 2012	2 September 2012	3	Recovered
	20 June 2012	28 August 2012	2 September 2012	5	Recovered
	30 August 2012	14 November 2012	17 November 2012	3	Recovered
	30 August 2012	8 January 2013	13 January 2013	5	Recovered
	30 August 2012	31 January 2013	10 February 2013	10	Recovered

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Blood and lymphatic system disorders	N00014/00028/002	Neutropenia	Fludarabine	Oral	2 August 2010	3 October 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	2 August 2010	3 October 2010	300	mg	Oral	Daily
				Rituximab	i.v.	2 August 2010	29 September 2010	1000	mg	i.v.	Monthly
FCR	Blood and lymphatic system disorders	N00076/00187/001	Platelet count decreased	Fludarabine	Oral	29 August 2012	22 November 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	29 August 2012	22 November 2012	300	mg	Oral	Daily
				Rituximab	i.v.	29 August 2012	22 November 2012	900	mg	i.v.	Once
FCR	Blood and lymphatic system disorders	N00080/00032/001	Infection	Fludarabine	Oral	2 September 2010	3 October 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	2 September 2010	3 October 2010	250	mg	Oral	Daily
				Rituximab	i.v.	2 September 2010	3 October 2010	850	mg	i.v.	STAT
FCR	Blood and lymphatic system disorders	N00098/00017/001	Extremely low Hb	Fludarabine	Oral	10 May 2010	11 October 2010	30	mg	Oral	Daily
				Cyclophosphamide	Oral	10 May 2010	11 October 2010	200	mg	Oral	Daily
				Rituximab	i.v.	10 May 2010	11 October 2010	700	mg	i.v.	Once
FCR	Blood and lymphatic system disorders	N00098/00017/002	Low Hb 5.9 g/dl on Pentra	Fludarabine	Oral	10 May 2010	11 October 2010	30	mg	Oral	Daily
				Cyclophosphamide	Oral	10 May 2010	11 October 2010	200	mg	Oral	Daily
				Rituximab	i.v.	10 May 2010	11 October 2010	700	mg	i.v.	Once
FCR	Blood and lymphatic system disorders	N00114/00088/001	Persistent neutropenia related to chemotherapy	Fludarabine	Oral	31 May 2011	24 September 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	24 September 2011	300	mg	Oral	Daily
				Rituximab	i.v.	31 May 2011	21 September 2011	1000	mg	i.v.	Daily

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Blood and lymphatic system disorders	N00175/ 00155/001	Anaemia	Fludarabine	Oral	7 June 2012	28 September 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	7 June 2012	28 September 2012	300	mg	Oral	Daily
				Rituximab	i.v.	7 June 2012	28 September 2012	950	mg	i.v.	Once a day
FCR	Blood and lymphatic system disorders	N00230/ 00033/002	Myelodysplasia: RAES	Fludarabine	Oral	16 September 2010	7 February 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	16 September 2010	7 February 2011	250	mg	Oral	Daily
				Rituximab	i.v.	16 September 2010	7 February 2011	900	mg	i.v.	Once
FCR	Gastrointestinal disorders	N00050/ 00120/001	Diarrhoea and vomiting	Fludarabine	Oral	9 November 2011	11 December 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	9 November 2011	11 December 2011	250	mg	Oral	Daily
				Rituximab	i.v.	9 November 2011	11 December 2011	670	mg	i.v.	Once
FCR	Gastrointestinal disorders	N00098/ 00060/002	Nausea and vomiting	Fludarabine	Oral	27 January 2011	25 April 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 January 2011	25 April 2011	250	mg	Oral	Daily
				Rituximab	i.v.	27 January 2011	21 April 2011	900	mg	i.v.	Day 1
FCR	Gastrointestinal disorders	N00114/ 00088/003	Gastroenteritis	Fludarabine	Oral	31 May 2011	24 September 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	24 September 2011	300	mg	Oral	Daily
				Rituximab	i.v.	31 May 2011	21 September 2011	1000	mg	i.v.	Over 2 days
FCR	Gastrointestinal disorders	N00349/ 00035/001	Nausea	Fludarabine	i.v.	5 October 2010	16 March 2011	27.5	mg	i.v.	Daily
				Cyclophosphamide	i.v.	5 October 2010	16 March 2011	280	mg	i.v.	Daily
				Rituximab	i.v.	5 October 2010	15 March 2011	700	mg	i.v.	Daily
FCR	General disorders and administration site conditions	N00014/ 00028/004	Infection/anaemia	Fludarabine	Oral	2 August 2010	28 November 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	2 August 2010	28 November 2010	200	mg	Oral	Daily
				Rituximab	i.v.	2 August 2010	24 November 2010	1000	mg	i.v.	Daily

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	General disorders and administration site conditions	N00014/00028/005	Anaemia grade 4	Fludarabine	Oral	2 August 2010	28 November 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	2 August 2010	28 November 2010	200	mg	Oral	Daily
				Rituximab	i.v.	2 August 2010	24 November 2010	1000	mg	i.v.	Monthly
FCR	General disorders and administration site conditions	N00014/00029/001	Rigors	Fludarabine	Oral	24 August 2010	28 August 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	24 August 2010	28 August 2010	250	mg	Oral	Daily
				Rituximab	i.v.	24 August 2010	25 August 2010	500	mg	i.v.	Monthly
FCR	General disorders and administration site conditions	N00098/00019/001	Pyrexial 38.2 °C post first dose of Rituximab	Rituximab	i.v.	17 June 2010	17 June 2010	100	mg	i.v.	Once
FCR	General disorders and administration site conditions	N00114/00055/001	Fever and rigors	Fludarabine	Oral	11 January 2011	15 January 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	11 January 2011	15 January 2011	300	mg	Oral	Daily
				Rituximab	i.v.	11 January 2011	12 January 2011	650	mg	i.v.	Daily
FCR	General disorders and administration site conditions	N00173/00011/001	Hypoxia	Fludarabine	Oral	15 April 2010	17 April 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	15 April 2010	16 April 2010	250	mg	Oral	Daily
				Rituximab	i.v.	15 April 2010	15 April 2010	85	mg	i.v.	Once
FCR	General disorders and administration site conditions	N00173/00137/001	Vomiting	Fludarabine	Oral	7 March 2012	8 April 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	7 March 2012	8 April 2012	250	mg	Oral	Daily
				Rituximab	i.v.	7 March 2012	8 April 2012	900	mg	i.v.	Once only
FCR	General disorders and administration site conditions	N00218/00168/001	Fever and non-specifically unwell	Fludarabine	Oral	9 July 2012	11 July 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	9 July 2012	11 July 2012	300	mg	Oral	Daily
				Rituximab	i.v.	9 July 2012	10 July 2012	750	mg	i.v.	Days 1–2

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	General disorders and administration site conditions	N00319/ 00125/001	Allergic reaction	Fludarabine	Oral	3 February 2012	3 February 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	3 February 2012	3 February 2012	250	mg	Oral	Daily
				Rituximab	i.v.	2 February 2012	2 February 2012	100	mg	i.v.	Once
FCR	General disorders and administration site conditions	N00391/ 00194/002	Probable rituximab reaction	Fludarabine	Oral	19 September 2012	9 January 2013	20	mg	Oral	Daily
				Cyclophosphamide	Oral	19 September 2012	9 January 2013	250	mg	Oral	Daily
				Rituximab	i.v.	19 September 2012	9 January 2013	950	mg	i.v.	Day 1
FCR	Infections and infestations	N00014/ 00028/003	Febrile neutropenia	Fludarabine	Oral	2 August 2010	28 November 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	2 August 2010	28 November 2010	200	mg	Oral	Daily
				Rituximab	i.v.	2 August 2010	24 November 2010	1000	mg	i.v.	Daily
FCR	Infections and infestations	N00014/ 00112/001	Shingles	Fludarabine	Oral	31 October 2011	4 February 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	31 October 2011	4 February 2012	300	mg	Oral	Daily
				Rituximab	i.v.	31 October 2011	30 January 2012	1000	mg	i.v.	Monthly
FCR	Infections and infestations	N00040/ 00056/001	Neutropenic sepsis	Fludarabine	Oral	12 January 2011	20 February 2011	54	mg	Oral	Daily
				Cyclophosphamide	Oral	12 January 2011	20 February 2011	340	mg	Oral	Daily
				Rituximab	i.v.	12 January 2011	20 February 2011	1100	mg	i.v.	Daily
FCR	Infections and infestations	N00046/ 00185/001	Infection with grade-4 neutrophils	Fludarabine	i.v.	23 August 2012	14 December 2012	50	mg	i.v.	Daily
				Cyclophosphamide	i.v.	23 August 2012	14 December 2012	500	mg	i.v.	Daily
				Rituximab	i.v.	23 August 2012	12 December 2012	1000	mg	i.v.	Daily

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00050/ 00041/001	Febrile neutropenia	Fludarabine	i.v.	3 November 2010	3 December 2010	42	mg	i.v.	Daily
				Cyclophosphamide	i.v.	3 November 2010	3 December 2010	420	mg	i.v.	Daily
				Rituximab	i.v.	3 November 2010	1 December 2010	840	mg	i.v.	OD 1/7
FCR	Infections and infestations	N00098/ 00001/001	Neutropenic sepsis	Fludarabine	Oral	15 December 2009	20 December 2009	50	mg	Oral	Daily
				Cyclophosphamide	Oral	15 December 2009	20 December 2009	300	mg	Oral	Daily
				Rituximab	i.v.	15 December 2009	16 December 2009	750	mg	i.v.	Daily
FCR	Infections and infestations	N00098/ 00060/001	Fever: no focus identified	Fludarabine	Oral	27 January 2011	28 February 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 January 2011	28 February 2011	250	mg	Oral	Daily
				Rituximab	i.v.	27 January 2011	24 February 2011	900	mg	i.v.	1 day
FCR	Infections and infestations	N00098/ 00060/003	Probable late PCP/PJP	Fludarabine	Oral	27 January 2011	19 June 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 January 2011	19 June 2011	250	mg	Oral	Daily
				Rituximab	i.v.	27 January 2011	15 June 2011	900	mg	i.v.	1 day
FCR	Infections and infestations	N00099/ 00084/001	Pyrexia ?neutropenic sepsis	Fludarabine	Oral	18 May 2011	9 October 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	18 May 2011	9 October 2011	300	mg	Oral	Daily
				Rituximab	i.v.	18 May 2011	5 October 2011	1000	mg	i.v.	Day 1
FCR	Infections and infestations	N00099/ 00105/001	Neutropenic sepsis	Fludarabine	Oral	5 September 2011	7 September 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	5 September 2011	7 September 2011	250	mg	Oral	Daily
				Rituximab	i.v.	5 September 2011	6 September 2011	600	mg	i.v.	1/2 dose daily

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00106/ 00130/001	Neutropenic sepsis	Fludarabine	Oral	23 January 2012	23 March 2012	50	mg	Oral	OD × 4 days
				Cyclophosphamide	Oral	23 January 2012	23 March 2012	300	mg	Oral	OD × 4 days
				Rituximab	i.v.	23 January 2012	19 March 2012	1000	mg	i.v.	1 Day
FCR	Infections and infestations	N00106/ 00130/002	Neutropenic sepsis	Fludarabine	Oral	23 January 2012	17 April 2012	50	mg	Oral	OD × 5 days
				Cyclophosphamide	Oral	23 January 2012	17 April 2012	300	mg	Oral	OD × 5 days
				Rituximab	i.v.	23 January 2012	17 April 2012	1000	mg	i.v.	OD × 1 day
FCR	Infections and infestations	N00106/ 00179/001	Pyrexial, neutropenic	Fludarabine	Oral	25 July 2012	30 July 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	25 July 2012	30 July 2012	250	mg	Oral	Daily
				Rituximab	i.v.	25 July 2012	25 July 2012	700	mg	i.v.	OD over 2 days
FCR	Infections and infestations	N00106/ 00179/003	Neutropenic sepsis	Fludarabine	Oral	25 July 2012	2 September 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	25 July 2012	2 September 2012	250	mg	Oral	Daily
				Rituximab	i.v.	25 July 2012	31 August 2012	900	mg	i.v.	Daily
FCR	Infections and infestations	N00114/ 00067/001	Neutropenic sepsis	Fludarabine	Oral	22 February 2011	21 May 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	22 February 2011	21 May 2011	250	mg	Oral	Daily
				Rituximab	i.v.	22 February 2011	21 May 2011	950	mg	i.v.	Day 1
FCR	Infections and infestations	N00114/ 00067/002	Neutropenic sepsis ?cause	Fludarabine	Oral	22 February 2011	16 July 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	22 February 2011	16 July 2011	200	mg	Oral	Daily
				Rituximab	i.v.	22 February 2011	13 July 2011	950	mg	i.v.	For second day of cycle

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00114/ 00067/003	?Neutropenic sepsis	Fludarabine	Oral	22 February 2011	16 July 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	22 February 2011	16 July 2011	250	mg	Oral	Daily
				Rituximab	i.v.	22 February 2011	16 July 2011	950	mg	i.v.	Once
FCR	Infections and infestations	N00114/ 00067/004	Neutropenic sepsis	Fludarabine	Oral	22 February 2011	16 July 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	22 February 2011	16 July 2011	250	mg	Oral	Daily
				Rituximab	i.v.	22 February 2011	16 July 2011	950	mg	i.v.	Over 2 days
FCR	Infections and infestations	N00114/ 00088/002	Neutropenic sepsis	Fludarabine	Oral	31 May 2011	24 September 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	24 September 2011	300	mg	Oral	Daily
				Rituximab	i.v.	31 May 2011	21 September 2011	1000	mg	i.v.	Over 2 days
FCR	Infections and infestations	N00153/ 00026/001	Infection	Fludarabine	Oral	28 July 2010	1 August 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	28 July 2010	1 August 2010	350	mg	Oral	Daily
				Rituximab	i.v.	28 July 2010	29 July 2010	800	mg	i.v.	Once (split 2 days)
FCR	Infections and infestations	N00153/ 00050/001	Chest infection	Fludarabine	Oral	30 November 2010	26 February 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	30 November 2010	26 February 2011	350	mg	Oral	Daily
				Rituximab	i.v.	30 November 2010	22 February 2011	1100	mg	i.v.	Once
FCR	Infections and infestations	N00173/ 00011/003	Lower respiratory tract infection	Fludarabine	Oral	15 April 2010	23 June 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	15 April 2010	23 June 2010	250	mg	Oral	Daily
				Rituximab	i.v.	15 April 2010	23 June 2010	850	mg	i.v.	Once only on day 1 of cycle

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00218/ 00168/002	Neutropenic sepsis	Fludarabine	Oral	9 July 2012	7 September 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	9 July 2012	7 September 2012	300	mg	Oral	Daily
				Rituximab	i.v.	9 July 2012	3 September 2012	1000	mg	i.v.	Day 1
FCR	Infections and infestations	N00230/ 00033/001	Neutropenic sepsis	Fludarabine	Oral	16 September 2010	14 October 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	16 September 2010	14 October 2010	250	mg	Oral	Daily
				Rituximab	i.v.	16 September 2010	14 October 2010	700	mg	i.v.	Once
FCR	Infections and infestations	N00231/ 00174/001	Febrile, rigors, ?septic. Episodes of diarrhoea for 2 days	Fludarabine	Oral	24 July 2012	22 August 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	24 July 2012	22 August 2012	250	mg	Oral	Daily
				Rituximab	i.v.	24 July 2012	21 August 2012	900	mg	i.v.	Per cycle
FCR	Infections and infestations	N00231/ 00174/002	Febrile illness (pyrexia, rigors)	Fludarabine	Oral	24 July 2012	22 August 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	24 July 2012	22 August 2012	250	mg	Oral	Daily
				Rituximab	i.v.	24 July 2012	21 August 2012	900	mg	i.v.	Per cycle
FCR	Infections and infestations	N00231/ 00174/003	Neutropenic sepsis	Fludarabine	Oral	24 July 2012	30 September 2012	44	mg	Oral	Daily
				Cyclophosphamide	Oral	24 July 2012	30 September 2012	270	mg	Oral	Daily
				Rituximab	i.v.	24 July 2012	25 September 2012	900	mg	i.v.	Once per cycle
FCR	Infections and infestations	N00255/ 00138/001	Neutropenic sepsis	Fludarabine	Oral	18 March 2012	22 March 2012	40	mg	Oral	OD × 5 days
				Cyclophosphamide	Oral	18 March 2012	22 March 2012	250	mg	Oral	OD × 5 days
				Rituximab	i.v.	16 March 2012	19 March 2012	600	mg	i.v.	Every 28 days

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00255/ 00166/001	Febrile neutropenia	Fludarabine	Oral	4 July 2012	12 September 2012	30	mg	Oral	Daily
				Cyclophosphamide	Oral	4 July 2012	12 September 2012	300	mg	Oral	Daily
				Rituximab	i.v.	4 July 2012	7 September 2012	950	mg	i.v.	Start dose
FCR	Infections and infestations	N00255/ 00166/002	Neutropenic sepsis	Fludarabine	Oral	4 July 2012	2 January 2013	20	mg	Oral	Daily
				Cyclophosphamide	Oral	4 July 2012	2 January 2013	200	mg	Oral	Daily
				Rituximab	i.v.	4 July 2012	2 January 2013	950	mg	i.v.	Start dose
FCR	Infections and infestations	N00280/ 00008/001	Neutropenic sepsis	Fludarabine	Oral	25 March 2010	31 May 2010	40	mg	Oral	40 mg daily for 5 days
				Cyclophosphamide	Oral	25 March 2010	31 May 2010	300	mg	Oral	300 mg daily for 5 days
				Rituximab	i.v.	25 March 2010	27 May 2010	900	mg	i.v.	Single dose
FCR	Infections and infestations	N00319/ 00125/002	Febrile neutropenia	Fludarabine	Oral	2 February 2012	6 February 2012	40	mg	Oral	Once a day for 5 days
				Cyclophosphamide	Oral	2 February 2012	6 February 2012	250	mg	Oral	Once a day for 5 days
				Rituximab	i.v.	2 February 2012	6 February 2012	500	mg	i.v.	Once a day
FCR	Infections and infestations	N00361/ 00123/002	Neutropenic sepsis	Fludarabine	Oral	5 December 2011	19 June 2012	20	mg	Oral	Daily
				Cyclophosphamide	Oral	5 December 2011	19 June 2012	120	mg	Oral	Daily
				Rituximab	i.v.	5 December 2011	19 June 2012	800	mg	i.v.	Daily

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Infections and infestations	N00391/ 00111/001	Neutropenic sepsis	Fludarabine	Oral	19 October 2011	23 October 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	19 October 2011	23 October 2011	250	mg	Oral	Daily
				Rituximab	i.v.	19 October 2011	19 October 2011	700	mg	i.v.	Days 1 and 2 of cycle 1
FCR	Infections and infestations	N00391/ 00194/001	?Neutropenic sepsis ?Viral infection ?Drug-induced gastritis	Fludarabine	Oral	19 September 2012	13 December 2012	20	mg	Oral	Daily
				Cyclophosphamide	Oral	19 September 2012	13 December 2012	250	mg	Oral	Daily
				Rituximab	i.v.	19 September 2012	12 December 2012	900	mg	i.v.	Day 1
FCR	Infections and infestations	N00698/ 00198/001	Febrile neutropenia	Fludarabine	Oral	20 September 2012	24 December 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	20 September 2012	24 December 2012	300	mg	Oral	Daily
				Rituximab	i.v.	20 September 2012	20 December 2012	900	mg	Oral	Daily
FCR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N00098/ 00002/001	SCC: two lesions (lower back and central chest)	Fludarabine	i.v.	14 January 2010	3 June 2010	55	mg	i.v.	Once
				Cyclophosphamide	i.v.	14 January 2010	3 June 2010	550	mg	i.v.	Once
				Rituximab	i.v.	14 January 2010	2 June 2010	1100	mg	i.v.	Once
FCR	Psychiatric disorders	N00349/ 00104/002	Psychotic episode	Fludarabine	Oral	13 September 2011	13 December 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	13 September 2011	13 December 2011	250	mg	Oral	Daily
				Rituximab	i.v.	13 September 2011	9 December 2011	800	mg	i.v.	Daily
FCR	Skin and subcutaneous tissue disorders	N00349/ 00070/001	Rash	Fludarabine	Oral	11 March 2011	12 April 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	11 March 2011	12 April 2011	300	mg	Oral	Daily
				Rituximab	i.v.	11 March 2011	12 April 2011	1000	mg	i.v.	OD

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCR	Skin and subcutaneous tissue disorders	N00353/ 00122/001	Erythemous rash grade 3	Fludarabine	Oral	17 November 2011	16 December 2011	20	mg	Oral	Daily
				Cyclophosphamide	Oral	17 November 2011	16 December 2011	300	mg	Oral	Daily
				Rituximab	i.v.	17 November 2011	15 December 2011	930	mg	i.v.	Once
FCM-miniR	Blood and lymphatic system disorders	N00009/ 00127/001	Pleural effusion and pulmonary embolism	Fludarabine	Oral	20 December 2011	24 December 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	20 December 2011	24 December 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	20 December 2011	20 December 2011	13	mg	i.v.	Daily
				Mini Rituximab	i.v.	20 December 2011	20 December 2011	100	mg	i.v.	Daily
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/001	Neutropenic sepsis	Fludarabine	Oral	22 July 2010	20 September 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 July 2010	20 September 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	22 July 2010	16 September 2010	10	mg	i.v.	15-minute infusion
				Mini Rituximab	i.v.	22 July 2010	16 September 2010	100	mg	i.v.	1 day
FCM-miniR	Blood and lymphatic system disorders	N00099/ 00027/002	Neutropenic sepsis	Fludarabine	Oral	22 July 2010	20 September 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 July 2010	20 September 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	22 July 2010	16 September 2010	10	mg	i.v.	15-minute infusion
				Mini Rituximab	i.v.	22 July 2010	16 September 2010	100	mg	i.v.	1 day
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/003	DCT-negative autoimmune haemolysis	Fludarabine	Oral	31 May 2011	8 October 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	8 October 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	31 May 2011	4 October 2011	12	mg	i.v.	Once
				Mini Rituximab	i.v.	31 May 2011	4 October 2011	100	mg	i.v.	Once

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Blood and lymphatic system disorders	N00114/ 00086/004	Pulmonary embolism	Fludarabine	Oral	31 May 2011	8 October 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	8 October 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	31 May 2011	4 October 2011	12	mg	i.v.	Once
				Mini Rituximab	i.v.	31 May 2011	4 October 2011	100	mg	i.v.	Once
FCM-miniR	Blood and lymphatic system disorders	N00153/ 00010/001	Neutropenia	Fludarabine	Oral	29 March 2010	10 July 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	29 March 2010	10 July 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	29 March 2010	5 July 2010	9	mg	i.v.	Once
				Mini Rituximab	i.v.	29 March 2010	5 July 2010	100	mg	i.v.	Once
FCM-miniR	Blood and lymphatic system disorders	N00391/ 00144/001	Marked pancytopenia post chemotherapy; cough and SOB	Fludarabine	Oral	3 May 2012	24 September 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	3 May 2012	24 September 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	3 May 2012	20 September 2012	10	mg	i.v.	Day 1 only
				Mini Rituximab	i.v.	3 May 2012	20 September 2012	100	mg	i.v.	Day 1 only
FCM-miniR	Blood and lymphatic system disorders	N01527/ 00030/001	Anaemia	Fludarabine	Oral	12 August 2010	17 August 2010	60	mg	Oral	5 days
				Cyclophosphamide	Oral	12 August 2010	17 August 2010	350	mg	Oral	5 days
				Mitoxantrone	i.v.	12 August 2010	12 August 2010	14.2	mg	i.v.	Every 28 days
				Mini Rituximab	i.v.	12 August 2010	12 August 2010	100	mg	i.v.	Every 28 days

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Gastrointestinal disorders	N00050/ 00083/001	Vomiting	Fludarabine	i.v.	11 May 2011	7 October 2011	52.5	mg	i.v.	Daily
				Cyclophosphamide	i.v.	11 May 2011	7 October 2011	520	mg	i.v.	Daily
				Mitoxantrone	i.v.	11 May 2011	5 October 2011	13	mg	i.v.	Daily
				Mini Rituximab	i.v.	11 May 2011	5 October 2011	100	mg	i.v.	Daily
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/001	Vomiting	Fludarabine	Oral	17 September 2010	21 September 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	17 September 2010	21 September 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	17 September 2010	17 September 2010	11	mg	i.v.	Once
				Mini Rituximab	i.v.	17 September 2010	17 September 2010	100	mg	i.v.	Once
FCM-miniR	Gastrointestinal disorders	N00153/ 00034/002	Nausea and vomiting	Fludarabine	Oral	17 September 2010	18 October 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	17 September 2010	18 October 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	17 September 2010	14 October 2010	11	mg	i.v.	Once
				Mini Rituximab	i.v.	17 September 2010	14 October 2010	100	mg	i.v.	Once
FCM-miniR	Gastrointestinal disorders	N01527/ 00184/001	Vomiting	Fludarabine	Oral	23 August 2012	27 September 2012	30	mg	Oral	Daily
				Cyclophosphamide	Oral	23 August 2012	27 September 2012	200	mg	Oral	Daily
				Mitoxantrone	i.v.	23 August 2012	27 September 2012	7.6	mg	i.v.	Daily
				Mini Rituximab	i.v.	23 August 2012	27 September 2012	100	mg	i.v.	Daily
FCM-miniR	General disorders and administration site conditions	N00040/ 00180/001	Serious rituximab reaction	Cyclophosphamide	Oral	30 July 2012	30 July 2012	300	mg	Oral	Daily
				Mini Rituximab	i.v.	30 July 2012	30 July 2012				

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	General disorders and administration site conditions	N00098/00004/001	High-grade fever	Fludarabine	Oral	25 February 2010	1 March 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	25 February 2010	1 March 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	24 February 2010	24 February 2010	11	mg	i.v.	Once (given on day 1 only)
				Mini Rituximab	i.v.	24 February 2010	24 February 2010	100	mg	i.v.	Once (given on day 1 only)
FCM-miniR	General disorders and administration site conditions	N00098/00005/003	Anaphylaxis	Mini Rituximab	i.v.	17 February 2010	17 February 2010	35	Other	i.v.	Once
FCM-miniR	General disorders and administration site conditions	N00098/00099/001	Vasovagal episode with first dose of rituximab	Fludarabine							
				Cyclophosphamide							
				Mitoxantrone	i.v.	10 August 2011	10 August 2011	12	mg	i.v.	Once
				Rituximab	i.v.	10 August 2011	10 August 2011	100	mg	i.v.	Once
FCM-miniR	General disorders and administration site conditions	N00099/00036/001	Reaction to rituximab	Fludarabine	Oral	27 September 2010	1 October 2010	50	mg	Oral	For 5 days
				Cyclophosphamide	Oral	27 September 2010	1 October 2010	300	mg	Oral	For 5 days
				Mitoxantrone	i.v.	27 September 2010	27 September 2010	12	mg	i.v.	1-day infusion
				Mini Rituximab	i.v.	27 September 2010	27 September 2010	15	mg	i.v.	1-day infusion

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	General disorders and administration site conditions	N00153/ 00156/001	Infusion reaction	Fludarabine	Oral	7 June 2012	11 June 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	7 June 2012	11 June 2012	300	mg	Oral	Daily
				Mitoxantrone	i.v.	7 June 2012	7 June 2012	11	mg	i.v.	OD
				Mini Rituximab	i.v.	7 June 2012	7 June 2012	100	mg	i.v.	OD
FCM-miniR	Immune system disorders	N00361/ 00109/001	Haemolytic anaemia	Fludarabine	Oral	20 October 2011	16 November 2011	36	mg	Oral	Daily
				Cyclophosphamide	Oral	20 October 2011	16 November 2011	230	mg	Oral	Daily
				Mitoxantrone	i.v.	20 October 2011	16 November 2011	9	mg	i.v.	D1 daily
				Mini Rituximab	i.v.	20 October 2011	16 November 2011	100	mg	i.v.	D1 daily
FCM-miniR	Infections and infestations	N00014/ 00054/001	Sepsis	Fludarabine	Oral	19 January 2011	23 January 2011	50	mg	Oral	5 × days/ 28 days
				Cyclophosphamide	Oral	19 January 2011	23 January 2011	300	mg	Oral	5 × days/ 28 days
				Mitoxantrone	i.v.	19 January 2011	19 January 2011	13	mg	i.v.	1 × 28 days
				Mini Rituximab	i.v.	19 January 2011	19 January 2011	100	mg	i.v.	28 days
FCM-miniR	Infections and infestations	N00040/ 00108/001	Neutropenic sepsis	Fludarabine	Oral	13 September 2011	17 September 2011	48	mg	Oral	Daily
				Cyclophosphamide	Oral	13 September 2011	17 September 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	13 September 2011	17 September 2011	12	mg	i.v.	Once
				Mini Rituximab	i.v.	13 September 2011	13 September 2011	100	mg	i.v.	Once

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00040/ 00108/002	Pyrexia	Fludarabine	Oral	13 September 2011	17 September 2011	48	mg	Oral	Daily
				Cyclophosphamide	Oral	13 September 2011	17 September 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	13 September 2011	17 September 2011	12	mg	i.v.	1 day
				Mini Rituximab	i.v.	13 September 2011	17 September 2011	100	mg	i.v.	1 day
FCM-miniR	Infections and infestations	N00040/ 00108/004	Neutropenic sepsis	Fludarabine	Oral	13 September 2011	21 December 2011	48	mg	Oral	Daily
				Cyclophosphamide	Oral	13 September 2011	21 December 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	13 September 2011	21 December 2011	12	mg	i.v.	Once
				Mini Rituximab	i.v.	13 September 2011	21 December 2011	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00050/ 00095/001	Neutropenic sepsis	Fludarabine	Oral	27 July 2011	25 December 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 July 2011	25 December 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	27 July 2011	21 December 2011	11	mg	i.v.	Once
				Mini Rituximab	i.v.	27 July 2011	21 December 2011	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00080/ 00058/001	Infection with grade 4 neutrophils	Fludarabine	Oral	26 January 2011	24 April 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	26 January 2011	24 April 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	26 January 2011	20 April 2011	12	mg	i.v.	STAT
				Mini Rituximab	i.v.	26 January 2011	20 April 2011	100	mg	i.v.	STAT
FCM-miniR	Infections and infestations	N00080/ 00058/002	Chest infection/ febrile neutropenia	Fludarabine	Oral	26 January 2011	3 July 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	26 January 2011	3 July 2011	200	mg	Oral	Daily
				Mitoxantrone	i.v.	26 January 2011	29 June 2011	9	mg	i.v.	Stat
				Mini Rituximab	i.v.	26 January 2011	29 June 2011	100	mg	i.v.	Stat

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00098/00005/001	Pyrexia and rigors	Fludarabine	Oral	17 February 2010	16 March 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	17 February 2010	16 March 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	17 February 2010	16 March 2010	12	mg	i.v.	Once
				Mini Rituximab	i.v.	17 February 2010	16 March 2010	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00098/00005/002	Pyrexia and diarrhoea	Fludarabine	Oral	17 February 2010	16 March 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	17 February 2010	16 March 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	17 February 2010	16 March 2010	12	mg	i.v.	Once
				Mini Rituximab	i.v.	17 February 2010	16 March 2010	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00098/00005/004	Neutropenic sepsis	Fludarabine	Oral	17 February 2010	18 April 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	17 February 2010	18 April 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	17 February 2010	14 April 2010	12	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00098/00005/005	Fever, unknown origin, nausea	Fludarabine	Oral	17 February 2010	12 May 2010	50	mg	Oral	5 days
				Cyclophosphamide	Oral	17 February 2010	12 May 2010	300	mg	Oral	5 days
				Mitoxantrone	i.v.	17 February 2010	12 May 2010	12	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00098/00115/001	Urinary tract infection	Fludarabine	Oral	2 November 2011	26 April 2012	50	mg	Oral	OD Days 1–5
				Cyclophosphamide	Oral	2 November 2011	26 April 2012	300	mg	Oral	OD Days 1–5
				Mitoxantrone	i.v.	2 November 2011	26 April 2012	13	mg	i.v.	Once only
				Mini Rituximab	i.v.	2 November 2011	26 April 2012	100	mg	i.v.	Once only

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00099/ 00027/003	Neutropenic sepsis	Fludarabine	Oral	22 July 2010	9 January 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 July 2010	9 January 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	22 July 2010	5 January 2011	10	mg	i.v.	15-minute infusion
				Mini Rituximab	i.v.	22 July 2010	5 January 2011	100	mg	i.v.	1 day
FCM-miniR	Infections and infestations	N00099/ 00036/002	Neutropenic sepsis	Fludarabine	Oral	27 September 2010	29 September 2010	50	mg	Oral	For 5 days
				Cyclophosphamide	Oral	27 September 2010	29 October 2010	300	mg	Oral	For 5 days
				Mitoxantrone	i.v.	27 September 2010	25 October 2010	12	mg	i.v.	1-day infusion
				Mini Rituximab	i.v.	27 September 2010	27 September 2010	15	mg	i.v.	1-day infusion
FCM-miniR	Infections and infestations	N00099/ 00045/001	Neutropenic sepsis	Fludarabine	Oral	17 November 2010	16 January 2011	50	mg	Oral	5 days
				Cyclophosphamide	Oral	17 November 2010	16 January 2011	300	mg	Oral	5 days
				Mitoxantrone	i.v.	17 November 2010	12 January 2011	12	mg	i.v.	Day 1 only
				Mini Rituximab	i.v.	17 November 2010	12 January 2011	100	mg	i.v.	Day 1 only
FCM-miniR	Infections and infestations	N00106/ 00075/001	URTI (not neutropenic) and anaemia	Fludarabine	Oral	23 March 2011	28 March 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	23 March 2011	28 March 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	23 March 2011	23 March 2011	11	mg	i.v.	Once
				Mini Rituximab	i.v.	23 March 2011	23 March 2011	100	mg	i.v.	Once

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00106/ 00075/003	Neutropenic sepsis	Fludarabine	Oral	23 March 2011	1 May 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	23 March 2011	2 May 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	23 March 2011	23 March 2011	11	mg	i.v.	Once
				Mini Rituximab	i.v.	23 March 2011	23 March 2011	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00111/ 00132/001	Pyrexia neutropenia	Fludarabine	Oral	1 February 2012	2 May 2012	45	mg	Oral	Daily
				Cyclophosphamide	Oral	1 February 2012	2 May 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	1 February 2012	27 April 2012	11.5	mg	i.v.	28 days
				Mini Rituximab	i.v.	1 February 2012	27 April 2012	100	mg	i.v.	28 days
FCM-miniR	Infections and infestations	N00111/ 00132/003	Opportunistic infection associated with > grade 2 lymphopenia	Fludarabine	Oral	1 February 2012	28 July 2012	30	mg	Oral	Daily
				Cyclophosphamide	Oral	1 February 2012	28 July 2012	200	mg	Oral	Daily
				Mitoxantrone	i.v.	1 February 2012	28 July 2012	8	mg	i.v.	Once
				Mini Rituximab	i.v.	1 February 2012	28 July 2012	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00114/ 00006/002	Infection	Fludarabine	Oral	2 March 2010	24 July 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	2 March 2010	24 July 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	2 March 2010	20 July 2010	12	mg	i.v.	Daily
				Mini Rituximab	i.v.	2 March 2010	20 July 2010	100	mg	i.v.	Daily
FCM-miniR	Infections and infestations	N00114/ 00023/001	Bilateral pneumonia	Fludarabine	Oral	13 July 2010	4 November 2010	50	mg	Oral	Daily
				Cyclophosphamide	Oral	13 July 2010	4 November 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	13 July 2010	30 November 2010	11	mg	i.v.	Once
				Mini Rituximab	i.v.	13 July 2010	30 November 2010	100	mg	i.v.	Once

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00114/ 00086/001	Neutropenic sepsis	Fludarabine	Oral	31 May 2011	4 August 2011	50	mg	Oral	Daily
				Cyclophosphamide	Oral	31 May 2011	4 August 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	31 May 2011	4 August 2011	12	mg	i.v.	Once
				Mini Rituximab	i.v.	31 May 2011	4 August 2011	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00114/ 00094/001	Dehydration and diarrhoea, secondary to low Hb	Fludarabine	Oral	9 August 2011	5 September 2011	20	mg	Oral	Daily
				Cyclophosphamide	Oral	9 August 2011	5 September 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	9 August 2011	5 September 2011	9	mg	i.v.	Once
				Mini Rituximab	i.v.	9 August 2011	5 September 2011	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00132/ 00069/001	Neutropenic sepsis	Fludarabine	Oral	27 April 2011	27 April 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 April 2011	27 April 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	27 April 2011	27 April 2011	10	mg	i.v.	Day 1
				Mini Rituximab	i.v.	27 April 2011	27 April 2011	100	mg	i.v.	Day 1
FCM-miniR	Infections and infestations	N00132/ 00069/002	Grade 2 fevers after chemotherapy	Fludarabine	Oral	27 April 2011	25 July 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	27 April 2011	25 July 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	27 April 2011	25 July 2011	10	mg	i.v.	1 day
				Mini Rituximab	i.v.	27 April 2011	25 July 2011	100	mg	i.v.	1 day
FCM-miniR	Infections and infestations	N00153/ 00010/002	Febrile neutropenia	Fludarabine	Oral	29 March 2010	10 July 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	29 March 2010	10 July 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	29 March 2010	5 July 2010	9	mg	i.v.	Once
				Mini Rituximab	i.v.	29 March 2010	5 July 2010	100	mg	i.v.	Once

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00153/00016/001	Neutropenic sepsis/ neutropenic fever	Fludarabine	Oral	5 May 2010	30 August 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	5 May 2010	30 August 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	5 May 2010	26 August 2010	11	mg	i.v.	Once
				Mini Rituximab	i.v.	5 May 2010	26 August 2010	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00153/00020/001	Neutropenic sepsis	Fludarabine	Oral	28 June 2010	23 August 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	28 June 2010	23 August 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	28 June 2010	23 August 2010	10	mg	i.v.	Once
				Mini Rituximab	i.v.	28 June 2010	23 August 2010	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00153/00020/002	Neutropenic sepsis	Fludarabine	Oral	28 June 2010	23 August 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	28 June 2010	23 August 2010	250	mg	Oral	Daily
				Mitoxantrone	i.v.	28 June 2010	23 August 2010	10	mg	i.v.	Once
				Mini Rituximab	i.v.	28 June 2010	23 August 2010	100	mg	i.v.	Once
FCM-miniR	Infections and infestations	N00153/00156/002	Lower respiratory tract infection	Fludarabine	Oral	7 June 2012	11 June 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	7 June 2012	11 June 2012	300	mg	Oral	Daily
				Mitoxantrone	i.v.	7 June 2012	7 June 2012	11	mg	i.v.	Daily
				Mini Rituximab	i.v.	7 June 2012	7 June 2012	100	mg	i.v.	Daily
FCM-miniR	Infections and infestations	N00161/00047/001	Neutropenic sepsis	Fludarabine	Oral	16 November 2010	20 November 2010	40	mg	Oral	Daily
				Cyclophosphamide	Oral	16 November 2010	20 November 2010	300	mg	Oral	Daily
				Mitoxantrone	i.v.	16 November 2010	16 November 2010	11	mg	i.v.	D1
				Mini Rituximab	i.v.	16 November 2010	16 November 2010	100	mg	i.v.	D1

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00161/ 00047/002	Suspected neutropenic sepsis	Fludarabine	i.v.	16 November 2010	12 June 2011	30	mg	i.v.	Daily
				Cyclophosphamide	i.v.	16 November 2010	12 June 2011	200	mg	i.v.	Daily
				Mitoxantrone	i.v.	16 November 2010	12 June 2011	8	mg	i.v.	Daily
				Mini Rituximab	i.v.	16 November 2010	12 June 2011	100	mg	i.v.	Daily
FCM-miniR	Infections and infestations	N00161/ 00047/003	Chest infection	Fludarabine	i.v.	16 November 2010	12 June 2011	30	mg	i.v.	Daily
				Cyclophosphamide	i.v.	16 November 2010	12 June 2011	200	mg	i.v.	Daily
				Mitoxantrone	i.v.	16 November 2010	12 June 2011	8	mg	i.v.	Daily
				Mini Rituximab	i.v.	16 November 2010	12 June 2011	100	mg	i.v.	Daily
FCM-miniR	Infections and infestations	N00280/ 00039/001	Septic/sepsis	Fludarabine	Oral	4 November 2010	1 February 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	4 November 2010	1 February 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	4 November 2010	27 January 2011	9	mg	i.v.	Daily
				Mini Rituximab	i.v.	4 November 2010	27 January 2011	100	mg	i.v.	Daily
FCM-miniR	Infections and infestations	N00319/ 00080/001	Neutropenia	Fludarabine	Oral	22 June 2011	26 June 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 June 2011	26 June 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	22 June 2011	26 June 2011	11	mg	i.v.	Once only
				Mini Rituximab	i.v.	22 June 2011	26 June 2011	100	mg	i.v.	Once only
FCM-miniR	Infections and infestations	N00319/ 00080/002	Temperature 37.8 °C	Fludarabine	Oral	22 June 2011	26 June 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 June 2011	26 June 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	22 June 2011	22 June 2011	11	mg	i.v.	Once
				Mini Rituximab	i.v.	22 June 2011	22 June 2011	100	mg	i.v.	Once

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00319/ 00080/003	Temperature 37.5 °C	Fludarabine	Oral	22 June 2011	17 August 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 June 2011	17 August 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	22 June 2011	17 August 2011	11	mg	i.v.	Stat
				Mini Rituximab	i.v.	22 June 2011	17 August 2011	100	mg	i.v.	Stat
FCM-miniR	Infections and infestations	N00319/ 00080/004	Fever grade 1	Fludarabine	Oral	22 June 2011	14 September 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	22 June 2011	14 September 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	22 June 2011	14 September 2011	11	mg	i.v.	1 day
				Mini Rituximab	i.v.	22 June 2011	14 September 2011	100	mg	i.v.	1 day
FCM-miniR	Infections and infestations	N00353/ 00065/001	Fever	Fludarabine	Oral	18 February 2011	20 April 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	18 February 2011	20 April 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	18 February 2011	15 April 2011	11	mg	i.v.	4 weekly
				Mini Rituximab	i.v.	18 February 2011	15 April 2011	100	mg	i.v.	4 weekly
FCM-miniR	Infections and infestations	N00391/ 00071/001	Grade 3 anaemia and grade 4 febrile neutropenia	Fludarabine	Oral	24 March 2011	21 April 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	24 March 2011	21 April 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	24 March 2011	21 April 2011	10	mg	i.v.	Day 1
				Mini Rituximab	i.v.	24 March 2011	21 April 2011	100	mg	i.v.	Day 1

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Infections and infestations	N00391/ 00142/001	Neutropenia and fever and sweats	Fludarabine	Oral	27 April 2012	1 May 2012	40	mg	Oral	OD Days 1–5
				Cyclophosphamide	Oral	27 April 2012	1 May 2012	250	mg	Oral	OD Days 1–5
				Mitoxantrone	i.v.	27 April 2012	1 May 2012	10	mg	i.v.	Day 1
				Mini Rituximab	i.v.	27 April 2012	1 May 2012	100	mg	i.v.	Day 1
FCM-miniR	Infections and infestations	N01527/ 00081/002	Febrile neutropenia	Fludarabine	Oral	12 May 2011	31 August 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	12 May 2011	31 August 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	12 May 2011	31 August 2011	10	mg	i.v.	OD
				Mini Rituximab	i.v.	12 May 2011	31 August 2011	100	mg	i.v.	OD
FCM-miniR	Infections and infestations	N01527/ 00081/003	Febrile neutropenia	Fludarabine	Oral	12 May 2011	31 August 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	12 May 2011	31 August 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	12 May 2011	31 August 2011	10	mg	i.v.	OD
				Mini Rituximab	i.v.	12 May 2011	31 August 2011	100	mg	i.v.	OD
FCM-miniR	Musculoskeletal and connective tissue disorders	N01527/ 00081/001	Infection with normal ANC; ?septic arthritis	Fludarabine	Oral	12 May 2011	9 June 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	12 May 2011	9 June 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	12 May 2011	9 June 2011	10	mg	i.v.	Once
				Mini Rituximab	i.v.	12 May 2011	9 June 2011	100	mg	i.v.	Once

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N01527/ 00081/004	EBV – associated lymphoproliferative disorder	Fludarabine	Oral	12 May 2011	8 August 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	12 May 2011	8 August 2011	250	mg	Oral	Daily
				Mitoxantrone	i.v.	12 May 2011	8 August 2011	10	mg	i.v.	Day 1 of cycle
				Mini Rituximab	i.v.	12 May 2011	8 August 2011	100	mg	i.v.	Day 1 of cycle
FCM-miniR	Renal and urinary disorders	N00071/ 00021/001	Acute renal failure – tumour lysis syndrome	Fludarabine	Oral	24 June 2010	28 June 2010	40	mg	Oral	4 weekly
				Cyclophosphamide	Oral	24 June 2010	28 June 2010	200	mg	Oral	4 weekly
				Mitoxantrone	i.v.	24 June 2010	24 June 2010	9	mg	i.v.	4 weekly
				Mini Rituximab	i.v.	24 June 2010	24 June 2010	100	mg	i.v.	4 weekly
FCM-miniR	Renal and urinary disorders	N00353/ 00165/001	Renal failure CTC grade 3	Fludarabine	Oral	6 July 2012	10 July 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	6 July 2012	10 July 2012	300	mg	Oral	Daily
				Mitoxantrone	i.v.	6 July 2012	6 July 2012	12	mg	i.v.	Once
				Mini Rituximab	i.v.	6 July 2012	6 July 2012	100	mg	i.v.	Once
FCM-miniR	Skin and subcutaneous tissue disorders	N00106/ 00075/002	Pyrexia/rash – macular/papular	Fludarabine	Oral	23 March 2011	23 April 2011	40	mg	Oral	Daily
				Cyclophosphamide	Oral	23 March 2011	23 April 2011	300	mg	Oral	Daily
				Mitoxantrone	i.v.	23 March 2011	20 April 2011	11	mg	i.v.	Once
				Mini Rituximab	i.v.	23 March 2011	20 April 2011	100	mg	i.v.	Once

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR/ FCR	Gastrointestinal disorders	N00173/ 00145/001	Nausea plus vomiting	Fludarabine	Oral	17 May 2012	18 June 2012	40	mg	Oral	Daily for 5 days
				Cyclophosphamide	Oral	17 May 2012	18 June 2012	300	mg	Oral	Daily for 5 days
				Mitoxantrone	i.v.	17 May 2012	18 June 2012	11	mg	i.v.	Once on day 1
				Mini Rituximab	i.v.	17 May 2012	18 June 2012	100	mg	i.v.	Once on day 1
FCM-miniR/ FCR	Gastrointestinal disorders	N00319/ 00189/001	Vomiting (grade 3)	Fludarabine	Oral	7 September 2012	12 September 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	7 September 2012	12 September 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	7 September 2012	7 September 2012	9	mg	i.v.	Once (Day 1)
				Mini Rituximab	i.v.	7 September 2012	7 September 2012	100	mg	i.v.	Once (Day 1)
FCM-miniR/ FCR	General disorders and administration site conditions	N00137/ 00196/002	Nausea, vomiting and dehydration	Fludarabine	Oral	18 September 2012	22 September 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	18 September 2012	22 September 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	18 September 2012	18 September 2012	10	mg	i.v.	Once (18 September 2012)
				Mini Rituximab	i.v.	18 September 2012	18 September 2012	100	mg	i.v.	Once (18 September 2012)

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/003	Fever (absence neutropenia)	Fludarabine	Oral	10 July 2012	14 July 2012	50	mg	Oral	Daily
				Cyclophosphamide	Oral	10 July 2012	14 July 2012	300	mg	Oral	Daily
				Mitoxantrone	i.v.	10 July 2012	14 August 2012	12	mg	i.v.	Once
				Mini Rituximab	i.v.	10 July 2012	14 August 2012	100	mg	i.v.	Once
FCM-miniR/ FCR	General disorders and administration site conditions	N00349/ 00164/004	Cytokine release grade 3	Fludarabine	Oral	10 July 2012	18 August 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	10 July 2012	18 August 2012	300	mg	Oral	Daily
				Mitoxantrone	i.v.	10 July 2012	14 August 2012	12	mg	i.v.	Daily
				Mini Rituximab	i.v.	10 July 2012	19 September 2012	100	mg	i.v.	Daily
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/001	Febrile neutropenia	Fludarabine	Oral	20 July 2012	25 July 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	20 July 2012	25 July 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	20 July 2012	20 July 2012	11	mg	i.v.	OD
				Mini Rituximab	i.v.	20 July 2012	20 July 2012	100	mg	i.v.	OD
FCM-miniR/ FCR	Infections and infestations	N00076/ 00169/002	Febrile	Fludarabine	Oral	20 July 2012	15 November 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	20 July 2012	15 November 2012	250	mg	Oral	Daily
				Rituximab	i.v.	20 July 2012	15 November 2012	900	mg	i.v.	Once
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/003	Neutropenic sepsis	Fludarabine	Oral	18 September 2012	7 February 2013	40	mg	Oral	Daily
				Cyclophosphamide	Oral	18 September 2012	7 February 2013	250	mg	Oral	Daily
				Mitoxantrone	i.v.	18 September 2012	18 September 2012				
				Rituximab	i.v.	16 October 2012	7 February 2013	840	mg	i.v.	Once
				Mini Rituximab	i.v.	18 September 2012	18 September 2012				

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR/ FCR	Infections and infestations	N00137/ 00196/004	Neutropenic sepsis	Fludarabine	Oral	18 September 2012	11 February 2013	40	mg	Oral	Daily
				Cyclophosphamide	Oral	18 September 2012	11 February 2013	250	mg	Oral	Daily
				Mitoxantrone	i.v.	18 September 2012	18 September 2012				
				Rituximab	i.v.	16 October 2012	11 February 2013	840	mg	i.v.	Once
				Mini Rituximab	i.v.	18 September 2012	18 September 2012				
FCM-miniR/ FCR	Infections and infestations	N00153/ 00148/001	Febrile neutropenia	Fludarabine	Oral	21 May 2012	21 May 2012	40	mg	Oral	OD for 5 days
				Cyclophosphamide	Oral	21 May 2012	21 May 2012	250	mg	Oral	OD for 5 days
				Mitoxantrone	i.v.	21 May 2012	21 May 2012	10	mg	i.v.	OD
				Mini Rituximab	i.v.	21 May 2012	21 May 2012	100	mg	i.v.	OD
FCM-miniR/ FCR	Infections and infestations	N00153/ 00177/001	Febrile neutropenia	Fludarabine	Oral	17 July 2012	21 July 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	17 July 2012	21 July 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	18 July 2012	18 July 2012	10	mg	i.v.	Daily
				Mini Rituximab	i.v.	17 July 2012	17 July 2012	100	mg	i.v.	Daily
FCM-miniR/ FCR	Infections and infestations	N00153/ 00186/001	Febrile neutropenia	Fludarabine	Oral	15 August 2012	15 August 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	15 August 2012	15 August 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	15 August 2012	15 August 2012	11	mg	i.v.	Daily
				Mini Rituximab	i.v.	15 August 2012	15 August 2012	100	mg	i.v.	Daily

continued

TABLE 81 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Trial medication	Product form	First trial dose	Date most recent dose	Most recent dose	Units	Route	Frequency
FCM-miniR/ FCR	Infections and infestations	N00218/ 00162/001	Neutropenic fever	Fludarabine	Oral	25 June 2012	24 August 2012	40	mg	Oral	Daily
				Cyclophosphamide	Oral	25 June 2012	24 August 2012	250	mg	Oral	Daily
				Mitoxantrone	i.v.	25 June 2012	20 August 2012	11	mg	i.v.	Once
				Mini Rituximab	i.v.	25 June 2012	20 August 2012	100	mg	i.v.	Once
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/002	Neutropenic sepsis (febrile neutropenia)	Fludarabine	i.v.	7 September 2012	2 November 2012	20	mg	i.v.	Every 28 days for 3 days
				Cyclophosphamide	i.v.	7 September 2012	2 November 2012	370	mg	i.v.	Every 28 days for 3 days
				Rituximab	i.v.	7 September 2012	31 October 2012	700	mg	i.v.	Every 28 days
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/003	Febrile neutropenia	Fludarabine	i.v.	7 September 2012	29 December 2012	20	mg	i.v.	Every 28 days for 3 days
				Cyclophosphamide	i.v.	7 September 2012	29 December 2012	370	mg	i.v.	Every 28 days for 3 days
				Rituximab	i.v.	7 September 2012	27 December 2012	700	mg	i.v.	Every 28 days
FCM-miniR/ FCR	Infections and infestations	N00319/ 00189/004	Neutropenia with fever 37.8 °C	Fludarabine	i.v.	7 September 2012	25 January 2013	20	mg	i.v.	Every 28 days for 3 days
				Cyclophosphamide	i.v.	7 September 2012	25 January 2013	370	mg	i.v.	Every 28 days for 3 days
				Rituximab	i.v.	7 September 2012	23 January 2013	700	mg	i.v.	Every 28 days

ANC, absolute neutrophil count; CTC, common toxicity criteria; EBV, Epstein–Barr virus; Hb, haemoglobin; i.v., intravenous; OD, once daily; PJP, *Pneumocystis jiroveci* pneumonia; SOB, shortness of breath; URTI, upper respiratory tract infection.
SAE ID number: centre code/patient ID/SAE number.

TABLE 82 Serious adverse events not suspected to be related to trial treatment (SAE description)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Blood and lymphatic system disorders	N00153/ 00091/001	Anaemia	UK	59	Female	Patient phoned feeling short of breath, palpitations. Hb found to be 7.6 g/dl. Admitted for blood transfusions. Follow-up report: discharged 28 June 2011	Required/prolonged hospitalisation
FCR	Cardiac disorders	N00050/ 00178/001	Atrial fibrillation	UK	61	Male	Admitted with gradual onset chest pain, associated SOB, palpitations and dizziness. Chest radiography and ECG done. Discharged apyrexial and asymptomatic. No action required. Neutropenic but well	Required/prolonged hospitalisation
FCR	Cardiac disorders	N00173/ 00011/002	Palpitations	UK	72	Female	Tachycardia, palpitations and heaviness in central chest area Awaiting 24 hour tape result	Required/prolonged hospitalisation
FCR	Cardiac disorders	N00173/ 00011/004	Pericardial effusion	UK	72	Female	Incidental finding of pericardial effusion at mid-point assessment on CT. An echo is requested, patient is well	Jeopardised patient/ required intervention to prevent one of the above
FCR	Eye disorders	N00014/ 00112/002	Left vitrectomy	UK	62	Male	Planned admission for eye surgery for removal of left vitreous haemorrhage	Required/prolonged hospitalisation
FCR	Infections and infestations	N00014/ 00028/001	?*Varicella zoster* infection	UK	67	Male	Rash and pruritus grade 3. Results from virology screen show inconclusive to *Varicella zoster* infection	Required/prolonged hospitalisation
FCR	Infections and infestations	N00098/ 00001/002	Viral infection, previously febrile neutropenia	UK	41	Male	Elevated temperature and mildly neutropenic. Fever with mild neutropenia. Temperature resolved. Blood cultures and chest radiograph = NAD. Probable viral infection	Required/prolonged hospitalisation

continued

TABLE 82 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Infections and infestations	N00098/ 00019/002	Pyrexia of unknown origin	UK	67	Male	Recurrent spikes of temperature above 38 °C for several days. No associated symptoms. Admitted 29 April 2011. 5 months since any chemotherapy. CRP high	Required/prolonged hospitalisation
FCR	Infections and infestations	N00349/ 00070/002	Pyrexia	UK	63	Male	History of rigors and pyrexia for 2 days – unknown cause of pyrexia. white blood cells 3.5, platelets 127, neutrophils 3.22, Hb 12.3, CRP 26 on 14/4/11. MSU result outstanding. Follow-up report: MSU negative, chest radiograph clear	Required/prolonged hospitalisation
FCR	Infections and infestations	N00361/ 00123/001	Infection? source	UK	67	Female	Admitted secondary to pyrexia 39.5, patient not neutropenic. × 6 episodes of loose stool 13 April 2012. Lower abdominal discomfort. Commenced i.v. Meropenem 1 g (× 3 daily) as allergic to Penicillin. Blood cultures + stool specimen taken. No other obvious source of infection	Required/prolonged hospitalisation
FCR	Injury, poisoning and procedural complications	N00014/ 00025/001	Corneal abrasion	UK	76	Female	Patient had fall and hit head/eye resulting in headache and loss of sight in left eye	Required/prolonged hospitalisation
FCR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N01527/ 00076/001	Dermatology/skin/ other. Metastatic SCC	UK	72	Male	Right neck large level II and III nodes and forehead lesions. ?early SCC recurrence from fully excised SCC December 2010. (1-cm margins and no CT evidence of active malignancy). Follow-up report: patient had radical right neck dissection	Jeopardised patient/ required intervention to prevent one of the above

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Psychiatric disorders	N00349/ 00104/001	Steroid-induced agitation	UK	69	Male	Steroid-induced psychosis. Intermittent mumbling, confusion, agitation	Required/prolonged hospitalisation
FCR	Renal and urinary disorders	N00230/ 00158/001	Kidney stone/ Renal colic	UK	53	Male	Admitted 11 August 2012 with renal colic. Ureteric stent inserted 11 August 2012. Temperature 40 °C. Tonsillitis ± LRTI treated with i.v. antibiotics. Temperature now stable, changed to oral antibiotics. Infection clearing. A/W lithotripsy and uteroscopy to treat kidney stone. Discharged 15 August 2012	Required/prolonged hospitalisation
FCR	Respiratory, thoracic and mediastinal disorders	N00218/ 00159/001	SOB?PE.	UK	65	Female	SOB, tachycardic, admitted to hospital. Additional information: CTPA result awaited – performed today. Chest radiograph – normal	Required/prolonged hospitalisation
FCR	Respiratory, thoracic and mediastinal disorders	N00391/ 00147/001	Pleural effusion	UK	69	Female	Increased SOB owing to right-sided pleural effusion. Admitted for insertion of right pleural drain, bloods, ECG and chest radiography	Required/prolonged hospitalisation
FCR	Skin and subcutaneous tissue disorders	N00050/ 00093/001	Rash	UK	44	Male	Rash developed within half an hour. On inside of arms, abdomen and thighs. Itchiness started after fourth cycle but rash not present then	Required/prolonged hospitalisation

continued

TABLE 82 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCR	Skin and subcutaneous tissue disorders	N00106/ 00179/002	Severe rash	UK	68	Female	Patient noticed knees very red on 22 August 2012, by 25 August 2012 spreading rash everywhere. 2 September 2012: eyes swollen and face swollen. 2 September 2012: seen by consultant – given prednisolone and piriton. 3 September 2012: antibiotics stopped, nausea and temperature 38 °C. Admitted 4 September 2012 owing to rash and associated symptoms. Cycle and fludarabine stopped early. Follow-up report: patient discharged 10 September 2012 – rash much improved	Required/prolonged hospitalisation
FCM-miniR	Cardiac disorders	N00098/ 00003/001	Tachycardia	UK	73	Male	Patient c/o high heart rate, asymptomatic	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N00050/ 00046/001	Diarrhoea	UK	66	Male	Started with severe diarrhoea, more than seven stools a day. Weight loss of over 10 lb since Monday. Struggling to drink. Awaiting investigations	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N00111/ 00132/002	Diarrhoea	UK	73	Male	4 days of diarrhoea	Required/prolonged hospitalisation
FCM-miniR	Gastrointestinal disorders	N00114/ 00006/001	Constipation	UK	70	Male	Day 1 course1 FCM-miniR on 2 March 2010. Following treatment, unable to open bowels. Admitted 7 March 2010 with nausea, abdominal discomfort and constipation. Ondansetron stopped, laxatives administered, symptoms settled. Discharged 9 March 2010	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Gastrointestinal disorders	N01527/ 00184/002	Bowel obstruction + femoral hernia (right side)	UK	63	Female	Patient was admitted to MAU at Royal Blackburn Hospital on 14 October 2012, as patient experienced 5–6 episodes of vomiting (coffee ground vomit), temperature 35.7 °C. Last cycle chemotherapy 27 September 2012. Initially diagnosis was ?GI bleed. However, OGD on 16 October 12 showed 'nothing abnormal detected'. Ultrasound scan performed on 19 October 12 suggested possible obstruction. CT scan performed on 23 October 12 suggested small bowel obstruction, possibly caused by a right inguinal hernia. Surgery Salpingo-Oophorectomy right side plus repair of right femoral hernia performed on 25 October 2012. Patient will remain in-patient until recovered	Required/prolonged hospitalisation
FCM-miniR	General disorders and administration site conditions	N00153/ 00121/001	Allergic reaction	UK	64	Male	Patient's wife phoned stating that patient's mouth was swollen, during phone call symptoms worsened, tongue swelling, throat pain, difficult swallowing. Advised to dial 999 – attended A&E. Had taken second dose Fludarabine 30 minutes prior. Co-trimoxazole started this morning. Further symptoms experienced in A&E when con meds administered again (no chemo taken)	Jeopardised patient/ required intervention to prevent one of the above

continued

TABLE 82 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	General disorders and administration site conditions	N01527/ 00184/003	Abdominal pain and vomiting	UK	63	Female	Patient admitted to Royal Blackburn Hospital 25 November 2012 with abdominal pain and bile-coloured vomiting. Observations Temperature 36.4 °C, RR14 sats 100%, RA blood pressure 138/102, heart rate 68, AXR – No obstructions. Additional information: Blood results attached. MSU report attached. Will update with more information when available. Additional information in updated SAE (7 December 2012). CT on 30 November 12 showed acute cholecystitis (see attached report). Antibiotic therapy given. Symptoms improved and patient discharged home on 5 December 12. Patient's case was discussed at Haematology MDT and, owing to abdominal complications recently and having achieved a satisfactory response to 2 cycles FCM-miniR, decision made to stop chemotherapy at this time. Any further treatment given will be off trial	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00098/ 00040/001	Neutropenic sepsis and infected shoulder	UK	63	Male	Patient admitted with neutropenic sepsis on 11 March 2011 – neutrophils 0.02 × 10/l. Patient gradually deteriorated and died on 3 April 2011	Patient died
FCM-miniR	Infections and infestations	N00099/ 00096/001	Low magnesium, neutropenic sepsis	UK	62	Female	Admitted from day unit, ?neutropenic sepsis on 29 December 2011, abnormal blood results. Borderline CMV antigen PCR positive	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Infections and infestations	N00114/ 00086/002	Ongoing line sepsis	UK	46	Male	Tachycardic. Spiking temperatures. 20 September 2011 Temperature 40 °C. Patient took paracetamol. Follow-up report: admitted with tachycardia, temperature spikes. 21 September 2011 sepsis of Hickman line. Discharge 25 September 11 after line removal	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N00349/ 00135/001	Pyrexia	UK	65	Male	Admitted with temperature 31.7 °C and feeling generally unwell. Neutrophils 1.13. Blood cultures on 1 June 12 *Staphylococcus aureus*	Required/prolonged hospitalisation
FCM-miniR	Infections and infestations	N01527/ 00081/005	Anaemia grade 3	UK	74	Female	Patient was already admitted to hospital on 17 August 2011 with neutropenic sepsis. Bloods taken on 18 August 2011 showed grade 3 anaemia and patient was treated with 2 units of blood	Jeopardised patient/ required intervention to prevent one of the above
FCM-miniR	Renal and urinary disorders	N00040/ 00108/003	Renal colic	UK	56	Male	Patient presented with loin pain – renal colic. No surgical input needed. Awaiting CT scan. Discharged home 2 December 2011. Follow-up report: CT scan 4 January 2012 – kidney stone visualised in left ureter at distal end. For radiography again on 17 January 2012 – may need future stone removal if pain persists. Follow-up report: 22 February 2012 No stones visible on radiograph. Discharged from Urology team	Required/prolonged hospitalisation

continued

TABLE 82 Serious adverse events not suspected to be related to trial treatment (SAE description) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR	Skin and subcutaneous tissue disorders	N00153/ 00014/001	Rash	UK	51	Male	All over body rash, swollen eyes, rash, red and inflamed not itchy. Subject went to A&E on 16.5.10. Grade 3 SAE. Temperature = 38.7 °C. Follow up: all over body rash – peeling skin, swollen eyes. Temperature 38.7 °C. Patient stopped co-trimoxazole, started pentamidine	Jeopardised patient/ required intervention to prevent one of the above
FCM-miniR/ FCR	Infections and infestations	N00349/ 00164/001	Viral URTI	UK	46	Male	Profound cough, mild intermittent pyrexia, general malaise	Required/prolonged hospitalisation
FCM-miniR/ FCR	Infections and infestations	N00349/ 00164/002	Pyrexia grade 1	UK	46	Male	Persisting cough since 16 July 12, none productive. Admitted on 4 August 2012 with cough and pyrexia	Required/prolonged hospitalisation
FCM-miniR/ FCR	Musculoskeletal and connective tissue disorders	N00137/ 00196/001	Back pain	UK	50	Female	Started chemotherapy 19 September 2012 and BM done 18 September 2012 pre-chemotherapy. c/o lethargic, nausea, sweaty and presented with lower back pain. Reviewed by Doctor at local hospital, localised pain owing to BM, infection ruled out. Admitted for observation and pain control. Discharged 20 September 2012 in stable condition. Cycle 1, Day 1 started 18 September 2012 – cycle ongoing at present. No disruptions to treatment	Required/prolonged hospitalisation

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Country	Age at randomisation, years	Sex	SAE case description	Seriousness criteria
FCM-miniR/ FCR	Skin and subcutaneous tissue disorders	N00153/ 00148/002	All over body rash	UK	54	Female	Patient has an all over body rash, admitted into hospital for i.v. fluids, piriton and hydrocortisone	Required/prolonged hospitalisation
FCM-miniR/ FCR	Skin and subcutaneous tissue disorders	N00218/ 00162/002	Allergic rash	UK	64	Male	Admitted to hospital c/o allergic rash following antibiotic therapy for neutropenic fever	Required/prolonged hospitalisation
FCM-miniR/ FCR	Skin and subcutaneous tissue disorders	N00218/ 00162/003	Rash + swelling of face	UK	64	Male	Patient admitted with rash and swelling over face after restarting septrin and aciclovir last week. History of fever at home. Treated with i.v. tazocin and gentamicin – afebrile. Treated with prednisolone. Discharged 17 September 2012. Additional comments Difficult case! Not sure which antibiotic/viral over last 2–3 weeks is responsible	Required/prolonged hospitalisation

A&E, accident and emergency; AXR, abdominal x-ray; BM, bone marrow; CMV, cytomegalovirous; CT, computerised tomography; ECG, electrocardiogram; GI, gastrointestinal; Hb, haemoglobin; i.v., intravenous; LRTI, lower respiratory tract infection; MSU, midstream urine sample; NAD, no active disease; OGD, oesophagogastroduodenoscopy; PE, pleural effusion; SCC, squamous cell carcinoma; SOB, shortness of breath; URTI, upper respiratory tract infection; WBC, white blood cell.
SAE ID number: centre code/patient ID/SAE number.

TABLE 83 Serious adverse events not suspected to be related to trial treatment (details of event)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment
FCR	Blood and lymphatic system disorders	N00153/00091/001	Anaemia	Not suspected
FCR	Cardiac disorders	N00050/00178/001	Atrial fibrillation	Not suspected
FCR	Cardiac disorders	N00173/00011/002	Palpitations	Not suspected
FCR	Cardiac disorders	N00173/00011/004	Pericardial effusion	Not suspected
FCR	Eye disorders	N00014/00112/002	Left vitrectomy	Not suspected
FCR	Infections and infestations	N00014/00028/001	?Varicella zoster virus infection	Not suspected
FCR	Infections and infestations	N00098/00001/002	Viral infection, previously febrile neutropenia	Not suspected
FCR	Infections and infestations	N00098/00019/002	Pyrexia of unknown origin	Not suspected
FCR	Infections and infestations	N00349/00070/002	Pyrexia	Not suspected
FCR	Infections and infestations	N00361/00123/001	Infection? source	Not suspected
FCR	Injury, poisoning and procedural complications	N00014/00025/001	Corneal abrasion	Not suspected
FCR	Neoplasms benign, malignant and unspecified (including cysts and polyps)	N01527/00076/001	Dermatology/skin/other. Metastatic SCC	Not suspected
FCR	Psychiatric disorders	N00349/00104/001	Steroid-induced agitation	Not suspected
FCR	Renal and urinary disorders	N00230/00158/001	Kidney stone/renal colic	Not suspected
FCR	Respiratory, thoracic and mediastinal disorders	N00218/00159/001	SOB ?PE	Not suspected
FCR	Respiratory, thoracic and mediastinal disorders	N00391/00147/001	Pleural effusion	Not suspected
FCR	Skin and subcutaneous tissue disorders	N00050/00093/001	Rash	Not suspected
FCR	Skin and subcutaneous tissue disorders	N00106/00179/002	Severe rash	Not suspected
FCM-miniR	Cardiac disorders	N00098/00003/001	Tachycardia	Not suspected
FCM-miniR	Gastrointestinal disorders	N00050/00046/001	Diarrhoea	Not suspected
FCM-miniR	Gastrointestinal disorders	N00111/00132/002	Diarrhoea	Not suspected
FCM-miniR	Gastrointestinal disorders	N00114/00006/001	Constipation	Not suspected

Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Causality (in addition to trial medications)	Outcome of SAE
21 June 2011	27 June 2011	28 June 2011	1	CLL	Recovered
16 July 2012	27 September 2012	28 September 2012	1	Presumed primary cardiac disorder	Recovered
29 March 2010	6 June 2010	7 June 2010	1	Has a history of palpitations	Recovered
29 March 2010	28 July 2010	18 January 2011	174	CLL	Recovered
19 October 2011	9 May 2012	9 May 2012	0	Vitreous haemorrhage caused by diabetic retinopathy	Recovered
21 July 2010	27 October 2010	3 August 2011	280	Varicella zoster virus infection	Recovered
14 December 2009	6 December 2009	10 December 2009	4	CLL	Recovered
8 June 2010	29 April 2011	4 May2011	5		Recovered
9 March 2011	14 June 2011	20 June 2011	6		Recovered
21 November 2011	11 April 2012	15 April 2012	4	Acquired viral infection	Recovered
16 July 2010	21 December 2010	23 December 2010	2	Patient tripped over shoe and fell	Recovered with sequelae
5 April 2011	26 May 2011	20 June 2011	25	Previous SCC	Recovered
25 August 2011	9 September 2011	12 September 2011	3	Concomitant medications	Recovered
12 June 2012	11 August 2012	15 August 2012	4	Pre-existing condition	Recovered with sequelae
14 June 2012	17 November 2012	3 December 2012	16	Immobility	Recovered with sequelae
3 May 2012	8 May 2012	10 May 2012	2	CLL	Recovered
6 July 2011	14 November 2011	14 November 2011	0	Viral fever	Recovered
17 July 2012	31 August 2012	10 September 2012	10	Concomitant medications	Recovered with sequelae
15 January 2010	29 January 2010	30 January 2010	1		Recovered
10 November 2010	24 March 2011	4 April 2011	11	Rotavirus infection	Recovered
30 January 2012	4 June 2012	7 June 2012	3	Gastroenteritis	Recovered
22 February 2010	7 March 2010	9 March 2010	2	Concomitant medications; past history of constipation and abdominal surgery	Recovered

continued

TABLE 83 Serious adverse events not suspected to be related to trial treatment (details of event) (*continued*)

Treatment received	MedDRA system organ class	SAE ID number	SAE medical description	Suspected relationship to trial treatment
FCM-miniR	Gastrointestinal disorders	N01527/00184/002	Bowel obstruction + femoral hernia (right side)	Not suspected
FCM-miniR	General disorders and administration site conditions	N00153/00121/001	Allergic reaction	Not suspected
FCM-miniR	General disorders and administration site conditions	N01527/00184/003	Abdominal pain and vomiting	Not suspected
FCM-miniR	Infections and infestations	N00098/00040/001	Neutropenic sepsis and infected shoulder	Not suspected
FCM-miniR	Infections and infestations	N00099/00096/001	Low magnesium, neutropenic sepsis	Not suspected
FCM-miniR	Infections and infestations	N00114/00086/002	Ongoing line sepsis	Not suspected
FCM-miniR	Infections and infestations	N00349/00135/001	Pyrexia	Not suspected
FCM-miniR	Infections and infestations	N01527/00081/005	Anaemia grade 3	Not suspected
FCM-miniR	Renal and urinary disorders	N00040/00108/003	Renal colic	Not suspected
FCM-miniR	Skin and subcutaneous tissue disorders	N00153/00014/001	Rash	Not suspected
FCM-miniR/FCR	Infections and infestations	N00349/00164/001	Viral URTI	Not suspected
FCM-miniR/FCR	Infections and infestations	N00349/00164/002	Pyrexia grade 1	Not suspected
FCM-miniR/FCR	Musculoskeletal and connective tissue disorders	N00137/00196/001	Back pain	Not suspected
FCM-miniR/FCR	Skin and subcutaneous tissue disorders	N00153/00148/002	All over body rash	Not suspected
FCM-miniR/FCR	Skin and subcutaneous tissue disorders	N00218/00162/002	Allergic rash	Not suspected
FCM-miniR/FCR	Skin and subcutaneous tissue disorders	N00218/00162/003	Rash + swelling of face	Not suspected

PE, pulmonary embolism; SCC, squamous cell carcinoma; SOB, shortness of breath; URTI, upper respiratory tract infection.
SAE duration: days from date SAE became serious to date of recovery/death (if known).
SAE ID number: centre code/patient ID/SAE number.

Randomisation date	Date SAE became serious	SAE recovery date	SAE duration (days)	Causality (in addition to trial medications)	Outcome of SAE
6 August 2012	15 October 2012	14 November 2012	30	Now known to have been a bowel obstruction + right sided femoral hernia	Recovered
7 November 2011	11 November 2011	11 November 2011	0	Concomitant medications: co-trimoxazole and aciclovir	Recovered with sequelae
6 August 2012	25 November 2012	5 December 2012	10	Cholecystitis	Recovered
15 October 2010	11 March 2011		23	CLL	Died
25 July 2011	29 December 2011	4 January 2012	6	Diarrhoea of unknown cause	Recovered with sequelae
18 May 2011	21 September 2011	27 September 2011	6	CLL	Recovered
22 February 2012	31 May 2012	4 June 2012	4	CLL	Recovered
5 May 2011	18 August 2011	8 September 2011	21	Sepsis	Recovered
8 September 2011	1 December 2011	20 February 2012	81	Kidney stone	Recovered
26 April 2010	16 May 2010	7 June 2010	22	Concomitant medications	Recovered
28 June 2012	13 July 2012	23 July 2012	10	Viral URTI	Recovered
28 June 2012	4 August 2012	10 August 2012	6	Viral illness	Recovered
17 September 2012	20 September 2012	20 September 2012	0		Recovered with sequelae
4 May 2012	15 June 2012	19 June 2012	4	Concomitant medications	Recovered
20 June 2012	5 September 2012	12 September 2012	7	Concomitant medications	Recovered with sequelae
20 June 2012	14 September 2012	17 September 2012	3	Concomitant medications	Recovered

Appendix 2 Adverse event listings

TABLE 84 Adverse events in participants receiving FCR

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
1	FCR	Infusional reaction		2	1	Unrelated
	FCR	Anaemia		3	1	Probably
	FCR	Anaemia		4	1	Probably
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Nausea		2	3	Probably
	FCR	Neutropenia		3	4	Probably
	FCR	Infections (not neutropenic sepsis)		1	4	Possibly
2	FCR	Hypotension		2	1	Unrelated
	FCR	Nausea		2	1	Probably
	FCR	Infusional reaction		2	2	Unlikely
	FCR	Nausea		2	2	Probably
	FCR	Vomiting		2	2	Probably
	FCR	Nausea		1	3	Probably
	FCR	Vomiting		1	3	Probably
	FCR	Nausea		2	4	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	4	Possibly
	FCR	Nausea		2	5	Almost certainly
	FCR	Vomiting		2	5	Almost certainly
	FCR	Nausea		2	6	Almost certainly
	FCR	Vomiting		2	6	Almost certainly
	FCR	Rash/flushing		1	6	Possibly
7	FCR	Constipation		1	1	Unrelated
	FCR	Mucositis/thrush		2	5	Unrelated
8	FCR	Fatigue		1	1	Probably
	FCR	Hypotension		1	1	Unrelated
	FCR	Diarrhoea		1	3	Unrelated
	FCR	Fatigue		2	6	Probably
9	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Diarrhoea		1	1	Almost certainly
	FCR	Fatigue		1	1	Almost certainly
	FCR	Fatigue		1	2	Almost certainly
	FCR	Non-specific pain		1	2	Unlikely
	FCR	Fatigue		1	3	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Almost certainly	15 December 2009	Yes	15 December 2009	0
Probably	Possibly	21 December 2009	No		
Probably	Possibly	2 January 2010	Yes	12 January 2010	10
Almost certainly	Possibly	20 January 2010	No		
Probably	Probably	17 February 2010	Yes	22 February 2010	5
Probably	Possibly	12 April 2010	No		
Possibly	Possibly		No		
Unrelated	Almost certainly	14 January 2010	Yes	14 January 2010	0
Probably	Possibly	15 January 2010	Yes	25 January 2010	10
Unlikely	Almost certainly	11 February 2010	Yes	11 February 2010	0
Probably	Possibly	11 February 2010	Yes	22 February 2010	11
Probably	Possibly	11 February 2010	Yes	22 February 2010	11
Probably	Possibly	11 March 2010	Yes	13 March 2010	2
Probably	Possibly	11 March 2010	Yes	11 March 2010	0
Almost certainly	Possibly	9 April 2010	Yes	15 April 2010	6
Possibly	Possibly	19 April 2010	Yes	29 April 2010	10
Almost certainly	Possibly	6 May 2010	Yes	12 May 2010	6
Almost certainly	Possibly	6 May 2010	Yes	7 May 2010	1
Almost certainly	Possibly	3 June 2010	Yes	8 June 2010	5
Almost certainly	Possibly	3 June 2010	Yes	4 June 2010	1
Possibly	Possibly		No		
Unrelated	Unrelated	24 March 2010	Yes	29 March 2010	5
Unrelated	Unrelated	14 July 2010	No		
Unrelated	Unrelated	26 March 2010	Yes	1 April 2010	6
Unrelated	Almost certainly	25 March 2010	Yes	25 March 2010	0
Unrelated	Possibly	26 March 2010	Yes	8 June 2010	74
Unrelated	Unrelated	3 August 2010	Yes	8 August 2010	5
Almost certainly	Almost certainly	31 March 2010	Yes	3 April 2010	3
Almost certainly	Almost certainly	31 March 2010	Yes	1 April 2010	1
Almost certainly	Almost certainly	2 April 2010	Yes	4 April 2010	2
Almost certainly	Almost certainly	31 March 2010	Yes	4 April 2010	4
Almost certainly	Almost certainly	27 April 2010	Yes	30 April 2010	3
Unlikely	Unlikely		Yes		
Almost certainly	Almost certainly	26 May 2010	Yes	28 May 2010	2

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Alopecia		1	3	Almost certainly
	FCR	Other AE description	Varicocele	2	3	Unlikely
	FCR	Fatigue		1	4	Almost certainly
	FCR	Dry skin/erythema		1	4	Unlikely
	FCR	Neutropenia		4	6	Almost certainly
	FCR	Thrombocytopenia		2	6	Almost certainly
11	FCR	Neutropenia		4	1	Almost certainly
	FCR	Anaemia		2	1	Almost certainly
	FCR	Nausea		1	1	Probably
	FCR	Constipation		1	1	Unrelated
	FCR	Thrombocytopenia		2	1	Almost certainly
	FCR	Anaemia		2	2	Almost certainly
	FCR	Neutropenia		2	2	Almost certainly
	FCR	Neutropenia		4	3	Almost certainly
	FCR	Anaemia		2	3	Almost certainly
	FCR	Renal impairment		1	3	Unlikely
13	FCR	Infusional reaction		2	2	Unrelated
	FCR	Vomiting		1	3	Probably
	FCR	Neutropenia		3	5	Almost certainly
17	FCR	Nausea		2	1	Almost certainly
	FCR	Vomiting		2	1	Almost certainly
	FCR	Rash/flushing		2	1	Possibly
	FCR	Cough		1	1	Possibly
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Rash/flushing		2	2	Possibly
	FCR	Headache		2	2	Possibly
	FCR	Nausea		2	3	Almost certainly
	FCR	Vomiting		2	3	Almost certainly
	FCR	Fatigue		2	3	Probably
	FCR	Cough		1	3	Possibly
	FCR	Anorexia/cachexia		1	3	Possibly
	FCR	Nausea		2	4	Almost certainly
	FCR	Vomiting		2	4	Almost certainly
	FCR	Fatigue		1	4	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly		No		
Unlikely	Unlikely		No		
Almost certainly	Almost certainly	22 July 2010	Yes	25 July 2010	3
Unlikely	Unlikely		No		
Almost certainly	Almost certainly	17 August 2010	No		
Almost certainly	Almost certainly	17 August 2010	No		
Almost certainly	Almost certainly	4 May 2010	Yes	26 May 2010	22
Almost certainly	Almost certainly	19 May 2010	Yes	26 May 2010	7
Probably	Unlikely	15 April 2010	Yes	26 April 2010	11
Unrelated	Unrelated	14 April 2010	Yes	26 April 2010	12
Almost certainly	Almost certainly	24 April 2010	Yes	4 May 2010	10
Almost certainly	Almost certainly	11 June 2010	No		
Almost certainly	Almost certainly	18 June 2010	No		
Almost certainly	Almost certainly	12 July 2010	No		
Almost certainly	Almost certainly	8 July 2010	Yes	27 July 2010	19
Unlikely	Unlikely	6 July 2010	Yes	7 July 2010	1
Unrelated	Unrelated	9 June 2010	Yes	9 June 2010	0
Probably	Unrelated	15 June 2010	Yes	16 June 2010	1
Almost certainly	Almost certainly	1 September 2010	Yes	6 September 2010	5
Almost certainly	Possibly	12 May 2010	Yes	17 May 2010	5
Almost certainly	Possibly	12 May 2010	Yes	12 May 2010	0
Possibly	Possibly	21 May 2010	Yes	28 May 2010	7
Possibly	Possibly	15 May 2010	Yes	25 May 2010	10
Almost certainly	Possibly		No		
Almost certainly	Possibly	7 June 2010	Yes		
Possibly	Possibly	12 June 2010	Yes	16 June 2010	4
Possibly	Possibly	28 June 2010	Yes	28 June 2010	0
Almost certainly	Possibly	7 July 2010	Yes	10 July 2010	3
Almost certainly	Possibly	8 July 2010	Yes	10 July 2010	2
Probably	Probably	7 July 2010	Yes	23 July 2010	16
Possibly	Possibly	12 July 2010	Yes		
Possibly	Possibly		No		
Almost certainly	Possibly	4 August 2010	Yes	6 August 2010	2
Almost certainly	Possibly	4 August 2010	Yes	4 August 2010	0
Almost certainly	Possibly	2 August 2010	Yes		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Nausea		2	5	Almost certainly
	FCR	Vomiting		1	5	Almost certainly
	FCR	Fatigue		1	5	Probably
	FCR	Nausea		3	6	Almost certainly
	FCR	Vomiting		2	6	Almost certainly
	FCR	Fatigue		2	6	Almost certainly
	FCR	Anaemia		4	6	Almost certainly
	FCR	Neutropenia		4	6	Almost certainly
	FCR	Thrombocytopenia		3	6	Almost certainly
	FCR	Fatigue		4	6	Probably
	FCR	Anorexia/cachexia		3	6	Probably
18	FCR	Nausea		1	1	Probably
	FCR	Neutropenia		3	1	Probably
	FCR	Nausea		1	2	Probably
	FCR	Neutropenia		4	2	Probably
	FCR	Diarrhoea		1	3	Possibly
	FCR	Neutropenia		4	3	Probably
	FCR	Headache		1	3	Unlikely
	FCR	Neutropenia		4	4	Probably
	FCR	Neutropenia		4	5	Probably
	FCR	Cough		1	5	Unlikely
19	FCR	Vomiting		2	1	Unrelated
	FCR	Nausea		2	1	Almost certainly
	FCR	Diarrhoea		1	1	Probably
	FCR	Constipation		1	1	Possibly
	FCR	Nausea		1	2	Almost certainly
	FCR	Vomiting		1	2	Almost certainly
	FCR	Constipation		1	2	Possibly
	FCR	Fatigue		1	2	Probably
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Anaemia		1	2	Probably
	FCR	Nausea		1	3	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Fatigue		1	4	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Possibly		No		
Almost certainly	Possibly	14 September 2010	Yes	21 September 2010	7
Almost certainly	Possibly	20 September 2010	Yes	21 September 2010	1
Probably	Probably		No		
Almost certainly	Possibly	13 October 2010	Yes	20 October 2010	7
Almost certainly	Possibly	13 October 2010	Yes	15 October 2010	2
Almost certainly	Possibly	13 October 2010	No		
Almost certainly	Possibly	3 November 2010	Yes	4 November 2010	1
Almost certainly	Possibly	5 November 2010	Yes	6 November 2010	1
Almost certainly	Possibly	4 November 2010	No		
Probably	Possibly	1 November 2010	Yes	4 November 2010	3
Probably	Unlikely	13 October 2010	Yes	4 November 2010	22
Probably	Unlikely	2 June 2010	Yes		
Probably	Probably	7 June 2010	Yes	10 June 2010	3
Probably	Unlikely		Yes		
Probably	Probably	6 July 2010	Yes	26 July 2010	20
Possibly	Unlikely		Yes		
Probably	Probably	23 August 2010	Yes	31 August 2010	8
Unlikely	Unlikely		Yes		
Probably	Probably	13 September 2010	Yes	27 September 2010	14
Probably	Probably	25 October 2010	Yes	01 November 2010	7
Unlikely	Unlikely		Yes		
Unrelated	Almost certainly	17 June 2010	Yes	17 June 2010	0
Almost certainly	Possibly	21 June 2010	Yes	25 June 2010	4
Probably	Possibly	19 June 2010	Yes	20 June 2010	1
Possibly	Possibly		Yes		
Almost certainly	Possibly	19 July 2010	Yes	25 July 2010	6
Almost certainly	Possibly	21 July 2010	Yes	22 July 2010	1
Possibly	Possibly	22 July 2010	Yes	23 July 2010	1
Probably	Probably	23 July 2010	Yes	25 July 2010	2
Almost certainly	Almost certainly	11 August 2010	Yes	8 September 2010	28
Probably	Probably	11 August 2010	Yes	8 September 2010	28
Almost certainly	Possibly	15 August 2010	Yes	22 August 2010	7
Almost certainly	Possibly	11 September 2010	Yes	19 September 2010	8
Probably	Possibly		Yes	19 September 2010	

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Other AE description	Gum recession resulting in loose tooth	1	4	Possibly
	FCR	Nausea		1	5	Almost certainly
	FCR	Nausea		2	6	Almost certainly
	FCR	Neutropenia		1	6	Almost certainly
24	FCR	Neutropenia		2	1	Almost certainly
	FCR	Abdominal pain/ bloating		1	1	Possibly
	FCR	Neutropenia		3	2	Almost certainly
	FCR	Neutropenia		2	3	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Anaemia		1	6	Almost certainly
	FCR	Neutropenia		1	6	Almost certainly
25	FCR	Vomiting		2	2	Probably
	FCR	Thrombocytopenia		2	2	Probably
	FCR	Vomiting		2	3	Almost certainly
	FCR	Diarrhoea		2	3	Almost certainly
	FCR	Infections (not neutropenic sepsis)		1	3	Unlikely
	FCR	Rash/flushing		2	3	Possibly
	FCR	Thrombocytopenia		2	4	Probably
	FCR	Diarrhoea		1	5	Unrelated
26	FCR	Rash/flushing		2	1	Unrelated
	FCR	Sore throat		1	6	Possibly
	FCR	Dyspnoea		1	6	Unlikely
28	FCR	Nausea		1	2	Almost certainly
	FCR	Pruritus		1	3	Unlikely
	FCR	Rash/flushing		3	4	Possibly
	FCR	Neutropenic sepsis		4	4	Almost certainly
	FCR	Fatigue		2	4	Probably
	FCR	Infections (not neutropenic sepsis)		3	4	Almost certainly
	FCR	Anaemia		2	4	Almost certainly
	FCR	Neutropenia		3	4	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly		No		
Almost certainly	Possibly	10 October 2010	No		
Almost certainly	Possibly	8 November 2010	Yes	13 November 2010	5
Almost certainly	Possibly	1 December 2010	No		
Almost certainly	Unlikely	29 July 2010	Yes	16 August 2010	18
Possibly	Possibly	22 July 2010	Yes	29 July 2010	7
Almost certainly	Unlikely	8 September 2010	Yes	13 September 2010	5
Almost certainly	Unlikely	6 October 2010	Yes	11 October 2010	5
Almost certainly	Unlikely	3 November 2010	No		
Almost certainly	Unlikely	3 November 2010	Yes	27 June 2011	236
Almost certainly	Unlikely	3 November 2010	Yes	6 December 2011	398
Probably	Unlikely	27 August 2010	Yes	29 August 2010	2
Probably	Probably	20 September 2010	No		
Almost certainly	Unlikely	29 September 2010	Yes	4 October 2010	5
Almost certainly	Unlikely	29 September 2010	Yes	4 October 2010	5
Unlikely	Unlikely	17 September 2010	Yes	29 September 2010	12
Possibly	Possibly	28 August 2010	Yes	29 September 2010	32
Probably	Unlikely	27 September 2010	Yes	29 November 2010	63
Unrelated	Unrelated	30 December 2010	Yes	10 January 2011	11
Unrelated	Unrelated	12 August 2010	Yes	14 August 2010	2
Possibly	Possibly				
Unlikely	Unlikely				
Almost certainly	Unlikely	3 August 2010	Yes	7 August 2010	4
Unlikely	Unlikely	15 September 2010	No		
Unlikely	Possibly	10 November 2010	Yes	22 December 2010	42
Almost certainly	Possibly	4 December 2010	Yes	13 December 2010	9
Probably	Possibly	4 December 2010	No		
Almost certainly	Almost certainly	28 December 2010	No		
Almost certainly	Almost certainly	4 January 2011	No		
Almost certainly	Almost certainly	4 January 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
29	FCR	Cough		2	3	Unlikely
	FCR	Vomiting		1	3	Unlikely
	FCR	Infections (not neutropenic sepsis)		1	4	Probably
	FCR	Nausea		1	6	Probably
32	FCR	Anorexia/cachexia		1	1	Almost certainly
	FCR	Fatigue		3	2	Almost certainly
	FCR	Nausea		2	2	Almost certainly
	FCR	Anorexia/cachexia		1	2	Almost certainly
33	FCR	Neutropenic sepsis		4	1	Probably
	FCR	Allergic reaction		3	1	Unrelated
	FCR	Nausea		1	2	Probably
	FCR	Neuropathy (sensory)		1	2	Probably
	FCR	Bone pain		1	2	Unlikely
	FCR	Anxiety/depression		1	2	Unrelated
	FCR	Fatigue		1	3	Probably
	FCR	Vomiting		1	3	Almost certainly
	FCR	Insomnia		1	3	Unrelated
	FCR	Alopecia		1	5	Possibly
	FCR	Vomiting		1	5	Missing
	FCR	Anxiety/depression		1	5	Unlikely
	FCR	Night sweats		1	5	Unrelated
	FCR	Insomnia		1	6	Unrelated
	FCR	Nausea		1	6	Almost certainly
	FCR	Taste alteration		1	6	Possibly
	FCR	Rash/flushing		1	6	Possibly
35	FCR	Dizziness		2	1	Possibly
	FCR	Nausea		2	1	Probably
	FCR	Fatigue		2	1	Probably
	FCR	Anorexia/cachexia		2	1	Probably
	FCR	Diarrhoea		1	1	Probably
	FCR	Anaemia		1	1	Probably
	FCR	Neutropenia		2	1	Probably
	FCR	Thrombocytopenia		1	1	Probably
	FCR	Nausea		2	2	Probably
	FCR	Vomiting		2	2	Probably
	FCR	Fatigue		2	2	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	4 October 2010	Yes	17 October 2010	13
Unlikely	Unlikely	22 October 2010	Yes	26 October 2010	4
Probably	Possibly	23 November 2010	Yes	30 December 2010	37
Probably	Unlikely	10 January 2011	Yes	18 January 2011	8
Almost certainly	Unlikely	8 September 2010	Yes	10 September 2010	2
Almost certainly	Unlikely	6 October 2010	Yes	7 October 2010	1
Almost certainly	Unlikely	6 October 2010	Yes	8 October 2010	2
Almost certainly	Unlikely	6 October 2010	Yes	9 October 2010	3
Probably	Probably	26 September 2010	Yes	5 October 2010	9
Unrelated	Unrelated	28 September 2010	Yes	8 October 2010	10
Probably	Probably	14 October 2010	Yes	18 October 2010	4
Probably	Probably	20 October 2010	No		
Unlikely	Unlikely	22 October 2010	Yes	7 December 2010	46
Unrelated	Unrelated	12 October 2010	Yes	7 December 2010	56
Probably	Probably	11 November 2010	No		
Almost certainly	Almost certainly	16 November 2010	Yes	19 November 2010	3
Unrelated	Unrelated	11 November 2010	No		
Possibly	Possibly	12 January 2011	No		
Missing	Missing	6 January 2011	Yes	12 January 2011	6
Unlikely	Unlikely	10 January 2011	Yes	3 February 2011	24
Unrelated	Unrelated	15 November 2010	Yes	3 February 2011	80
Unrelated	Unrelated	11 December 2010	No		
Almost certainly	Almost certainly	10 December 2010	Yes	1 March 2011	81
Possibly	Possibly	26 February 2011	Yes	01 March 2011	3
Possibly	Possibly	1 February 2011	Yes	1 March 2011	28
Possibly	Unlikely	8 October 2010	Yes	10 October 2010	2
Probably	Unlikely	8 October 2010	Yes	10 October 2010	2
Probably	Unlikely	8 October 2010	Yes	10 October 2010	2
Probably	Unlikely	8 October 2010	Yes	10 October 2010	2
Probably	Unlikely	10 October 2010	Yes	10 October 2010	0
Probably	Unlikely	5 October 2010	No		
Probably	Unlikely	19 October 2010	Yes	5 November 2010	17
Probably	Unlikely	7 October 2010	Yes	12 October 2010	5
Probably	Unlikely	7 November 2010	Yes	26 November 2010	19
Probably	Unlikely	7 November 2010	Yes	9 November 2010	2
Probably	Unlikely	7 November 2010	Yes	12 November 2010	5

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Diarrhoea		2	2	Probably
	FCR	Anorexia/cachexia		2	2	Probably
	FCR	Anaemia		2	2	Probably
	FCR	Nausea		2	3	Probably
	FCR	Vomiting		3	3	Probably
	FCR	Neutropenia		4	3	Almost certainly
	FCR	Fatigue		2	3	Probably
	FCR	Anorexia/cachexia		2	3	Probably
	FCR	Anaemia		1	3	Probably
	FCR	Thrombocytopenia		1	3	Almost certainly
	FCR	Anorexia/cachexia		2	4	Probably
	FCR	Fatigue		2	4	Probably
	FCR	Infections (not neutropenic sepsis)		2	4	Unlikely
	FCR	Neutropenia		3	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Nausea		1	5	Probably
	FCR	Fatigue		2	5	Probably
	FCR	Non-specific pain		2	5	Unlikely
	FCR	Infections (not neutropenic sepsis)		2	5	Unlikely
	FCR	Neutropenia		3	5	Almost certainly
	FCR	Anaemia		2	5	Probably
	FCR	Thrombocytopenia		1	5	Almost certainly
	FCR	Nausea		2	6	Probably
	FCR	Neutropenia		3	6	Almost certainly
	FCR	Fatigue		2	6	Probably
	FCR	Anaemia		2	6	Probably
	FCR	Thrombocytopenia		1	6	Almost certainly
38	FCR	Dry skin/erythema		1	1	Unrelated
	FCR	Chest pain		1	1	Unrelated
	FCR	Fever		1	1	Unrelated
	FCR	Rigors		2	1	Unrelated
	FCR	Nausea		1	1	Possibly
	FCR	Thrombocytopenia		2	1	Unlikely
	FCR	Thrombocytopenia		2	6	Unlikely

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Unlikely	10 November 2010	Yes	10 November 2010	0
Probably	Unlikely	7 November 2010	Yes	12 November 2010	5
Probably	Unlikely	18 November 2010	No		
Probably	Unlikely	7 December 2010	No		
Probably	Unlikely	8 December 2010	Yes	9 December 2010	1
Almost certainly	Unlikely	18 November 2010	Yes	9 December 2010	21
Probably	Unlikely	7 December 2010	Yes	24 December 2010	17
Unlikely	Unlikely	7 December 2010	Yes	10 December 2010	3
Probably	Unlikely	18 December 2010	No		
Almost certainly	Unlikely	17 December 2010	Yes	23 December 2010	6
Probably	Unlikely	4 January 2011	Yes	21 January 2011	17
Probably	Unlikely	4 January 2011	No		
Unlikely	Unlikely	19 January 2011	No		
Almost certainly	Unlikely	11 January 2011	Yes	1 February 2011	21
Almost certainly	Unlikely	4 January 2011	No		
Probably	Unlikely	6 February 2011	Yes	4 March 2011	26
Probably	Unlikely	1 February 2011	Yes	4 March 2011	31
Unlikely	Unlikely	7 January 2011	Yes	4 March 2011	56
Unlikely	Unlikely	11 February 2011	Yes	21 February 2011	10
Almost certainly	Almost certainly	11 February 2011	No		
Probably	Unlikely	11 February 2011	No		
Almost certainly	Unlikely	11 February 2011	No		
Probably	Unlikely	15 March 2011	Yes	15 April 2011	31
Almost certainly	Unlikely	7 April 2011	No		
Probably	Unlikely	15 March 2011	No		
Probably	Unlikely	31 March 2011	No		
Almost certainly	Unlikely	15 March 2011	No		
Unrelated	Probably	12 October 2010	Yes	12 October 2010	0
Unrelated	Probably	12 October 2010	Yes	12 October 2010	0
Unrelated	Probably	12 October 2010	Yes	12 October 2010	0
Unrelated	Probably	13 October 2010	Yes	13 October 2010	0
Possibly	Unlikely		Yes		
Unlikely	Unlikely	11 October 2010	No		
Unlikely	Unlikely	11 October 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
41	FCR	Rigors		1	1	Unrelated
	FCR	Back pain		1	1	Unrelated
	FCR	Headache		1	1	Unrelated
	FCR	Nausea		1	1	Unrelated
	FCR	Diarrhoea		1	1	Possibly
	FCR	Neutropenia		4	1	Probably
	FCR	Nasal symptoms		2	1	Unrelated
	FCR	Infections (not neutropenic sepsis)		3	2	Probably
	FCR	Infections (not neutropenic sepsis)		3	2	Probably
	FCR	Neutropenia		4	2	Probably
42	FCR	Nausea		1	1	Almost certainly
	FCR	Neutropenia		1	1	Possibly
	FCR	Anaemia		1	1	Possibly
	FCR	Infusional reaction		2	1	Unrelated
	FCR	Vomiting		2	2	Possibly
	FCR	Diarrhoea		1	2	Possibly
	FCR	Thrombocytopenia		1	3	Possibly
	FCR	Lymphopenia		2	3	Possibly
	FCR	Lymphopenia		3	3	Possibly
	FCR	Anaemia		1	3	Possibly
	FCR	Myalgias		1	4	Possibly
	FCR	Cutaneous herpes/ shingles		2	5	Possibly
	FCR	Vomiting		1	5	Probably
	FCR	Fatigue		1	5	Probably
	FCR	Neutropenia		1	5	Possibly
	FCR	Nausea		2	6	Probably
	FCR	Neutropenia		2	6	Possibly
43	FCR	Anaemia		1	1	Probably
	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Fatigue		1	1	Probably
	FCR	Rigors		1	1	Possibly
	FCR	Nausea		1	2	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	3	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Almost certainly	3 November 2010	Yes	3 November 2010	0
Unrelated	Almost certainly	3 November 2010	Yes	3 November 2010	0
Unrelated	Almost certainly	3 November 2010	Yes	3 November 2010	0
Unrelated	Almost certainly	3 November 2010	Yes	4 November 2010	1
Possibly	Unlikely		Yes		
Probably	Probably	15 November 2010	Yes	29 November 2010	14
Unrelated	Unrelated	26 November 2010	No		
Probably	Probably	11 December 2010	Yes	11 January 2011	31
Probably	Probably	14 January 2011	Yes	21 January 2011	7
Probably	Probably	11 December 2010	Yes	14 December 2010	3
Almost certainly	Probably		Yes		
Possibly	Possibly	23 November 2010	Yes	25 November 2010	2
Possibly	Possibly	19 July 2010	Yes	23 November 2010	127
Unrelated	Almost certainly	28 October 2010	Yes	28 October 2010	0
Possibly	Possibly	27 November 2010	Yes	27 November 2010	0
Possibly	Possibly		Yes	20 January 2011	
Possibly	Possibly	21 September 2010	Yes	18 January 2011	119
Possibly	Possibly	21 December 2010	Yes	18 January 2011	28
Possibly	Possibly	18 January 2011	No		
Possibly	Possibly	18 January 2011	No		
Possibly	Possibly		Yes	17 February 2011	
Possibly	Possibly	18 February 2011	Yes	5 March 2011	15
Probably	Possibly	2 March 2011	Yes	3 March 2011	1
Probably	Possibly		Yes	19 March 2011	
Possibly	Possibly	15 February 2011	Yes	15 March 2011	28
Probably	Probably	2 March 2011	Yes	14 April 2011	43
Possibly	Possibly	18 January 2011	Yes	14 April 2011	86
Probably	Possibly		No		
Almost certainly	Possibly	26 October 2010	Yes		
Almost certainly	Possibly		Yes		
Probably	Probably		Yes		
Possibly	Probably	26 October 2010	Yes	26 October 2010	0
Almost certainly	Possibly	25 November 2010	Yes	28 November 2010	3
Possibly	Possibly		Yes		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Nausea		1	4	Almost certainly
	FCR	Constipation		1	4	Possibly
	FCR	Pruritus		1	4	Probably
	FCR	Nausea		1	5	Almost certainly
44	FCR	Nausea		1	1	Almost certainly
	FCR	Constipation		2	1	Almost certainly
	FCR	Fatigue		1	1	Almost certainly
	FCR	Alopecia		1	1	Almost certainly
	FCR	Mucositis/thrush		1	1	Almost certainly
	FCR	Thrombocytopenia		2	1	Almost certainly
	FCR	Neutropenia		2	1	Almost certainly
	FCR	Neuropathy (sensory)		1	1	Unlikely
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Neutropenic sepsis		1	2	Almost certainly
	FCR	Diarrhoea		2	3	Unrelated
	FCR	Myalgias		1	3	Possibly
	FCR	Constipation		1	4	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Infections (not neutropenic sepsis)		1	4	Unrelated
	FCR	Fatigue		2	4	Almost certainly
	FCR	Nausea		2	5	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	5	Unrelated
	FCR	Vomiting		2	5	Almost certainly
48	FCR	Headache		2	3	Unlikely
	FCR	Sore throat		2	4	Possibly
	FCR	Urinary symptoms		2	4	Possibly
	FCR	Dizziness		1	5	Unrelated
	FCR	Abdominal pain/ bloating		1	5	Possibly
	FCR	Fatigue		1	6	Almost certainly
	FCR	Nausea		2	6	Almost certainly
50	FCR	Infections (not neutropenic sepsis)		3	5	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Possibly	20 January 2011	Yes	29 January 2011	9
Possibly	Possibly		Yes	16 February 2011	
Unlikely	Unlikely		Yes	16 February 2011	
Almost certainly	Possibly	17 February 2011	Yes		
Almost certainly	Almost certainly	4 November 2010	Yes	10 November 2010	6
Almost certainly	Almost certainly	4 November 2010	No		
Almost certainly	Almost certainly	4 November 2010	No		
Almost certainly	Almost certainly	4 November 2010	No		
Almost certainly	Almost certainly	4 November 2010	Yes		
Almost certainly	Almost certainly	30 November 2010	Yes	14 December 2010	14
Almost certainly	Almost certainly	30 November 2010	Yes	14 December 2010	14
Unlikely	Unlikely		No		
Almost certainly	Almost certainly	11 January 2011	Yes	13 January 2011	2
Almost certainly	Almost certainly	11 January 2011	No		
Almost certainly	Almost certainly	16 December 2010	Yes		
Almost certainly	Almost certainly	24 December 2010	Yes	27 December 2010	3
Unrelated	Unrelated		Yes		
Possibly	Possibly		No		
Almost certainly	Almost certainly		Yes		
Almost certainly	Almost certainly		Yes		
Unrelated	Unrelated	1 March 2011	Yes	8 March 2011	7
Almost certainly	Almost certainly	10 February 2011	Yes	14 February 2011	4
Almost certainly	Almost certainly	15 March 2011	Yes		
Unrelated	Unrelated	21 March 2011	Yes		
Almost certainly	Almost certainly	15 March 2011	Yes	15 March 2011	0
Unlikely	Unlikely	26 December 2010	No		
Possibly	Possibly	14 February 2011	Yes	14 March 2011	28
Possibly	Possibly	14 February 2011	Yes	14 March 2011	28
Unrelated	Unrelated	14 March 2011	Yes	11 April 2011	28
Possibly	Possibly	14 March 2011	Yes	11 April 2011	28
Unlikely	Unlikely	11 April 2011	Yes	9 May 2011	28
Almost certainly	Almost certainly	11 April 2011	Yes	9 May 2011	28
Almost certainly	Almost certainly	27 February 2011	Yes	1 March 2011	2

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
51	FCR	Neutropenia		4	1	Probably
	FCR	Anaemia		2	2	Almost certainly
	FCR	Neutropenia		3	3	Missing
	FCR	Thrombocytopenia		1	3	Missing
	FCR	Thrombocytopenia		1	4	Probably
	FCR	Neutropenia		3	4	Probably
	FCR	Anaemia		1	4	Probably
55	FCR	Thrombocytopenia		3	1	Almost certainly
	FCR	Neutropenia		3	1	Almost certainly
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Anaemia		1	2	Almost certainly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Neutropenia		1	4	Almost certainly
	FCR	Neutropenia		3	6	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly
	FCR	Rash/flushing		2	6	Unrelated
59	FCR	Nausea		1	3	Probably
	FCR	Anaemia		1	3	Possibly
	FCR	Nausea		1	4	Probably
	FCR	Neutropenia		1	6	Almost certainly
60	FCR	Vomiting		2	1	Almost certainly
	FCR	Infusional reaction		2	1	Unrelated
	FCR	Fever		3	2	Probably
	FCR	Nausea		1	2	Unlikely
	FCR	Dyspnoea		1	2	Unlikely
	FCR	Neutropenia		1	2	Probably
	FCR	Nausea		1	3	Almost certainly
	FCR	Vomiting		3	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Probably
	FCR	Neutropenia		1	4	Probably
	FCR	Nausea		3	5	Almost certainly
	FCR	Vomiting		3	5	Almost certainly
	FCR	Neutropenia		2	5	Almost certainly
	FCR	Anaemia		1	5	Almost certainly
	FCR	Fatigue		2	5	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	30 December 2010	Yes	31 January 2011	32
Almost certainly	Missing	12 February 2011	Yes	14 March 2011	30
Missing	Missing	11 April 2011	Yes	15 April 2011	4
Missing	Missing	14 March 2011	No		
Probably	Probably	6 May 2011	No		
Probably	Probably	12 May 2011	No		
Probably	Probably	12 May 2011	No		
Almost certainly	Almost certainly	14 January 2011	Yes	7 February 2011	24
Almost certainly	Almost certainly	14 January 2011	Yes	15 February 2011	32
Almost certainly	Almost certainly	7 March 2011	Yes	4 April 2011	28
Almost certainly	Almost certainly	15 February 2011	Yes	4 April 2011	48
Almost certainly	Almost certainly	22 March 2011	Yes	4 April 2011	13
Almost certainly	Almost certainly	22 March 2011	Yes	4 April 2011	13
Almost certainly	Almost certainly	7 February 2011	No		
Almost certainly	Almost certainly	15 June 2011	Yes	29 June 2011	14
Almost certainly	Almost certainly	7 February 2011	Yes	20 September 2011	225
Unrelated	Unrelated	12 September 2011	No		
Probably	Unlikely	22 March 2011	Yes	26 March 2011	4
Possibly	Unlikely	19 April 2011	No		
Probably	Unlikely	19 April 2011	Yes	23 April 2011	4
Almost certainly	Unlikely	17 May 2011	Yes	8 September 2011	114
Almost certainly	Almost certainly	24 January 2011	Yes	27 January 2011	3
Unrelated	Almost certainly	27 January 2011	Yes	27 January 2011	0
Probably	Probably	4 March 2011	Yes	7 March 2011	3
Unlikely	Unlikely	7 March 2011	Yes	11 March 2011	4
Unlikely	Unlikely	7 March 2011	Yes	11 March 2011	4
Probably	Probably	4 March 2011	Yes	23 March 2011	19
Almost certainly	Possibly	26 March 2011	Yes	31 March 2011	5
Almost certainly	Unlikely	23 April 2011	Yes	04 May 2011	11
Probably	Possibly	4 March 2011	Yes	18 May 2011	75
Probably	Probably	20 April 2011	Yes	18 May 2011	28
Almost certainly	Possibly	21 May 2011	Yes	8 June 2011	18
Almost certainly	Possibly	21 May 2011	Yes	8 June 2011	18
Almost certainly	Possibly		No		
Almost certainly	Possibly	15 June 2011	No		
Possibly	Probably	19 May 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Constipation		1	5	Unlikely
	FCR	Nausea		1	6	Almost certainly
	FCR	Vomiting		1	6	Almost certainly
	FCR	Sore throat		1	6	Almost certainly
	FCR	Neutropenia		3	6	Almost certainly
61	FCR	Infections (not neutropenic sepsis)		2	1	Missing
	FCR	Thrombocytopenia		2	1	Missing
	FCR	Neutropenia		4	1	Missing
	FCR	Constipation		1	1	Unlikely
	FCR	Infections (not neutropenic sepsis)		2	2	Almost certainly
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Other AE description	Pancytopenia	2	2	Almost certainly
	FCR	Thrombocytopenia		2	3	Almost certainly
	FCR	Neutropenia		3	3	Almost certainly
	FCR	Fatigue		1	3	Almost certainly
	FCR	Fatigue		1	4	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	4	Almost certainly
	FCR	Neutropenia		4	4	Almost certainly
	FCR	Thrombocytopenia		3	4	Almost certainly
	FCR	Neutropenia		4	5	Almost certainly
	FCR	Fatigue		1	5	Almost certainly
	FCR	Neutropenia		4	6	Almost certainly
	FCR	Thrombocytopenia		2	6	Almost certainly
62	FCR	Hypotension		1	1	Unlikely
	FCR	Fever		1	1	Unlikely
	FCR	Vomiting		1	3	Probably
	FCR	Bone pain		1	3	Unlikely
66	FCR	Thrombocytopenia		1	1	Almost certainly
	FCR	Neutropenia		2	1	Almost certainly
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Anaemia		1	2	Almost certainly
	FCR	Neutropenia		4	3	Almost certainly
	FCR	Diarrhoea		2	3	Possibly
	FCR	Neutropenia		4	4	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	18 May 2011	Yes	1 June 2011	14
Almost certainly	Possibly	24 February 2011	Yes	2 July 2011	128
Almost certainly	Possibly	27 June 2011	Yes	2 July 2011	5
Almost certainly	Unlikely		Yes		
Almost certainly	Possibly	13 July 2011	Yes	27 July 2011	14
Missing	Missing	15 February 2011	Yes	24 February 2011	9
Missing	Missing	8 February 2011	Yes	18 February 2011	10
Missing	Missing	18 February 2011	Yes	24 February 2011	6
Unlikely	Unlikely	18 February 2011	Yes	24 February 2011	6
Almost certainly	Almost certainly	7 March 2011	Yes	13 March 2011	6
Almost certainly	Almost certainly	24 March 2011	Yes	24 March 2011	0
Almost certainly	Almost certainly	7 March 2011	Yes	24 March 2011	17
Almost certainly	Almost certainly	28 April 2011	Yes	5 May 2011	7
Almost certainly	Almost certainly	14 April 2011	Yes	28 April 2011	14
Almost certainly	Almost certainly	14 April 2011	Yes	28 April 2011	14
Almost certainly	Almost certainly	5 May 2011	No		
Almost certainly	Almost certainly	16 May 2011	Yes	24 May 2011	8
Almost certainly	Almost certainly	19 May 2011	Yes	15 June 2011	27
Almost certainly	Almost certainly	15 June 2011	No		
Almost certainly	Almost certainly	6 July 2011	Yes	20 July 2011	14
Almost certainly	Almost certainly	6 July 2011	Yes	14 July 2011	8
Almost certainly	Almost certainly	4 August 2011	Yes	22 September 2011	49
Almost certainly	Almost certainly	17 August 2011	Yes	26 August 2011	9
Unlikely	Unlikely	2 February 2011	Yes	2 February 2011	0
Unlikely	Unlikely	2 February 2011	Yes	2 February 2011	0
Probably	Unlikely		Yes		
Unlikely	Unlikely		No		
Almost certainly	Almost certainly	15 March 2011	Yes	22 March 2011	7
Almost certainly	Almost certainly	22 March 2011	Yes	29 March 2011	7
Almost certainly	Almost certainly	20 April 2011	Yes	26 April 2011	6
Almost certainly	Almost certainly	12 April 2011	Yes	20 April 2011	8
Almost certainly	Almost certainly	10 May 2011	Yes	23 May 2011	13
Possibly	Possibly	3 May 2011	Yes	5 May 2011	2
Almost certainly	Almost certainly	7 June 2011	Yes	20 June 2011	13

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Diarrhoea		1	4	Probably
	FCR	Neutropenia		2	5	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly
	FCR	Neutropenia		2	6	Almost certainly
67	FCR	Anaemia		1	1	Almost certainly
	FCR	Neutropenia		1	1	Almost certainly
	FCR	Nausea		1	1	Almost certainly
	FCR	Neutropenia		4	3	Almost certainly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Anaemia		1	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Anaemia		1	5	Almost certainly
	FCR	Neutropenia		3	5	Almost certainly
	FCR	Anaemia		2	6	Almost certainly
	FCR	Thrombocytopenia		2	6	Almost certainly
	FCR	Neutropenia		4	6	Almost certainly
	FCR	Nausea		2	6	Almost certainly
	FCR	Vomiting		2	6	Almost certainly
68	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Infusional reaction		3	1	Unrelated
	FCR	Neutropenia		2	1	Almost certainly
	FCR	Neutropenia		2	2	Almost certainly
	FCR	Nausea		2	2	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
	FCR	Allergic reaction		2	2	Unrelated
	FCR	Vomiting		1	3	Almost certainly
	FCR	Nausea		2	3	Almost certainly
	FCR	Constipation		1	3	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Headache		2	4	Probably
	FCR	Dizziness		2	4	Probably
	FCR	Constipation		1	4	Unlikely
	FCR	Nausea		1	5	Almost certainly
	FCR	Fatigue		1	5	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	31 May 2011	Yes	7 June 2011	7
Probably	Probably	29 May 2011	Yes	30 May 2011	1
Almost certainly	Almost certainly	5 July 2011	Yes	26 July 2011	21
Almost certainly	Almost certainly	26 July 2011	Yes	2 August 2011	7
Almost certainly	Almost certainly	2 August 2011	No		
Almost certainly	Almost certainly	8 March 2011	Yes	21 March 2011	13
Almost certainly	Almost certainly	8 March 2011	Yes	21 March 2011	13
Almost certainly	Almost certainly	9 March 2011	Yes	9 March 2011	0
Almost certainly	Almost certainly	16 May 2011	Yes	1 June 2011	16
Almost certainly	Almost certainly	3 May 2011	Yes	16 May 2011	13
Almost certainly	Almost certainly	23 May 2011	No		
Almost certainly	Almost certainly	23 May 2011	Yes	28 May 2011	5
Almost certainly	Almost certainly	14 June 2011	No		
Almost certainly	Almost certainly	24 June 2011	No		
Almost certainly	Almost certainly	16 May 2011	No		
Almost certainly	Almost certainly	18 July 2011	Yes	29 July 2011	11
Almost certainly	Almost certainly	21 June 2011	Yes	29 July 2011	38
Almost certainly	Almost certainly	17 July 2011	Yes	19 July 2011	2
Almost certainly	Unrelated	17 July 2011	Yes	19 July 2011	2
Almost certainly	Possibly	6 March 2011	Yes	13 March 2011	7
Almost certainly	Possibly	8 March 2011	Yes	9 March 2011	1
Unrelated	Almost certainly	3 March 2011	Yes	3 March 2011	0
Almost certainly	Possibly		No		
Almost certainly	Almost certainly	27 April 2011	No		
Almost certainly	Almost certainly	5 April 2011	Yes	14 April 2011	9
Almost certainly	Almost certainly	5 April 2011	Yes	11 April 2011	6
Unrelated	Almost certainly	4 April 2011	Yes	4 April 2011	0
Almost certainly	Almost certainly	4 May 2011	Yes	10 May 2011	6
Almost certainly	Almost certainly	4 May 2011	Yes	13 May 2011	9
Almost certainly	Almost certainly	5 May 2011	Yes	7 May 2011	2
Almost certainly	Possibly	3 June 2011	Yes	5 June 2011	2
Unlikely	Possibly	2 June 2011	Yes	2 June 2011	0
Unlikely	Possibly	3 June 2011	Yes	3 June 2011	0
Unlikely	Unlikely	4 June 2011	Yes	7 June 2011	3
Almost certainly	Possibly	2 July 2011	Yes	6 July 2011	4
Possibly	Probably	2 July 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Rash/flushing		2	6	Unrelated
	FCR	Nausea		2	6	Possibly
	FCR	Anxiety/depression		2	6	Unrelated
	FCR	Headache		1	6	Unrelated
	FCR	Abdominal pain/ bloating		2	6	Unrelated
70	FCR	Anaemia		3	1	Almost certainly
	FCR	Neutropenia		4	1	Almost certainly
	FCR	Thrombocytopenia		3	1	Almost certainly
	FCR	Allergic reaction		1	1	Unlikely
	FCR	Infections (not neutropenic sepsis)		3	1	Probably
	FCR	Anaemia		2	2	Almost certainly
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Allergic reaction		1	2	Unlikely
	FCR	Urinary symptoms		1	2	Unlikely
	FCR	Myalgias		1	2	Unlikely
	FCR	Anaemia		1	3	Almost certainly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Infections (not neutropenic sepsis)		3	4	Probably
	FCR	Constipation		1	4	Unlikely
	FCR	Anaemia		1	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Neutropenia		3	4	Almost certainly
	FCR	Abnormal electrolytes		1	4	Unlikely
	FCR	Neutropenia		4	5	Almost certainly
	FCR	Thrombocytopenia		1	5	Almost certainly
	FCR	Non-specific pain		1	5	Unlikely
	FCR	Constipation		1	5	Unlikely
	FCR	Neutropenia		3	6	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly
72	FCR	Neutropenia		4	1	Almost certainly
	FCR	Thrombocytopenia		2	1	Unrelated
	FCR	Anaemia		1	1	Unrelated
	FCR	Nausea		1	1	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	31 July 2011	Yes	4 August 2011	4
Possibly	Unrelated	30 July 2011	Yes	1 August 2011	2
Unrelated	Unrelated		Yes	26 October 2011	
Unrelated	Unrelated	27 July 2011	Yes	29 July 2011	2
Unrelated	Unrelated	7 August 2011	Yes	8 August 2011	1
Almost certainly	Possibly	11 March 2011	No		
Almost certainly	Possibly	11 March 2011	No		
Almost certainly	Possibly	11 March 2011	No		
Unlikely	Almost certainly	11 March 2011	Yes	12 March 2011	1
Probably	Possibly	12 March 2011	Yes	25 March 2011	13
Almost certainly	Possibly	12 April 2011	No		
Almost certainly	Possibly	12 April 2011	No		
Almost certainly	Possibly	12 April 2011	Yes	27 April 2011	15
Unlikely	Almost certainly	12 April 2011	Yes	12 April 2011	0
Possibly	Unlikely	1 May 2011	Yes	12 May 2011	11
Unlikely	Unlikely		No		
Almost certainly	Possibly	12 May 2011	No		
Almost certainly	Possibly	12 May 2011	No		
Probably	Possibly	14 June 2011	Yes	20 June 2011	6
Unlikely	Unlikely	11 June 2011	Yes	16 June 2011	5
Almost certainly	Possibly	10 June 2011	Yes	14 July 2011	34
Almost certainly	Possibly	14 June 2011	Yes	23 June 2011	9
Almost certainly	Possibly	17 June 2011	No		
Unlikely	Unlikely	16 June 2011	Yes	17 June 2011	1
Almost certainly	Possibly	4 August 2011	No		
Almost certainly	Possibly	15 July 2011	No		
Unlikely	Unlikely	22 July 2011	No		
Unlikely	Unlikely	9 July 2011	Yes	13 July 2011	4
Almost certainly	Possibly	19 August 2011	No		
Almost certainly	Possibly	12 August 2011	No		
Almost certainly	Almost certainly	6 April 2011	Yes	3 May 2011	27
Unrelated	Unrelated	23 February 2011	No		
Unrelated	Unrelated	10 March 2011	No		
Almost certainly	Almost certainly	20 March 2011	Yes	22 March 2011	2

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Anaemia		1	2	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Neutropenia		2	3	Almost certainly
	FCR	Nausea		1	3	Almost certainly
	FCR	Vomiting		2	3	Almost certainly
	FCR	Neutropenia		1	4	Almost certainly
	FCR	Diarrhoea		1	4	Almost certainly
	FCR	Nausea		1	5	Almost certainly
	FCR	Thrombocytopenia		3	5	Unrelated
	FCR	Neutropenia		1	5	Almost certainly
	FCR	Anaemia		1	6	Almost certainly
	FCR	Neutropenia		1	6	Almost certainly
	FCR	Nausea		1	6	Almost certainly
74	FCR	Infusional reaction		2	1	Unrelated
	FCR	Myalgias		1	1	Possibly
	FCR	Nausea		1	1	Probably
	FCR	Vomiting		1	1	Probably
	FCR	Infections (not neutropenic sepsis)		2	1	Unlikely
	FCR	Rash/flushing		1	1	Unlikely
	FCR	Constipation		1	1	Possibly
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Fatigue		1	2	Almost certainly
	FCR	Nausea		3	3	Possibly
	FCR	Vomiting		3	3	Possibly
	FCR	Neutropenia		2	3	Almost certainly
	FCR	Nausea		3	4	Almost certainly
	FCR	Vomiting		2	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Possibly
	FCR	Nausea		1	5	Almost certainly
	FCR	Vomiting		1	5	Almost certainly
	FCR	Constipation		1	5	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	3 May 2011	Yes	17 May 2011	14
Almost certainly	Almost certainly	24 April 2011	Yes	26 April 2011	2
Almost certainly	Almost certainly	22 April 2011	Yes	24 April 2011	2
Almost certainly	Almost certainly	1 June 2011	Yes	5 July 2011	34
Almost certainly	Almost certainly	14 June 2011	Yes	5 July 2011	21
Almost certainly	Almost certainly	22 May 2011	Yes	23 May 2011	1
Almost certainly	Almost certainly	22 May 2011	Yes	23 May 2011	1
Almost certainly	Almost certainly	12 July 2011	Yes	2 August 2011	21
Almost certainly	Almost certainly	21 July 2011	Yes	27 July 2011	6
Almost certainly	Almost certainly	13 July 2011	Yes	17 July 2011	4
Unrelated	Unrelated	23 February 2001	No		
Almost certainly	Almost certainly	9 August 2011	Yes	6 September 2011	28
Almost certainly	Unrelated	6 September 2011	No		
Almost certainly	Unrelated	16 August 2011	Yes	6 September 2011	21
Almost certainly	Unrelated	17 August 2011	Yes	25 August 2011	8
Unrelated	Almost certainly	22 March 2011	Yes	22 March 2011	0
Possibly	Possibly	27 March 2011	Yes	27 March 2011	0
Probably	Possibly	28 March 2011	Yes	28 March 2011	0
Probably	Possibly	28 March 2011	Yes	28 March 2011	0
Unlikely	Unlikely	4 April 2011	Yes	10 April 2011	6
Unlikely	Unlikely	19 April 2011	No		
Possibly	Possibly	28 March 2011	Yes	31 March 2011	3
Almost certainly	Possibly	17 May 2011	No		
Possibly	Probably	20 April 2011	No		
Possibly	Possibly	21 May 2011	Yes	22 May 2011	1
Possibly	Possibly	21 May 2011	Yes	22 May 2011	1
Almost certainly	Possibly	14 June 2011	No		
Almost certainly	Possibly	18 June 2011	Yes	20 June 2011	2
Almost certainly	Possibly	19 June 2011	Yes	20 June 2011	1
Possibly	Possibly	29 April 2009	Yes	13 July 2011	805
Almost certainly	Possibly	16 July 2011	Yes	19 July 2011	3
Almost certainly	Possibly	17 July 2011	Yes	17 July 2011	0
Possibly	Unlikely		No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Vomiting		2	6	Probably
	FCR	Nausea		1	6	Probably
78	FCR	Diarrhoea		1	1	Possibly
	FCR	Anorexia/cachexia		1	1	Unlikely
	FCR	Fever		1	1	Possibly
	FCR	Anaemia		2	1	Possibly
	FCR	Thrombocytopenia		1	1	Possibly
	FCR	Anaemia		1	3	Possibly
	FCR	Urinary symptoms		1	3	Unlikely
	FCR	Fatigue		1	4	Possibly
	FCR	Diarrhoea		1	4	Possibly
	FCR	Vomiting		1	4	Possibly
	FCR	Rash/flushing		1	5	Possibly
	FCR	Fatigue		2	6	Possibly
	FCR	Anorexia/cachexia		1	6	Possibly
82	FCR	Neutropenia		4	1	Almost certainly
	FCR	Anaemia		2	2	Almost certainly
	FCR	Thrombocytopenia		2	2	Almost certainly
	FCR	Neutropenia		3	2	Probably
	FCR	Neutropenia		4	3	Probably
	FCR	Thrombocytopenia		3	3	Probably
	FCR	Anaemia		2	3	Probably
	FCR	Infections (not neutropenic sepsis)		3	6	Unlikely
	FCR	Thrombocytopenia		2	6	Possibly
84	FCR	Neutropenia		1	1	Possibly
	FCR	Myalgias		1	1	Unlikely
	FCR	Neuropathy (sensory)		1	1	Possibly
	FCR	Nausea		1	2	Almost certainly
	FCR	Rash/flushing		1	3	Unlikely
	FCR	Infections (not neutropenic sepsis)		2	3	Unlikely
	FCR	Ophthalmic infections		1	4	Unlikely
	FCR	Neuropathy (sensory)		1	4	Possibly
	FCR	Nausea		1	5	Almost certainly
	FCR	Fever		2	5	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Unlikely	15 September 2011	Yes	16 September 2011	1
Probably	Unlikely	11 September 2011	Yes	17 September 2011	6
Possibly	Possibly	8 May 2011	Yes	11 May 2011	3
Unlikely	Unlikely	9 May 2011	Yes	31 May 2011	22
Possibly	Possibly	6 May 2011	Yes	3 June 2011	28
Possibly	Possibly	9 May 2011	No		
Possibly	Possibly	9 May 2011	Yes	28 June 2011	50
Possibly	Possibly	26 July 2011	No		
Unlikely	Unlikely	3 June 2011	Yes	26 July 2011	53
Possibly	Possibly	9 May 2011	Yes	26 August 2011	109
Possibly	Possibly	1 July 2011	Yes	26 August 2011	56
Possibly	Possibly	2 August 2011	Yes	26 August 2011	24
Possibly	Possibly	26 August 2011	Yes	20 September 2011	25
Possibly	Possibly	23 September 2011	Yes	30 September 2011	7
Possibly	Possibly	23 September 2011	Yes	30 September 2011	7
Almost certainly	Almost certainly	29 June 2011	Yes	4 July 2011	5
Almost certainly	Unlikely	20 July 2011	No		
Almost certainly	Unlikely	20 July 2011	No		
Almost certainly	Unlikely	3 August 2011	No		
Probably	Probably	10 August 2011	No		
Probably	Probably	5 August 2011	No		
Probably	Probably	12 August 2011	No		
Unlikely	Unlikely	9 December 2011	No		
Possibly	Possibly	30 September 2011	No		
Almost certainly	Unrelated	9 June 2011	No		
Unlikely	Unlikely	25 May 2011	No		
Unlikely	Possibly	25 May 2011	No		
Almost certainly	Unlikely	20 June 2011	Yes	22 June 2011	2
Unlikely	Unlikely	17 July 2011	No		
Possibly	Unlikely	17 July 2011	No		
Unlikely	Unlikely	17 July 2011	No		
Unlikely	Unlikely	26 August 2011	No		
Almost certainly	Unlikely	7 October 2011	Yes	24 October 2011	17
Possibly	Unlikely	22 October 2011	Yes	28 October 2011	6

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Neutropenia		2	5	Almost certainly
	FCR	Nausea		1	6	Almost certainly
87	FCR	Rash/flushing		1	1	Unlikely
	FCR	Thrombocytopenia		1	5	Probably
	FCR	Anaemia		1	6	Probably
88	FCR	Thrombocytopenia		1	1	Unrelated
	FCR	Neutropenia		1	1	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Neutropenia		1	2	Almost certainly
	FCR	Diarrhoea		1	4	Almost certainly
	FCR	Neutropenia		3	4	Almost certainly
	FCR	Thrombocytopenia		1	6	Possibly
89	FCR	Neutropenia		2	1	Almost certainly
	FCR	Nausea		2	1	Almost certainly
	FCR	Vomiting		2	1	Almost certainly
	FCR	Nausea		2	2	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
	FCR	Fatigue		2	2	Almost certainly
	FCR	Nausea		2	3	Almost certainly
	FCR	Vomiting		2	3	Almost certainly
	FCR	Fatigue		2	3	Almost certainly
	FCR	Abdominal pain/ bloating		2	3	Possibly
	FCR	Vomiting		2	4	Almost certainly
	FCR	Nausea		2	4	Almost certainly
	FCR	Abdominal pain/ bloating		2	4	Possibly
	FCR	Vomiting		1	5	Almost certainly
	FCR	Nausea		1	5	Almost certainly
	FCR	Fatigue		1	5	Almost certainly
	FCR	Nausea		1	6	Almost certainly
	FCR	Vomiting		1	6	Almost certainly
91	FCR	Anxiety/depression		2	1	Unrelated
	FCR	Mucositis/thrush		1	2	Unrelated
	FCR	Anxiety/depression		2	3	Unrelated
	FCR	Mucositis/thrush		1	3	Unrelated

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Unlikely	24 October 2011	Yes	1 November 2011	8
Almost certainly	Unlikely	9 September 2011	Yes	21 September 2011	12
Unlikely	Unlikely	15 June 2011	Yes	1 August 2011	47
Probably	Probably	31 October 2011	No		
Probably	Unlikely	30 November 2011	No		
Unrelated	Unrelated	24 May 2011	No		
Almost certainly	Almost certainly	15 June 2011	Yes	28 June 2011	13
Almost certainly	Almost certainly		No		
Almost certainly	Almost certainly	13 July 2011	No		
Almost certainly	Almost certainly	28 August 2011	Yes	29 August 2011	1
Almost certainly	Almost certainly	17 July 2011	No		
Possibly	Possibly	3 July 2009	No		
Almost certainly	Possibly	5 July 2011	No		
Almost certainly	Unlikely	12 June 2011	Yes	16 June 2011	4
Almost certainly	Unlikely	12 June 2011	Yes	16 June 2011	4
Almost certainly	Unlikely	8 July 2011	Yes	17 July 2011	9
Almost certainly	Unlikely	8 July 2011	Yes	17 July 2011	9
Almost certainly	Unlikely	8 July 2011	Yes	22 July 2011	14
Almost certainly	Unlikely	5 August 2011	Yes	15 August 2011	10
Almost certainly	Unlikely	5 August 2011	Yes	15 August 2011	10
Almost certainly	Unlikely	5 August 2011	Yes	19 August 2011	14
Possibly	Unlikely	4 August 2011	No		
Almost certainly	Unlikely	8 September 2011	Yes	20 September 2011	12
Almost certainly	Unlikely	8 September 2011	No		
Possibly	Unlikely	8 September 2011	No		
Almost certainly	Unlikely	6 October 2011	Yes	9 October 2011	3
Almost certainly	Unlikely	5 October 2011	Yes	12 October 2011	7
Almost certainly	Unlikely	5 October 2011	No		
Almost certainly	Unlikely	2 November 2011	Yes	5 November 2011	3
Almost certainly	Unlikely	2 November 2011	Yes	2 November 2011	0
Unrelated	Unrelated	1 July 2011	Yes	21 July 2011	20
Unrelated	Unrelated	21 July 2011	No		
Unrelated	Unrelated	18 August 2011	No		
Unrelated	Unrelated	18 August 2011	Yes	19 September 2011	32

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Anxiety/depression		2	4	Unrelated
	FCR	Anxiety/depression		2	5	Unrelated
	FCR	Anaemia		2	6	Possibly
92	FCR	Diarrhoea		1	1	Possibly
	FCR	Non-specific pain		1	3	Unrelated
	FCR	Neutropenia		2	6	Almost certainly
93	FCR	Headache		1	1	Unlikely
	FCR	Allergic reaction		1	2	Unrelated
	FCR	Lymphopenia		1	4	Probably
	FCR	Pruritus		1	4	Unlikely
	FCR	Rash/flushing		3	5	Unlikely
	FCR	Neutropenia		4	5	Probably
	FCR	Fever		2	5	Probably
	FCR	Lymphopenia		3	5	Probably
	FCR	Lymphopenia		1	6	Probably
98	FCR	Back pain		1	1	Possibly
	FCR	Non-specific pain		1	1	Possibly
	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
	FCR	Abdominal pain/ bloating		1	2	Almost certainly
	FCR	Dizziness		2	2	Possibly
	FCR	Nausea		1	3	Almost certainly
	FCR	Abdominal pain/ bloating		1	3	Almost certainly
	FCR	Headache		1	3	Possibly
	FCR	Constipation		1	3	Probably
	FCR	Fatigue		1	4	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Nausea		2	5	Almost certainly
	FCR	Vomiting		2	5	Almost certainly
	FCR	Vomiting		1	6	Almost certainly
	FCR	Nausea		2	6	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	19 September 2011	No		
Unrelated	Unrelated	17 October 2011	No		
Possibly	Possibly	14 November 2011	Yes	28 November 2011	14
Possibly	Possibly	28 June 2011	Yes	4 July 2011	6
Unrelated	Unrelated	31 August 2011	Yes	26 September 2011	26
Almost certainly	Possibly	23 November 2011	Yes	30 November 2011	7
Unlikely	Unlikely		Yes		
Unrelated	Probably	12 July 2011	Yes	12 July 2011	0
Probably	Probably	5 September 2011	No		
Unlikely	Unlikely	5 October 2011	No		
Unlikely	Unlikely	13 November 2011	Yes		
Probably	Probably	14 November 2011	Yes	28 November 2011	14
Probably	Probably		Yes		
Probably	Probably	14 November 2011	No		
Probably	Probably	28 November 2011	No		
Possibly	Possibly	30 August 2011	No		
Possibly	Possibly	30 August 2011	No		
Almost certainly	Unlikely	15 August 2011	Yes	19 August 2011	4
Almost certainly	Unlikely	15 August 2011	Yes	29 August 2011	14
Almost certainly	Unlikely	15 September 2011	Yes	16 September 2011	1
Almost certainly	Unlikely	15 September 2011	Yes	6 October 2011	21
Possibly	Possibly	16 September 2011	Yes	20 September 2011	4
Almost certainly	Unlikely	10 October 2011	Yes	12 October 2011	2
Almost certainly	Unlikely	7 October 2011	Yes	7 October 2011	0
Possibly	Possibly	8 October 2011	Yes	8 October 2011	0
Probably	Unlikely	15 September 2011	Yes	20 September 2011	5
Probably	Unlikely	6 November 2011	No		
Almost certainly	Unlikely	6 November 2011	Yes	10 November 2011	4
Almost certainly	Unlikely	4 December 2011	Yes	8 December 2011	4
Almost certainly	Unlikely	4 December 2011	Yes	8 December 2011	4
Almost certainly	Unlikely	7 January 2012	Yes	10 January 2012	3
Almost certainly	Unlikely	7 January 2012	Yes	10 January 2012	3

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
101	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Otalgia		2	1	Possibly
	FCR	Infusional reaction		1	1	Possibly
	FCR	Neutropenia		3	1	Probably
	FCR	Allergic reaction		1	2	Unrelated
	FCR	Neutropenia		3	2	Probably
	FCR	Infections (not neutropenic sepsis)		2	4	Unlikely
	FCR	Infections (not neutropenic sepsis)		2	5	Unrelated
	FCR	Nausea		1	6	Almost certainly
	FCR	Fatigue		1	6	Almost certainly
102	FCR	Anaemia		2	1	Probably
	FCR	Thrombocytopenia		2	1	Probably
104	FCR	Fatigue		2	1	Probably
	FCR	Nausea		2	1	Probably
	FCR	Vomiting		2	1	Probably
	FCR	Anaemia		2	1	Possibly
	FCR	Neutropenia		4	1	Possibly
	FCR	Anxiety/depression		2	1	Unlikely
	FCR	Taste alteration		1	1	Possibly
	FCR	Thrombocytopenia		1	1	Possibly
	FCR	Fatigue		1	2	Probably
	FCR	Nausea		2	2	Probably
	FCR	Anaemia		2	2	Possibly
	FCR	Neutropenia		2	2	Probably
	FCR	Anorexia/cachexia		1	2	Probably
	FCR	Infections (not neutropenic sepsis)		2	2	Possibly
	FCR	Rash/flushing		2	2	Probably
	FCR	Rash/flushing		2	3	Unlikely
	FCR	Nausea		1	3	Probably
	FCR	Fatigue		1	3	Probably
	FCR	Neutropenia		4	3	Probably
	FCR	Anaemia		2	3	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Unrelated	25 August 2011	Yes	25 August 2011	0
Almost certainly	Unrelated	26 August 2011	Yes	28 August 2011	2
Possibly	Unrelated	28 September 2011	No		
Possibly	Unrelated	25 August 2011	Yes	26 August 2011	1
Probably	Unrelated	14 September 2011	Yes	23 September 2011	9
Unrelated	Almost certainly	26 September 2011	Yes	26 September 2011	0
Probably	Unrelated	21 October 2011	Yes	4 November 2011	14
Unlikely	Unlikely	4 January 2012	No		
Unrelated	Unrelated	23 January 2012	Yes	27 January 2012	4
Almost certainly	Unrelated	9 February 2012	Yes	13 February 2012	4
Almost certainly	Unrelated	8 February 2012	Yes	15 February 2012	7
Probably	Probably	6 September 2011	Yes	12 September 2011	6
Probably	Probably	6 September 2011	Yes	12 September 2011	6
Possibly	Unlikely	13 September 2011	Yes	23 September 2011	10
Probably	Unlikely	16 September 2011	Yes	18 September 2011	2
Probably	Unlikely	17 September 2011	Yes	18 September 2011	1
Possibly	Unlikely	13 September 2011	No		
Possibly	Unlikely	13 September 2011	Yes	29 September 2011	16
Unlikely	Unlikely	9 September 2011	Yes	19 September 2011	10
Possibly	Unlikely	23 September 2011	No		
Possibly	Unlikely	13 September 2011	Yes	29 September 2011	16
Possibly	Unlikely	14 October 2011	Yes	4 November 2011	21
Probably	Unlikely	15 October 2011	Yes	21 October 2011	6
Possibly	Unlikely	14 October 2011	No		
Probably	Unlikely	1 November 2011	No		
Probably	Unlikely	21 October 2011	Yes	11 November 2011	21
Possibly	Unlikely	28 October 2011	No		
Probably	Unlikely	18 October 2011	Yes	19 October 2011	1
Unlikely	Unlikely	28 October 2011	Yes	2 December 2011	35
Probably	Unlikely	14 November 2011	Yes	15 November 2011	1
Possibly	Unlikely	18 November 2011	Yes	25 November 2011	7
Probably	Unlikely	18 November 2011	Yes	25 November 2011	7
Probably	Unlikely	25 November 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Anxiety/depression		2	3	Unlikely
	FCR	Pruritus		1	3	Unrelated
	FCR	Rash/flushing		2	4	Possibly
	FCR	Anxiety/depression		3	4	Unlikely
	FCR	Other AE description	Confusion	3	4	Unlikely
	FCR	Anaemia		2	4	Probably
	FCR	Thrombocytopenia		1	4	Probably
	FCR	Neutropenia		4	4	Probably
	FCR	Nausea		1	5	Probably
	FCR	Anaemia		1	5	Probably
	FCR	Neutropenia		2	5	Probably
	FCR	Thrombocytopenia		1	5	Probably
	FCR	Nausea		1	6	Probably
	FCR	Anxiety/depression		2	6	Unlikely
	FCR	Anaemia		1	6	Probably
	FCR	Neutropenia		2	6	Probably
	FCR	Thrombocytopenia		1	6	Probably
105	FCR	Infusional reaction		2	1	Unlikely
	FCR	Nausea		1	1	Almost certainly
	FCR	Oedema		1	1	Unlikely
	FCR	Constipation		1	1	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Infusional reaction		2	2	Unlikely
	FCR	Constipation		1	2	Almost certainly
	FCR	Neutropenia		3	3	Almost certainly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Lymphopenia		3	3	Almost certainly
	FCR	Non-specific pain		2	3	Unlikely
	FCR	Urinary symptoms		2	3	Unlikely
107	FCR	Anaemia		1	1	Possibly
	FCR	Vomiting		2	1	Possibly
	FCR	Neutropenia		2	2	Possibly
	FCR	Vomiting		2	2	Possibly
	FCR	Constipation		1	2	Unlikely
	FCR	Thrombocytopenia		2	3	Possibly
	FCR	Nausea		1	3	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	29 November 2011	No		
Unrelated	Unrelated	9 December 2011	No		
Possibly	Unlikely	16 December 2011	Yes	18 December 2011	2
Unlikely	Unlikely	16 December 2011	No		
Unlikely	Unlikely	20 December 2011	Yes	6 January 2012	17
Probably	Unlikely	24 December 2011	No		
Probably	Unlikely	16 December 2011	No		
Probably	Possibly	21 December 2011	Yes	6 January 2012	16
Probably	Unlikely	6 January 2012	Yes	10 January 2012	4
Probably	Unlikely	6 January 2012	No		
Probably	Possibly	13 January 2012	No		
Probably	Unlikely	6 January 2012	No		
Probably	Unlikely	6 February 2012	Yes	8 February 2012	2
Unlikely	Unlikely	20 December 2011	Yes	24 February 2012	66
Probably	Unlikely	3 February 2012	No		
Probably	Possibly	03 February 2012	No		
Probably	Unlikely	3 February 2012	No		
Unlikely	Almost certainly	5 September 2011	Yes	5 September 2011	0
Almost certainly	Possibly	6 September 2011	Yes	7 September 2011	1
Unlikely	Unlikely	22 October 2011	Yes	24 October 2011	2
Almost certainly	Unlikely	7 September 2011	Yes	14 September 2011	7
Almost certainly	Possibly	4 October 2011	Yes	5 October 2011	1
Unlikely	Almost certainly	3 October 2011	Yes	3 October 2011	0
Almost certainly	Unlikely	5 October 2011	Yes	12 October 2011	7
Almost certainly	Possibly	27 October 2011	Yes	11 November 2011	15
Almost certainly	Possibly	27 October 2011	Yes	11 November 2011	15
Almost certainly	Possibly	27 October 2011	No		
Unlikely	Unlikely		No		
Unlikely	Unlikely		No		
Possibly	Unlikely	5 September 2011	No		
Possibly	Unlikely	19 September 2011	Yes	22 September 2011	3
Possibly	Unlikely	13 October 2011	Yes	10 November 2011	28
Possibly	Unlikely	14 October 2011	Yes	19 October 2011	5
Unlikely	Unlikely	20 October 2011	Yes	22 October 2011	2
Possibly	Unlikely	22 September 2011	Yes	10 November 2011	49
Probably	Unlikely	10 November 2011	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Thrombocytopenia		1	4	Possibly
	FCR	Fatigue		1	4	Possibly
	FCR	Nausea		2	5	Almost certainly
	FCR	Diarrhoea		2	5	Possibly
110	FCR	Nausea		1	1	Almost certainly
	FCR	Rash/flushing		1	3	Unrelated
	FCR	Diarrhoea		1	5	Possibly
111	FCR	Diarrhoea		1	1	Possibly
	FCR	Rash/flushing		2	1	Unrelated
	FCR	Neutropenic sepsis		3	1	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Fatigue		1	4	Unlikely
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Rash/flushing		1	5	Unlikely
	FCR	Pruritus		1	5	Unlikely
	FCR	Thrombocytopenia		2	6	Almost certainly
	FCR	Anorexia/cachexia		1	6	Unrelated
112	FCR	Pruritus		2	2	Unrelated
	FCR	Rash/flushing		2	3	Unrelated
116	FCR	Thrombocytopenia		3	1	Unrelated
	FCR	Anaemia		2	1	Unrelated
	FCR	Neutropenia		2	2	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
	FCR	Nausea		1	3	Almost certainly
	FCR	Vomiting		1	3	Almost certainly
	FCR	Fatigue		1	4	Almost certainly
	FCR	Neutropenia		4	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Nausea		1	5	Almost certainly
	FCR	Fatigue		1	5	Almost certainly
	FCR	Thrombocytopenia		2	5	Almost certainly
	FCR	Fatigue		1	6	Almost certainly
120	FCR	Nausea		1	1	Probably
	FCR	Rash/flushing		1	2	Unlikely
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Fatigue		1	3	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Unlikely	5 December 2011	No		
Possibly	Unlikely	8 December 2011	Yes	15 December 2011	7
Almost certainly	Unlikely	5 January 2012	Yes	2 February 2012	28
Possibly	Unlikely	28 January 2012	Yes	16 February 2012	19
Almost certainly	Unlikely		Yes		
Unrelated	Unrelated	16 January 2012	Yes	12 March 2012	56
Possibly	Unlikely	14 February 2012	Yes	18 February 2012	4
Possibly	Possibly		Yes	16 November 2011	
Unrelated	Unrelated	2 November 2011	Yes	10 November 2011	8
Almost certainly	Unlikely	4 November 2011	Yes	10 November 2011	6
Almost certainly	Possibly	19 October 2011	No		
Unlikely	Unlikely		Yes	11 January 2012	
Almost certainly	Possibly	19 December 2011	No		
Unlikely	Unlikely		Yes	6 February 2012	
Unlikely	Unlikely		Yes	6 February 2012	
Almost certainly	Possibly	5 March 2012	No		
Unrelated	Unrelated		Yes	8 February 2012	
Unrelated	Unrelated	13 December 2011	No		
Unrelated	Unrelated		Yes	27 February 2012	
Unrelated	Unrelated	31 October 2011	No		
Unrelated	Unrelated	31 October 2011	No		
Almost certainly	Unlikely	23 November 2011	No		
Almost certainly	Possibly	28 November 2011	Yes	1 December 2011	3
Almost certainly	Possibly	28 December 2011	Yes	6 January 2012	9
Almost certainly	Possibly	28 December 2011	Yes	2 January 2012	5
Almost certainly	Almost certainly	25 January 2012	Yes	8 February 2012	14
Almost certainly	Almost certainly	8 February 2012	Yes	21 February 2012	13
Almost certainly	Almost certainly	8 February 2012	No		
Almost certainly	Almost certainly	24 February 2012	Yes		
Almost certainly	Almost certainly	24 February 2012	Yes		
Almost certainly	Almost certainly	20 March 2012	No		
Almost certainly	Almost certainly	30 March 2012	Yes		
Probably	Unlikely		Yes		
Unlikely	Unlikely		Yes		
Almost certainly	Almost certainly	30 January 2012	Yes	27 February 2012	28
Possibly	Possibly	11 January 2012	Yes		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Nausea		1	4	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	4	Unlikely
	FCR	Fatigue		1	4	Possibly
	FCR	Neutropenia		2	5	Almost certainly
	FCR	Mucositis/thrush		1	5	Almost certainly
	FCR	Cough		1	5	Unlikely
	FCR	Fatigue		1	5	Possibly
	FCR	Fatigue		1	6	Possibly
122	FCR	Nausea		1	1	Probably
	FCR	Vomiting		2	1	Probably
	FCR	Rash/flushing		2	1	Unlikely
	FCR	Anaemia		1	1	Possibly
	FCR	Nausea		1	2	Probably
	FCR	Rash/flushing		3	2	Probably
	FCR	Allergic reaction		1	2	Probably
	FCR	Anaemia		2	2	Possibly
123	FCR	Fatigue		1	1	Unlikely
	FCR	Common cold		1	1	Possibly
	FCR	Anaemia		2	1	Unlikely
	FCR	Thrombocytopenia		2	1	Possibly
	FCR	Neutropenia		3	3	Almost certainly
	FCR	Abdominal pain/ bloating		1	4	Unlikely
	FCR	Headache		2	5	Unlikely
	FCR	Back pain		1	6	Unlikely
	FCR	Dizziness		2	6	Unlikely
	FCR	Neutropenia		4	6	Probably
	FCR	Anaemia		2	6	Possibly
125	FCR	Anorexia/cachexia		3	1	Possibly
	FCR	Alopecia		1	1	Possibly
	FCR	Diarrhoea		1	1	Unlikely
	FCR	Infections (not neutropenic sepsis)		3	1	Probably
	FCR	Rash/flushing		1	1	Unlikely
	FCR	Fatigue		1	2	Probably
	FCR	Rash/flushing		1	3	Unlikely

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Possibly	1 February 2012	Yes		
Unlikely	Unlikely	14 February 2012	Yes		
Possibly	Possibly	8 February 2012	Yes		
Almost certainly	Almost certainly	26 March 2012	Yes	23 April 2012	28
Almost certainly	Possibly	29 February 2012	Yes	13 March 2012	13
Unlikely	Unlikely		No		
Possibly	Possibly	7 March 2012	Yes		
Possibly	Possibly	4 April 2012	Yes		
Probably	Unlikely	18 November 2011	Yes	23 November 2011	5
Probably	Unlikely	18 November 2011	Yes	23 November 2011	5
Unlikely	Unlikely	27 November 2011	No		
Possibly	Unlikely	18 November 2011	No		
Probably	Unlikely	16 December 2011	Yes	20 December 2011	4
Unlikely	Unlikely	9 December 2011	Yes	9 January 2012	31
Unlikely	Unlikely	18 November 2011	Yes	9 January 2012	52
Possibly	Unlikely	21 December 2011	Yes	9 January 2012	19
Unlikely	Unlikely	5 December 2011	No		
Possibly	Unlikely	5 December 2011	No		
Unlikely	Unlikely		Yes	10 January 2012	
Possibly	Possibly	5 December 2011	No		
Almost certainly	Possibly	22 December 2011	Yes	22 March 2012	91
Unlikely	Unlikely	11 April 2012	Yes		
Unlikely	Unlikely	15 March 2012	Yes	26 May 2012	72
Unlikely	Unlikely	28 May 2012	Yes	5 June 2012	8
Unlikely	Unlikely	29 May 2012	Yes	3 June 2012	5
Probably	Probably	14 April 2012	Yes	30 July 2012	107
Possibly	Possibly	6 July 2012	Yes	2 August 2012	27
Possibly	Possibly		No		
Possibly	Unlikely		No		
Unlikely	Unlikely	22 February 2012	Yes	24 February 2012	2
Probably	Probably	20 February 2012	Yes	24 February 2012	4
Unlikely	Unlikely	20 February 2012	Yes	24 February 2012	4
Probably	Possibly		Yes		
Unlikely	Unlikely		No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Anaemia		3	4	Almost certainly
	FCR	Neutropenia		3	5	Probably
	FCR	Nausea		1	5	Possibly
	FCR	Bone pain		2	5	Unlikely
	FCR	Fatigue		2	6	Unrelated
	FCR	Constipation		1	6	Unrelated
	FCR	Non-specific pain		2	6	Unrelated
129	FCR	Nausea		1	1	Almost certainly
	FCR	Neutropenia		1	1	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Neutropenia		3	2	Almost certainly
	FCR	Anaemia		1	2	Almost certainly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Urinary symptoms		2	3	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Anaemia		1	4	Almost certainly
	FCR	Thrombocytopenia		1	4	Almost certainly
	FCR	Fatigue		1	5	Almost certainly
	FCR	Anaemia		1	5	Almost certainly
	FCR	Thrombocytopenia		1	5	Almost certainly
	FCR	Anaemia		1	6	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly
130	FCR	Nausea		1	1	Almost certainly
	FCR	Vomiting		1	2	Possibly
	FCR	Anaemia		2	2	Possibly
	FCR	Neutropenia		4	2	Possibly
	FCR	Neutropenia		4	3	Possibly
	FCR	Thrombocytopenia		2	3	Possibly
	FCR	Anaemia		2	3	Possibly
	FCR	Anaemia		2	3	Possibly
	FCR	Neutropenia		4	4	Possibly
	FCR	Anaemia		2	5	Possibly
	FCR	Thrombocytopenia		1	5	Possibly
	FCR	Anaemia		2	6	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	22 May 2012	Yes	5 June 2012	14
Probably	Possibly	25 May 2012	Yes	20 June 2012	26
Possibly	Unlikely	8 June 2012	Yes	10 June 2012	2
Unlikely	Unlikely	13 June 2012	No		
Unrelated	Unrelated	12 July 2012	No		
Unrelated	Unrelated		Yes		
Unrelated	Unrelated	12 July 2012	No		
Almost certainly	Almost certainly	2 February 2012	Yes	3 February 2012	1
Almost certainly	Almost certainly	14 February 2012	No		
Almost certainly	Almost certainly	1 March 2012	Yes	2 March 2012	1
Almost certainly	Almost certainly	12 March 2012	Yes	17 April 2012	36
Almost certainly	Almost certainly	12 March 2012	Yes	2 April 2012	21
Almost certainly	Almost certainly	12 March 2012	Yes	26 March 2012	14
Almost certainly	Almost certainly	26 March 2012	Yes	17 April 2012	22
Almost certainly	Almost certainly	17 April 2012	Yes	30 April 2012	13
Almost certainly	Almost certainly	18 April 2012	No		
Almost certainly	Almost certainly	1 May 2012	Yes	5 May 2012	4
Almost certainly	Almost certainly	14 May 2012	Yes	28 May 2012	14
Almost certainly	Almost certainly	14 May 2012	Yes	28 May 2012	14
Almost certainly	Almost certainly	29 May 2012	No		
Almost certainly	Almost certainly	11 June 2012	Yes	25 June 2012	14
Almost certainly	Almost certainly	11 June 2012	No		
Almost certainly	Almost certainly	9 July 2012	Yes	26 September 2012	79
Almost certainly	Almost certainly	25 June 2012	No		
Almost certainly	Almost certainly	26 January 2012	Yes	29 January 2012	3
Probably	Possibly	24 February 2012	Yes	27 February 2012	3
Probably	Unlikely	13 March 2012	No		
Possibly	Unlikely	13 March 2012	Yes	19 March 2012	6
Possibly	Unlikely	25 March 2012	Yes	10 April 2012	16
Possibly	Possibly	25 March 2012	Yes	27 March 2012	2
Probably	Unlikely	22 March 2012	Yes	28 March 2012	6
Probably	Unlikely	10 April 2012	No		
Possibly	Unlikely	24 April 2012	Yes	1 May 2012	7
Probably	Unlikely	15 May 2012	No		
Possibly	Possibly	15 May 2012	No		
Probably	Unlikely	12 June 2012	Yes	10 July 2012	28

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
134	FCR	Thrombocytopenia		1	1	Unlikely
	FCR	Rash/flushing		2	2	Unrelated
	FCR	Nausea		1	2	Possibly
	FCR	Nausea		2	2	Probably
	FCR	Nausea		2	3	Probably
	FCR	Neutropenia		3	5	Possibly
	FCR	Nausea		2	5	Probably
	FCR	Fatigue		1	5	Probably
136	FCR	Fatigue		2	1	Unrelated
	FCR	Nausea		2	1	Probably
	FCR	Pruritus		1	1	Possibly
	FCR	Constipation		1	1	Unlikely
	FCR	Pruritus		2	3	Probably
	FCR	Nausea		1	3	Probably
	FCR	Rigors		1	3	Unlikely
	FCR	Nausea		2	4	Probably
	FCR	Mucositis/thrush		1	5	Probably
	FCR	Nausea		2	5	Probably
	FCR	Constipation		1	5	Probably
	FCR	Other AE description	Sore gums	1	5	Probably
	FCR	Otalgia		1	5	Unlikely
	FCR	Common cold		1	5	Unlikely
	FCR	Nausea		1	5	Probably
	FCR	Constipation		1	5	Probably
137	FCR	Neutropenia		3	1	Almost certainly
	FCR	Vomiting		1	1	Almost certainly
	FCR	Visual symptoms		1	1	Unlikely
	FCR	Fatigue		1	1	Almost certainly
	FCR	Diarrhoea		1	1	Possibly
	FCR	Anorexia/cachexia		1	1	Probably
	FCR	Rash/flushing		3	2	Unlikely
	FCR	Fatigue		1	2	Almost certainly
	FCR	Pruritus		1	2	Unlikely
	FCR	Neutropenia		3	2	Almost certainly
	FCR	Nausea		3	2	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	8 November 2011	No		
Unrelated	Unrelated	29 March 2012	Yes	1 April 2012	3
Possibly	Possibly	21 March 2012	Yes	22 March 2012	1
Probably	Possibly	14 April 2012	Yes	18 April 2012	4
Probably	Possibly	12 May 2012	Yes	16 May 2012	4
Possibly	Possibly	3 July 2012	No		
Probably	Possibly	10 July 2012	Yes	14 July 2012	4
Probably	Probably	10 July 2012	Yes	24 July 2012	14
Unrelated	Unrelated		No		
Probably	Unlikely	16 April 2012	Yes	18 April 2012	2
Possibly	Possibly	5 May 2012	No		
Unlikely	Unlikely	21 April 2012	Yes	25 April 2012	4
Probably	Unlikely	16 April 2012	No		
Probably	Unlikely	13 May 2012	Yes	16 May 2012	3
Unlikely	Probably	9 May 2012	Yes	9 May 2012	0
Probably	Unlikely	10 June 2012	Yes	16 June 2012	6
Probably	Unlikely		Yes	27 August 2012	
Probably	Unlikely	5 July 2012	Yes	8 July 2012	3
Probably	Possibly	4 July 2012	Yes	11 July 2012	7
Probably	Possibly		Yes	01 August 2012	
Unlikely	Unlikely	14 August 2012	No		
Unlikely	Unlikely		No		
Probably	Unlikely	3 August 2012	Yes	10 August 2012	7
Probably	Possibly	5 August 2012	Yes	11 August 2012	6
Almost certainly	Almost certainly	23 March 2012	Yes	2 April 2012	10
Almost certainly	Unlikely	10 March 2012	Yes	10 March 2012	0
Unlikely	Unlikely	2 April 2012	No		
Almost certainly	Almost certainly	16 March 2012	Yes	2 April 2012	17
Possibly	Possibly	14 March 2012	Yes	14 March 2012	0
Probably	Probably	16 March 2012	Yes	2 April 2012	17
Unlikely	Unlikely	4 April 2012	Yes	9 April 2012	5
Almost certainly	Almost certainly	19 April 2012	Yes	30 April 2012	11
Unlikely	Unlikely	2 April 2012	Yes	3 April 2012	1
Almost certainly	Almost certainly	19 April 2012	Yes	30 April 2012	11
Almost certainly	Almost certainly	7 April 2012	Yes	9 April 2012	2

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Diarrhoea		1	2	Almost certainly
	FCR	Neutropenia		2	3	Almost certainly
	FCR	Nausea		1	3	Almost certainly
	FCR	Nausea		1	4	Almost certainly
	FCR	Vomiting		1	4	Almost certainly
138	FCR	Rash/flushing		2	1	Probably
	FCR	Headache			1	Possibly
	FCR	Fever		3	1	Possibly
	FCR	Neutropenic sepsis		4	2	Almost certainly
	FCR	Other AE description	Weight change	1	2	Probably
	FCR	Diarrhoea		2	4	Possibly
	FCR	Allergic reaction		2	4	Unlikely
140	FCR	Nausea		1	1	Almost certainly
	FCR	Constipation		1	1	Almost certainly
	FCR	Fatigue		1	1	Almost certainly
	FCR	Non-specific pain		1	1	Possibly
	FCR	Nausea		1	2	Almost certainly
	FCR	Constipation		1	2	Almost certainly
	FCR	Fatigue		1	2	Almost certainly
	FCR	Back pain		1	2	Possibly
	FCR	Nausea		2	3	Almost certainly
	FCR	Taste alteration		1	3	Almost certainly
	FCR	Nausea		2	4	Almost certainly
	FCR	Vomiting		1	4	Almost certainly
141	FCR	Nausea		1	2	Almost certainly
	FCR	Vomiting		1	2	Almost certainly
	FCR	Back pain		1	4	Unrelated
	FCR	Vomiting		1	4	Almost certainly
	FCR	Other AE description	Dry mouth	1	4	Almost certainly
	FCR	Mucositis/thrush		1	4	Almost certainly
	FCR	Other AE description	Lump on leg	1	4	Almost certainly
	FCR	Infections (not neutropenic sepsis)		4	5	Probably
	FCR	Night sweats		2	5	Unrelated
	FCR	Neutropenia		3	6	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	8 April 2012	Yes	9 April 2012	1
Almost certainly	Almost certainly	16 May 2012	Yes	28 May 2012	12
Almost certainly	Almost certainly	2 May 2012	Yes	7 May 2012	5
Almost certainly	Almost certainly	30 May 2012	Yes	3 June 2012	4
Almost certainly	Almost certainly	30 May 2012	Yes	3 June 2012	4
Probably	Probably	7 April 2012	No		
Possibly	Possibly	7 April 2012	Yes	11 April 2012	4
Possibly	Possibly	7 April 2012	Yes	10 April 2012	3
Almost certainly	Almost certainly	7 April 2012	Yes	16 April 2012	9
Probably	Probably		Yes		
Possibly	Possibly	15 July 2012	Yes	15 July 2012	0
Unlikely	Unlikely	13 April 2012	Yes	13 April 2012	0
Almost certainly	Unlikely	6 April 2012	Yes	7 April 2012	1
Almost certainly	Unlikely	7 April 2012	No		
Almost certainly	Unlikely	7 April 2012	No		
Possibly	Possibly	7 April 2012	Yes	3 May 2012	26
Almost certainly	Unlikely	11 April 2012	No		
Almost certainly	Unlikely	3 April 2012	No		
Almost certainly	Unlikely	3 April 2012	No		
Possibly	Possibly	3 April 2012	Yes	3 May 2012	30
Almost certainly	Unlikely	1 May 2012	Yes	27 May 2012	26
Almost certainly	Unlikely	3 April 2012	No		
Almost certainly	Almost certainly	3 July 2012	Yes	9 July 2012	6
Almost certainly	Almost certainly	3 July 2012	No		
Almost certainly	Almost certainly	2 May 2012	Yes	30 May 2012	28
Almost certainly	Almost certainly	2 May 2012	Yes	30 May 2012	28
Unrelated	Unrelated	15 May 2012	Yes	27 June 2012	43
Almost certainly	Almost certainly	23 June 2012	Yes	25 July 2012	32
Almost certainly	Almost certainly	27 June 2012	Yes	25 July 2012	28
Almost certainly	Almost certainly	27 June 2012	Yes	25 July 2012	28
Almost certainly	Almost certainly	27 June 2012	Yes	25 July 2012	28
Probably	Probably	25 July 2012	Yes	15 August 2012	21
Unrelated	Unrelated	25 July 2012	Yes	15 August 2012	21
Almost certainly	Almost certainly	12 September 2012	Yes	17 September 2012	5

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
143	FCR	Infusional reaction		2	1	Unrelated
	FCR	Nausea		2	1	Almost certainly
	FCR	Diarrhoea		1	2	Unlikely
	FCR	Fatigue		3	2	Unlikely
	FCR	Other AE description	Worsening of diabetes	2	2	Unlikely
	FCR	Urinary symptoms		2	2	Unlikely
	FCR	Neutropenia		3	3	Almost certainly
	FCR	Thrombocytopenia		2	3	Almost certainly
	FCR	Gout/hyperuricemia		2	4	Probably
	FCR	Neutropenia		3	5	Probably
	FCR	Thrombocytopenia		2	5	Probably
146	FCR	Neutropenia		3	1	Almost certainly
	FCR	Anaemia		1	1	Almost certainly
	FCR	Rash/flushing		3	1	Unrelated
	FCR	Urinary symptoms		2	3	Unrelated
	FCR	Mucositis/thrush		1	5	Probably
	FCR	Constipation		2	5	Probably
	FCR	Dyspnoea		1	5	Possibly
	FCR	Rash/flushing		1	6	Unrelated
	FCR	Abdominal pain/ bloating		1	6	Unrelated
	FCR	Thrombocytopenia		1	6	Almost certainly
	FCR	Neutropenia		3	6	Almost certainly
147	FCR	Fever		2	1	Almost certainly
	FCR	Mucositis/thrush		1	1	Almost certainly
	FCR	Anaemia		2	1	Almost certainly
	FCR	Constipation		1	2	Possibly
	FCR	Nausea		1	3	Almost certainly
	FCR	Neutropenia		2	3	Almost certainly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Fatigue		1	4	Unlikely
	FCR	Rash/flushing		2	5	Unlikely
151	FCR	Fatigue		1	1	Possibly
	FCR	Anaemia		3	2	Possibly
	FCR	Neutropenia		1	3	Probably
	FCR	Thrombocytopenia		2	3	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Almost certainly	30 April 2012	Yes	30 April 2012	0
Almost certainly	Unrelated	5 May 2012	Yes	7 May 2012	2
Unlikely	Unlikely	2 June 2012	Yes	3 June 2012	1
Unlikely	Unlikely	19 June 2012	Yes	20 June 2012	1
Unlikely	Unlikely	20 June 2012	No		
Unlikely	Unlikely	20 June 2012	No		
Almost certainly	Unlikely	20 July 2012	Yes	31 August 2012	42
Almost certainly	Unlikely	20 July 2012	No		
Probably	Unrelated	16 August 2012	Yes	31 August 2013	380
Probably	Unlikely	3 October 2012	No		
Probably	Unlikely	26 September 2012	No		
Probably	Probably	26 June 2012	Yes	1 August 2012	36
Probably	Probably	26 June 2012	Yes	28 June 2012	2
Unrelated	Unrelated	3 July 2012	Yes	1 August 2012	29
Probably	Unrelated	4 September 2012	Yes		
Probably	Probably		Yes		
Probably	Probably		Yes	21 November 2012	
Unlikely	Possibly		Yes		
Unrelated	Unrelated	27 November 2012	Yes	3 December 2012	6
Unrelated	Unrelated	25 December 2012	No		
Almost certainly	Almost certainly	30 January 2013	No		
Almost certainly	Almost certainly	30 January 2013	No		
Almost certainly	Almost certainly	16 May 2012	Yes	20 May 2012	4
Almost certainly	Unlikely		Yes	13 June 2012	
Almost certainly	Possibly	18 May 2012	Yes	22 May 2012	4
Possibly	Possibly		Yes	11 July 2012	
Almost certainly	Almost certainly	11 July 2012	Yes	15 July 2012	4
Almost certainly	Unlikely	22 May 2012	Yes	7 August 2012	77
Almost certainly	Unlikely	7 August 2012	No		
Unlikely	Unlikely		Yes	5 September 2012	
Unlikely	Unlikely		No		
Possibly	Possibly		Yes		
Possibly	Possibly	9 July 2012	Yes	23 July 2012	14
Probably	Unrelated	20 August 2012	Yes	17 September 2012	28
Probably	Unrelated	20 August 2012	Yes	28 August 2012	8

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Lymphopenia		3	3	Probably
	FCR	Neutropenia		3	4	Probably
	FCR	Thrombocytopenia		1	6	Probably
155	FCR	Vomiting		2	1	Probably
	FCR	Vomiting		2	2	Probably
	FCR	Vomiting		3	3	Probably
	FCR	Neutropenia		3	4	Probably
	FCR	Anaemia		4	5	Probably
157	FCR	Nausea		1	2	Almost certainly
	FCR	Fatigue		1	2	Unrelated
	FCR	Diarrhoea		1	3	Unrelated
	FCR	Nausea		2	4	Almost certainly
	FCR	Diarrhoea		2	4	Almost certainly
	FCR	Cough		1	5	Unrelated
	FCR	Diarrhoea		2	5	Almost certainly
	FCR	Nausea		1	5	Almost certainly
	FCR	Diarrhoea		1	6	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	6	Almost certainly
158	FCR	Pruritus		2	1	Unlikely
	FCR	Rash/flushing		1	1	Unlikely
	FCR	Diarrhoea		1	1	Unlikely
	FCR	Nausea		2	1	Unlikely
	FCR	Headache		1	1	Unlikely
	FCR	Common cold		2	2	Unlikely
	FCR	Mucositis/thrush		1	2	Unlikely
	FCR	Back pain		2	2	Unrelated
	FCR	Nausea		2	2	Unlikely
	FCR	Vomiting		2	2	Unlikely
	FCR	Other AE description	Kidney stone – had lithotripsy and surgery	3	3	Unrelated
	FCR	Nausea		2	3	Unlikely
	FCR	Vomiting		2	3	Unlikely
	FCR	Insomnia		1	3	Unrelated
	FCR	Common cold		2	3	Unlikely
	FCR	Fatigue		1	3	Unlikely

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Probably	20 August 2012	No		
Probably	Unrelated	17 September 2012	Yes	24 September 2012	7
Probably	Unrelated	22 October 2012	No		
Probably	Unlikely	8 June 2012	Yes	10 June 2012	2
Probably	Unlikely	7 July 2012	Yes	9 July 2012	2
Probably	Unrelated	4 August 2012	Yes	6 August 2012	2
Probably	Unrelated	27 September 2012	Yes	15 October 2012	18
Probably	Unrelated	15 October 2012	No		
Almost certainly	Almost certainly	6 June 2012	No		
Unrelated	Unrelated	6 June 2012	No		
Unrelated	Unrelated	1 August 2012	No		
Almost certainly	Almost certainly	23 August 2012	Yes	27 August 2012	4
Almost certainly	Almost certainly	23 August 2012	Yes	27 August 2012	4
Unrelated	Unrelated	26 September 2012	No		
Almost certainly	Almost certainly	28 September 2012	Yes	7 October 2012	9
Almost certainly	Almost certainly	26 September 2012	Yes	2 October 2012	6
Almost certainly	Almost certainly	17 October 2012	Yes	23 October 2012	6
Almost certainly	Almost certainly	2 December 2012	Yes	2 January 2013	31
Unlikely	Unlikely	1 July 2012	Yes	6 July 2012	5
Unlikely	Unlikely	1 July 2012	Yes	6 July 2012	5
Probably	Unlikely	20 June 2012	Yes	25 June 2012	5
Probably	Unlikely	20 June 2012	Yes	25 June 2012	5
Unlikely	Probably	18 June 2012	Yes	19 June 2012	1
Unlikely	Unrelated	31 July 2012	Yes	10 August 2012	10
Probably	Unrelated	9 August 2012	No		
Unrelated	Unrelated	9 August 2012	No		
Probably	Unrelated	20 July 2012	Yes	22 July 2012	2
Probably	Unlikely	20 July 2012	Yes	22 July 2012	2
Unrelated	Unrelated	9 August 2012	Yes	26 September 2012	48
Probably	Unlikely	3 October 2012	Yes	9 October 2012	6
Probably	Unlikely	4 October 2012	Yes	5 October 2012	1
Unrelated	Unrelated	4 October 2012	Yes	5 October 2012	1
Unlikely	Unlikely	2 October 2012	No		
Unlikely	Unlikely	18 June 2012	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Nausea		1	4	Unlikely
	FCR	Nausea		1	5	Unlikely
	FCR	Vomiting		1	5	Unlikely
	FCR	Diarrhoea		1	5	Unlikely
	FCR	Non-specific pain		1	5	Unrelated
	FCR	Nausea		1	6	Unlikely
	FCR	Diarrhoea		1	6	Unlikely
	FCR	Rash/flushing		2	6	Unlikely
	FCR	Arthralgias		1	6	Unlikely
159	FCR	Nausea		2	1	Probably
	FCR	Fatigue		2	1	Possibly
	FCR	Taste alteration		2	1	Possibly
	FCR	Anorexia/cachexia		2	1	Probably
	FCR	Nausea		1	2	Probably
	FCR	Anorexia/cachexia		1	2	Probably
	FCR	Alopecia		1	2	Possibly
	FCR	Thrombocytopenia		1	2	Almost certainly
	FCR	Taste alteration		1	3	Possibly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Nausea		1	4	Probably
	FCR	Thrombocytopenia		2	4	Almost certainly
166	FCR	Infusional reaction			1	Unlikely
	FCR	Infections (not neutropenic sepsis)		2	1	Possibly
	FCR	Fatigue		2	1	Possibly
	FCR	Constipation		1	1	Possibly
	FCR	Anaemia		3	1	Possibly
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Neutropenia		4	4	Possibly
	FCR	Neutropenia		4	5	Almost certainly
	FCR	Urinary symptoms		1	5	Unlikely
	FCR	Anaemia		1	5	Almost certainly
	FCR	Neutropenia		4	6	Almost certainly
	FCR	Raised GGT/bilirubin		1	6	Possibly
167	FCR	Nausea		1	1	Probably
	FCR	Vomiting		1	1	Probably
	FCR	Nausea		1	2	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Unlikely	1 November 2012	Yes	6 November 2012	5
Probably	Unlikely	27 November 2012	Yes	4 December 2012	7
Probably	Unlikely	29 November 2012	Yes	29 November 2012	0
Probably	Unlikely	30 November 2012	Yes	5 December 2012	5
Unrelated	Unrelated	30 November 2012	No		
Probably	Unlikely	26 December 2012	Yes	1 January 2013	6
Probably	Unlikely	29 December 2012	Yes	3 January 2013	5
Unlikely	Unlikely	9 January 2013	No		
Unlikely	Unlikely	15 January 2013	Yes	18 January 2013	3
Probably	Possibly	19 July 2012	Yes	25 July 2012	6
Possibly	Possibly	25 July 2012	No		
Possibly	Unlikely	19 July 2012	No		
Probably	Unlikely	19 July 2012	No		
Probably	Possibly	18 August 2012	Yes	21 August 2012	3
Probably	Unlikely	20 August 2012	No		
Possibly	Unlikely	20 August 2012	No		
Almost certainly	Possibly	30 August 2012	Yes	6 September 2012	7
Possibly	Unlikely	11 September 2012	No		
Almost certainly	Possibly	21 September 2012	No		
Probably	Possibly	11 September 2012	Yes	5 November 2012	55
Almost certainly	Possibly	16 October 2012	No		
Unlikely	Probably	4 July 2012	Yes	5 July 2012	1
Possibly	Unlikely	23 July 2012	Yes	6 August 2012	14
Possibly	Possibly	10 July 2012	Yes	6 August 2012	27
Possibly	Possibly	11 July 2012	Yes	26 July 2012	15
Possibly	Possibly	30 July 2012	Yes	6 August 2012	7
Almost certainly	Almost certainly	20 August 2012	Yes	4 September 2012	15
Possibly	Possibly	30 October 2012	Yes	20 November 2012	21
Probably	Probably	14 December 2012	Yes	21 December 2012	7
Unlikely	Unlikely	28 December 2012			
Possibly	Possibly	21 December 2012	No		
Probably	Probably	28 December 2012	Yes	22 January 2013	25
Possibly	Possibly	14 December 2012	No		
Probably	Possibly	25 July 2012	Yes	27 July 2012	2
Probably	Possibly	25 July 2012	Yes	27 July 2012	2
Probably	Possibly	25 August 2012	Yes	26 August 2012	1

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Vomiting		1	2	Probably
	FCR	Nausea		1	3	Probably
	FCR	Vomiting		1	3	Probably
	FCR	Neuropathy (sensory)		1	3	Possibly
	FCR	Fatigue		1	3	Probably
	FCR	Nausea		1	4	Probably
	FCR	Vomiting		1	4	Probably
	FCR	Nausea		1	5	Probably
	FCR	Nausea		1	6	Probably
168	FCR	Anaemia		1	1	Almost certainly
	FCR	Nausea		1	1	Probably
	FCR	Rash/flushing		1	1	Probably
	FCR	Neutropenia		4	3	Almost certainly
	FCR	Infections (not neutropenic sepsis)		3	3	Probably
	FCR	Anaemia		1	4	Almost certainly
	FCR	Anaemia		1	5	Almost certainly
	FCR	Neutropenia		3	5	Almost certainly
	FCR	Neutropenia		1	5	Almost certainly
	FCR	Taste alteration		1	5	Possibly
	FCR	Infections (not neutropenic sepsis)		2	6	Almost certainly
171	FCR	Abnormal electrolytes		3	1	Unrelated
	FCR	Neutropenia		3	1	Almost certainly
	FCR	Constipation		2	1	Unlikely
	FCR	Nausea		1	1	Probably
	FCR	Nausea		1	2	Probably
	FCR	Constipation		2	2	Possibly
	FCR	Back pain		1	2	Unrelated
	FCR	Nausea			3	Probably
	FCR	Constipation			3	Possibly
	FCR	Neutropenia		1	3	Probably
	FCR	Renal impairment		1	3	Possibly
	FCR	Nausea			4	Probably
	FCR	Renal impairment		1	4	Possibly
	FCR	Rash/flushing		2	5	Unlikely
	FCR	Renal impairment		1	5	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Possibly	25 August 2012	Yes	26 August 2012	1
Probably	Possibly	19 September 2012	Yes	23 September 2012	4
Probably	Possibly	19 September 2012	Yes	23 September 2012	4
Unlikely	Unlikely	17 September 2012	No		
Unlikely	Probably	15 October 2012	No		
Probably	Possibly	17 October 2012	Yes	19 October 2012	2
Probably	Possibly	19 October 2012	Yes	19 October 2012	0
Probably	Possibly	15 November 2012	Yes	16 November 2012	1
Probably	Unlikely	13 December 2012	Yes	14 December 2012	1
Almost certainly	Possibly	1 August 2012	Yes	6 August 2012	5
Probably	Possibly	10 July 2012	Yes	13 July 2012	3
Possibly	Unlikely	9 July 2012	Yes	9 July 2012	0
Almost certainly	Possibly	1 August 2012	Yes	27 September 2012	57
Probably	Possibly	21 September 2012	Yes	1 October 2012	10
Almost certainly	Possibly	15 August 2012	Yes	1 October 2012	47
Almost certainly	Possibly	4 October 2012	No		
Almost certainly	Possibly	7 November 2012	Yes	21 November 2012	14
Almost certainly	Possibly	5 December 2012	No		
Possibly	Possibly	12 November 2012	Yes	20 November 2012	8
Almost certainly	Possibly	25 December 2012	No		
Unrelated	Unrelated	9 July 2012	Yes	11 July 2012	2
Almost certainly	Unlikely	30 July 2012	Yes	6 August 2012	7
Unlikely	Unlikely	9 July 2012	Yes	12 July 2012	3
Probably	Unlikely	9 July 2012	Yes	12 July 2012	3
Probably	Unlikely	6 August 2012	Yes	14 August 2012	8
Possibly	Unlikely	6 August 2012	Yes	14 August 2012	8
Unrelated	Unrelated	4 July 2012	Yes	3 September 2012	61
Probably	Unlikely	3 September 2012	Yes	11 September 2012	8
Possibly	Unlikely	3 September 2012	Yes	11 September 2012	8
Probably	Unlikely	27 September 2012	Yes	8 October 2012	11
Possibly	Possibly	6 August 2012	No		
Probably	Unlikely	1 October 2012	Yes		
Possibly	Possibly	3 September 2012	No		
Unlikely	Unlikely				
Possibly	Possibly	1 October 2012	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Rash/flushing		2	6	Unlikely
	FCR	Infections (not neutropenic sepsis)		3	6	Unlikely
174	FCR	Infusional reaction		1	1	Unrelated
	FCR	Thrombocytopenia		2	1	Unlikely
	FCR	Anaemia		1	1	Unlikely
	FCR	Mucositis/thrush		1	1	Possibly
	FCR	Other AE description	Unstable diabetes control hyperglycaemia – insulin	3	2	Unlikely
	FCR	Neutropenia		4	3	Probably
	FCR	Fever		1	3	Possibly
	FCR	Sore throat		1	3	Unrelated
	FCR	Anxiety/depression		1	3	Unlikely
	FCR	Other AE description	Unstable diabetes control (hyperglycaemia)	3	3	Unlikely
	FCR	Taste alteration		1	4	Probably
	FCR	Fatigue		1	4	Probably
	FCR	Neutropenia		4	5	Probably
	FCR	Neutropenia		2	6	Probably
	FCR	Infections (not neutropenic sepsis)		1	6	Possibly
	FCR	Arthralgias		1	6	Unrelated
	FCR	Other AE description	Unstable diabetic control	1	6	Unlikely
175	FCR	Infections (not neutropenic sepsis)		2	2	Almost certainly
	FCR	Dyspnoea		2	2	Unrelated
	FCR	Chest pain		2	2	Unrelated
178	FCR	Diarrhoea		1	1	Possibly
	FCR	Nausea		1	1	Possibly
	FCR	Thrombocytopenia		1	3	Probably
	FCR	Lymphopenia		3	3	Probably
	FCR	Pruritus		2	4	Unlikely
	FCR	Other AE description	Squamous cell carcinoma	3	4	Unrelated
	FCR	Lymphopenia		3	5	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	29 October 2012	No		
Unlikely	Unlikely	1 January 2013	Yes	8 January 2013	7
Unrelated	Almost certainly	24 July 2012	Yes	24 July 2012	0
Unlikely	Unlikely	24 July 2012	No		
Unlikely	Unlikely	24 July 2012	No		
Probably	Unlikely	7 August 2012	Yes	21 August 2012	14
Unlikely	Unlikely	7 September 2012	No		
Probably	Unlikely	28 August 2012	Yes	7 October 2012	40
Possibly	Unrelated	17 September 2012	Yes	18 October 2012	31
Unrelated	Unrelated	29 August 2012	Yes	23 October 2012	55
Unlikely	Unlikely	21 August 2012	Yes	23 October 2012	63
Unlikely	Unlikely	7 September 2012	No		
Probably	Unlikely	21 August 2012	Yes	27 November 2012	98
Probably	Possibly	24 July 2012	Yes	7 November 2012	106
Probably	Unlikely	7 November 2012	Yes	27 December 2012	50
Probably	Unlikely	4 January 2013	No		
Possibly	Unrelated	31 December 2012	Yes	22 January 2013	22
Unrelated	Unrelated		Yes	12 December 2012	
Unlikely	Unlikely	7 September 2012	Yes	26 February 2013	172
Almost certainly	Almost certainly	25 September 2012	No		
Unrelated	Unrelated	23 August 2012	Yes	24 August 2012	1
Unrelated	Unrelated	23 August 2012	Yes	24 August 2012	1
Possibly	Unlikely		Yes		
Possibly	Unlikely		Yes		
Probably	Probably	10 September 2012	No		
Probably	Probably	10 September 2012	Yes	8 October 2012	28
Unlikely	Unlikely	15 October 2012	Yes		
Unrelated	Unrelated	22 October 2012	Yes		
Probably	Probably	5 November 2012	No		

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Infections (not neutropenic sepsis)		2	6	Possibly
	FCR	Other AE description	Squamous cell carcinoma in situ of wrist	3	6	Unrelated
	FCR	Neutropenia		1	6	Probably
	FCR	Back pain		1	6	Unrelated
	FCR	Fatigue		1	6	Unlikely
179	FCR	Neutropenia		4	1	Probably
	FCR	Anaemia		3	1	Probably
	FCR	Thrombocytopenia		2	1	Possibly
	FCR	Nausea		2	1	Unlikely
	FCR	Vomiting		2	1	Unlikely
	FCR				1	Missing
	FCR	Diarrhoea		1	2	Unlikely
	FCR	Thrombocytopenia		1	2	Possibly
	FCR	Anaemia		1	2	Probably
	FCR	Rash/flushing		3	2	Unrelated
181	FCR	Neutropenia		3	2	Almost certainly
	FCR	Rash/flushing		2	2	Unrelated
	FCR	Neutropenia		3	3	Almost certainly
	FCR	Fatigue		1	3	Almost certainly
	FCR	Anorexia/cachexia		1	3	Almost certainly
	FCR	Oedema		1	3	Almost certainly
	FCR	Anxiety/depression		2	4	Almost certainly
	FCR	Neutropenia		3	5	Almost certainly
	FCR	Anxiety/depression		2	5	Almost certainly
	FCR	Neutropenia		3	6	Almost certainly
182	FCR	Rash/flushing		2	3	Unlikely
	FCR	Other AE description	Keratoacanthoma (removed)	2	4	Unrelated
	FCR	Nausea		1	6	Probably
	FCR	Headache		1	6	Unlikely
185	FCR	Nausea		2	1	Almost certainly
	FCR	Fatigue		3	1	Almost certainly
	FCR	Fatigue		1	1	Almost certainly
	FCR	Constipation		1	1	Unlikely
	FCR	Nausea		1	2	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly		Yes		
Unrelated	Unrelated		Yes		
Probably	Probably	21 January 2013	Yes	18 February 2013	28
Unrelated	Unrelated		No		
Unlikely	Unlikely		No		
Probably	Unlikely	25 July 2012	Yes	7 August 2012	13
Probably	Possibly	3 August 2012	Yes	14 August 2012	11
Possibly	Possibly	25 July 2012	No		
Unlikely	Possibly	31 July 2012	Yes	24 August 2012	24
Unlikely	Possibly	31 July 2012	Yes	24 August 2012	24
Missing	Missing		Yes		
Unlikely	Possibly	8 September 2012	Yes	12 September 2012	4
Possibly	Possibly	7 September 2012	Yes	20 September 2012	13
Probably	Possibly	9 September 2012	Yes	18 September 2012	9
Unrelated	Unrelated	22 August 2012	No		
Almost certainly	Almost certainly	22 August 2012	Yes	30 August 2012	8
Unrelated	Unrelated	22 August 2012	Yes	9 October 2012	48
Almost certainly	Almost certainly	26 September 2012	Yes	9 October 2012	13
Almost certainly	Almost certainly	26 September 2012	Yes	27 September 2012	1
Almost certainly	Almost certainly	26 September 2012	Yes	27 September 2012	1
Almost certainly	Almost certainly	26 September 2012	Yes	27 September 2012	1
Almost certainly	Almost certainly	6 November 2012	No		
Almost certainly	Almost certainly	4 December 2012	Yes	17 December 2012	13
Almost certainly	Almost certainly	17 December 2012	No		
Almost certainly	Almost certainly	14 January 2013	Yes	22 January 2013	8
Unlikely	Unlikely	12 September 2012	No		
Unrelated	Unrelated		Yes	4 December 2012	
Probably	Possibly	11 December 2012	Yes	17 December 2012	6
Unlikely	Possibly	11 December 2012	Yes	17 December 2012	6
Almost certainly	Probably	25 August 2012	Yes	30 August 2012	5
Possibly	Probably	27 August 2012	Yes	31 August 2012	4
Possibly	Probably	16 September 2012	No		
Unlikely	Possibly	25 August 2012	No		
Almost certainly	Probably	20 September 2012	Yes	21 September 2012	1

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Mucositis/thrush		1	2	Possibly
	FCR	Rash/flushing		2	2	Unlikely
	FCR	Vomiting		1	3	Almost certainly
	FCR	Nausea		1	3	Almost certainly
	FCR	Infections (not neutropenic sepsis)		2	4	Possibly
	FCR	Neutropenic sepsis		4	5	Almost certainly
	FCR	Neutropenia		4	5	Almost certainly
187	FCR	Neutropenia		1	4	Almost certainly
	FCR	Anaemia		2	4	Almost certainly
	FCR	Thrombocytopenia		4	4	Almost certainly
191	FCR	Fatigue		1	1	Possibly
	FCR	Cystitis		1	1	Unrelated
	FCR	Anaemia		1	1	Unrelated
	FCR	Thrombocytopenia		1	1	Unrelated
	FCR	Neutropenia		4	2	Almost certainly
	FCR	Anaemia		1	2	Almost certainly
	FCR	Thrombocytopenia		1	2	Almost certainly
192	FCR	Infusional reaction		2	1	Unrelated
	FCR	Nausea		1	1	Probably
	FCR	Fatigue		2	1	Possibly
	FCR	Anaemia		1	1	Unrelated
	FCR	Neutropenia		2	1	Unrelated
	FCR	Infusional reaction		1	2	Unrelated
	FCR	Vomiting		1	2	Almost certainly
	FCR	Nausea		1	2	Almost certainly
	FCR	Neuropathy (sensory)		1	2	Possibly
	FCR	Fatigue		2	2	Probably
	FCR	Thrombocytopenia		1	2	Possibly
	FCR	Lymphopenia		3	2	Almost certainly
	FCR	Bone pain		2	3	Possibly
	FCR	Nausea		1	3	Almost certainly
	FCR	Fatigue		2	3	Almost certainly
	FCR	Neutropenia		1	3	Almost certainly
	FCR	Thrombocytopenia		1	3	Probably
	FCR	Vomiting		1	4	Possibly
	FCR	Nausea		1	4	Almost certainly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Possibly	20 September 2012	Yes	27 September 2012	7
Unlikely	Unlikely	11 October 2012	No		
Almost certainly	Probably	19 October 2012	Yes	19 October 2012	0
Almost certainly	Probably	18 October 2012	Yes	20 October 2012	2
Possibly	Possibly	17 November 2012	Yes	19 November 2012	2
Almost certainly	Probably	28 December 2012	Yes	4 January 2013	7
Almost certainly	Probably	31 December 2012	Yes	8 January 2013	8
Almost certainly	Almost certainly	11 December 2012	Yes	20 December 2012	9
Almost certainly	Almost certainly	11 December 2012	No		
Almost certainly	Almost certainly	11 December 2012	No		
Possibly	Possibly		No		
Unrelated	Unrelated	5 November 2012	No		
Unrelated	Unrelated	19 October 2011	No		
Unrelated	Unrelated	30 March 2011	No		
Almost certainly	Unlikely	17 December 2012	No		
Almost certainly	Unlikely		No		
Almost certainly	Unlikely		No		
Unrelated	Almost certainly	10 September 2012	Yes	10 September 2012	0
Probably	Probably	13 September 2012	Yes	17 September 2012	4
Possibly	Possibly	12 September 2012	Yes	17 September 2012	5
Unrelated	Unrelated	28 July 2012	Yes	9 October 2012	73
Unrelated	Unrelated	7 September 2012	No		
Unrelated	Almost certainly	10 October 2012	Yes	10 October 2012	0
Almost certainly	Unlikely	15 October 2012	Yes	15 October 2012	0
Almost certainly	Unlikely	10 October 2012	Yes	17 October 2012	7
Unlikely	Unlikely	5 November 2012	Yes	05 November 2012	0
Probably	Possibly	10 October 2012	Yes	17 October 2012	7
Possibly	Possibly	28 July 2012	Yes	6 November 2012	101
Almost certainly	Possibly	6 November 2012	No		
Possibly	Possibly	28 November 2012	No		
Almost certainly	Almost certainly	8 November 2012	Yes	15 November 2012	7
Almost certainly	Possibly	7 November 2012	Yes	14 November 2012	7
Almost certainly	Possibly	4 December 2012	No		
Probably	Possibly	4 December 2012	No		
Possibly	Possibly	8 December 2012	Yes	8 December 2012	0
Almost certainly	Almost certainly	9 December 2012	Yes	16 December 2012	7

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Fatigue		2	4	Almost certainly
	FCR	Cystitis		1	4	Unlikely
	FCR	Rash/flushing		1	4	Possibly
	FCR	Nausea		1	5	Almost certainly
	FCR	Constipation		1	5	Unlikely
	FCR	Fatigue		2	5	Almost certainly
	FCR	Vomiting		2	6	Almost certainly
193	FCR	Neutropenia		4	1	Almost certainly
	FCR	Anaemia		1	1	Almost certainly
	FCR	Thrombocytopenia		1	3	Almost certainly
	FCR	Other AE description	Ruptured Achilles tendon	2	4	Unrelated
	FCR	Thrombocytopenia		1	4	Probably
	FCR	Neutropenia		4	5	Almost certainly
	FCR	Thrombocytopenia		1	5	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly
	FCR	Neutropenia		1	6	Almost certainly
194	FCR	Abdominal pain/ bloating		1	1	Possibly
	FCR	Neutropenia		4	1	Almost certainly
	FCR	Nausea		1	1	Almost certainly
	FCR	Anaemia		1	1	Unlikely
	FCR	Cystitis		2	2	Possibly
	FCR	Nausea		1	2	Almost certainly
	FCR	Anaemia		1	3	Possibly
	FCR	Fatigue		2	3	Unlikely
	FCR	Cystitis		1	3	Almost certainly
	FCR	Pruritus		1	3	Unlikely
	FCR	Alopecia		2	3	Almost certainly
	FCR	Cough		1	4	Unlikely
	FCR	Fever		2	4	Unlikely
	FCR	Dyspnoea		1	4	Unlikely
	FCR	Vomiting		2	4	Possibly
	FCR	Abdominal pain/ bloating		2	4	Possibly
	FCR	Fever		2	4	Unlikely
	FCR	Vomiting		2	4	Possibly

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Possibly	7 December 2012	Yes	14 December 2012	7
Unlikely	Unlikely	5 November 2012	Yes	26 November 2012	21
Possibly	Possibly	27 November 2012	Yes	4 December 2012	7
Almost certainly	Almost certainly	4 January 2013	Yes	12 January 2013	8
Unlikely	Unlikely	7 January 2013	Yes	9 February 2013	33
Almost certainly	Possibly	5 January 2013	Yes	12 January 2013	7
Almost certainly	Possibly	31 January 2013	Yes	6 February 2013	6
Almost certainly	Almost certainly	26 October 2012	Yes	5 November 2012	10
Almost certainly	Almost certainly	26 October 2012	Yes	5 November 2012	10
Almost certainly	Almost certainly	31 December 2012	No		
Unrelated	Unrelated	21 January 2013	No		
Probably	Probably	28 January 2013	No		
Almost certainly	Almost certainly	14 February 2013	Yes	26 February 2013	12
Almost certainly	Almost certainly	14 February 2013	Yes	26 February 2013	12
Almost certainly	Almost certainly	14 March 2013	No		
Almost certainly	Almost certainly	14 March 2013	Yes	25 March 2013	11
Possibly	Possibly		No		
Almost certainly	Almost certainly	3 October 2012	Yes	16 October 2012	13
Almost certainly	Almost certainly		Yes		
Unlikely	Unlikely	27 June 2012	Yes	16 October 2012	111
Almost certainly	Unlikely	24 September 2012	Yes	17 October 2012	23
Almost certainly	Almost certainly	17 October 2012	Yes	22 October 2012	5
Possibly	Possibly	29 October 2012	Yes	12 December 2012	44
Unlikely	Unlikely		No		
Almost certainly	Unlikely		Yes		
Unlikely	Unlikely		No		
Almost certainly	Unlikely		No		
Unlikely	Unlikely		Yes	30 January 2013	
Unlikely	Possibly	13 December 2012	Yes	15 December 2012	2
Unlikely	Possibly		Yes	9 January 2013	
Possibly	Possibly	12 December 2012	Yes	15 December 2012	3
Possibly	Possibly	12 December 2012	Yes	15 December 2012	3
Unlikely	Possibly	10 January 2013	Yes	14 January 2013	4
Possibly	Possibly	10 January 2013	Yes	14 January 2013	4

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
195	FCR	Nausea		2	2	Almost certainly
	FCR	Neutropenia		2	2	Almost certainly
	FCR	Vomiting		2	2	Almost certainly
198	FCR	Thrombocytopenia		3	1	Probably
	FCR	Urinary symptoms		2	1	Possibly
	FCR	Fatigue		1	1	Probably
	FCR	Bone pain		2	1	Unrelated
	FCR	Dizziness		1	1	Unlikely
	FCR	Fatigue		1	2	Probably
	FCR	Constipation		1	2	Unlikely
	FCR	Nasal symptoms		1	2	Unlikely
	FCR	Arthralgias		1	2	Unlikely
	FCR	Nausea		1	3	Almost certainly
	FCR	Constipation		1	3	Unlikely
	FCR	Taste alteration		1	3	Almost certainly
	FCR	Urinary symptoms		1	3	Unlikely
	FCR	Nasal symptoms		1	4	Unlikely
	FCR	Fatigue		2	4	Probably
	FCR	Urinary symptoms		1	4	Unlikely
	FCR	Nasal symptoms		2	4	Unlikely
	FCR	Anorexia/cachexia		1	4	Almost certainly
	FCR	Fatigue		2	5	Almost certainly
	FCR	Constipation		1	5	Unlikely
	FCR	Fatigue		2	6	Almost certainly
	FCR	Fatigue		1	6	Almost certainly
	FCR	Other AE description	Bruising to L orbital region	1	6	Probably
199	FCR	Vomiting		2	2	Probably
	FCR	Allergic reaction		2	2	Unlikely
	FCR	Myalgias		1	2	Unlikely
	FCR	Other AE description	Right upper jaw lump	1	2	Unlikely
	FCR	Fatigue		1	3	Probably
	FCR	Nausea		2	3	Probably
	FCR	Other AE description	Right upper jaw lump	1	3	Unlikely
	FCR	Vomiting		2	3	Probably

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Unlikely	17 October 2012	Yes	16 January 2013	91
Almost certainly	Almost certainly	11 October 2012	Yes	17 October 2012	6
Almost certainly	Unlikely	17 October 2012	Yes	16 January 2013	91
Probably	Possibly	4 October 2012	Yes	24 October 2012	20
Possibly	Unlikely	22 September 2012	Yes	26 September 2012	4
Probably	Unlikely	21 September 2012	No		
Unrelated	Unrelated		No		
Unlikely	Unlikely	11 October 2012	Yes	18 October 2012	7
Probably	Unlikely		No		
Unlikely	Possibly	27 October 2012	Yes	1 November 2012	5
Unlikely	Possibly	2 November 2012	No		
Unlikely	Possibly	26 October 2012	No		
Almost certainly	Unlikely	22 November 2012	Yes	26 November 2012	4
Unlikely	Possibly	22 November 2012	Yes	26 November 2012	4
Almost certainly	Unlikely		No		
Probably	Unrelated	29 November 2012	No		
Unlikely	Possibly		No		
Probably	Unlikely	22 November 2012	No		
Probably	Unrelated		No		
Unlikely	Unlikely	10 January 2013	No		
Almost certainly	Unlikely		No		
Almost certainly	Unlikely	17 January 2013	Yes	21 January 2013	4
Unlikely	Possibly	14 February 2013	No		
Almost certainly	Unlikely	14 February 2013	Yes	28 February 2013	14
Almost certainly	Unlikely	1 March 2013	Yes	14 March 2013	13
Probably	Unlikely		Yes		
Almost certainly	Unlikely	14 October 2012	Yes	14 October 2012	0
Unlikely	Almost certainly	10 October 2012	Yes	10 October 2012	0
Unlikely	Unlikely	2 November 2012	Yes	2 November 2012	0
Unlikely	Unlikely		No		
Probably	Unrelated	10 October 2012	Yes	10 December 2012	61
Almost certainly	Unlikely	14 October 2012	Yes	10 December 2012	57
Unlikely	Unlikely		Yes		
Almost certainly	Unlikely	7 December 2012	Yes	9 December 2012	2

continued

TABLE 84 Adverse events in participants receiving FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCR	Nausea		2	4	Probably
	FCR	Vomiting		2	4	Probably
	FCR	Fatigue		1	4	Probably
	FCR	Nausea		2	6	Probably
	FCR	Common cold		2	6	Unrelated
	FCR	Abdominal pain/ bloating		1	6	Unrelated
	FCR	Night sweats		1	6	Possibly
200	FCR	Constipation		2	1	Unrelated
	FCR	Vomiting		2	1	Unrelated
	FCR	Neutropenia		3	1	Almost certainly
	FCR	Anaemia		2	1	Almost certainly
	FCR	Thrombocytopenia		1	1	Almost certainly
	FCR	Neutropenia		2	2	Almost certainly
	FCR	Renal impairment		1	2	Unrelated
	FCR	Dry skin/erythema		1	3	Possibly
	FCR	Abdominal pain/ bloating		1	3	Possibly
	FCR	Anaemia		1	3	Almost certainly
	FCR	Lymphopenia		2	4	Almost certainly
	FCR	Neutropenia		1	5	Almost certainly
	FCR	Lymphopenia		1	5	Almost certainly
	FCR	Anaemia		1	6	Almost certainly
	FCR	Thrombocytopenia		1	6	Almost certainly

GGT, gamma-glutamyl transpeptidase.
Duration of AE: days from date of onset to date of recovery (if known).

Related to cyclophosphamide?	Related to rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Unlikely	7 January 2013	Yes	10 January 2013	3
Almost certainly	Unlikely	7 January 2013	Yes	10 January 2013	3
Probably	Unrelated	10 December 2012	No		
Almost certainly	Unlikely	6 February 2013	Yes	8 February 2013	2
Unrelated	Unrelated	18 February 2013	No		
Unrelated	Unrelated	5 February 2013	Yes	9 February 2013	4
Possibly	Unrelated	21 February 2013	Yes	24 February 2013	3
Unrelated	Unrelated	10 October 2012	Yes	12 October 2012	2
Unrelated	Possibly	8 October 2012	Yes	8 October 2012	0
Almost certainly	Almost certainly	31 October 2012	No		
Almost certainly	Almost certainly	22 October 2012	No		
Almost certainly	Almost certainly	10 September 2012	No		
Almost certainly	Almost certainly	24 September 2012	No		
Unrelated	Unrelated	31 October 2012	Yes	5 November 2012	5
Possibly	Possibly		No		
Possibly	Possibly		Yes		
Almost certainly	Almost certainly	3 October 2012	Yes		
Almost certainly	Almost certainly	22 October 2012	No		
Almost certainly	Almost certainly	27 February 2013	No		
Almost certainly	Almost certainly		No		
Almost certainly	Unlikely	10 April 2013	No		
Almost certainly	Unlikely	10 April 2013	No		

TABLE 85 Adverse events in participants receiving FCM-miniR

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
3	FCM-miniR	Infusional reaction		1	1	Unrelated
	FCM-miniR	Arrhythmias/ palpitation		1	1	Unrelated
	FCM-miniR	Anaemia		4	1	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		1	2	Unlikely
	FCM-miniR	Anaemia		2	3	Almost certainly
	FCM-miniR	Fatigue		1	4	Almost certainly
	FCM-miniR	Sore throat		1	4	Unlikely
	FCM-miniR	Anaemia		2	4	Almost certainly
	FCM-miniR	Pruritus		2	5	Possibly
	FCM-miniR	Thrombocytopenia		1	6	Probably
4	FCM-miniR	Hypotension		2	1	Unrelated
	FCM-miniR	Allergic reaction		2	1	Unrelated
	FCM-miniR	Dizziness		2	1	Unrelated
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Hypotension		2	2	Unlikely
	FCM-miniR	Hypotension		1	3	Unlikely
	FCM-miniR	Nausea		1	4	Almost certainly
	FCM-miniR	Nausea		1	6	Probably
	FCM-miniR	Fatigue		1	6	Probably
5	FCM-miniR	Neutropenia		1	1	Probably
	FCM-miniR	Anaemia		1	1	Probably
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Abdominal pain/ bloating		2	2	Possibly
	FCM-miniR	Diarrhoea		1	2	Possibly
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Vomiting		1	3	Almost certainly
	FCM-miniR	Anaemia		2	3	Almost certainly
	FCM-miniR	Nausea		2	4	Almost certainly
	FCM-miniR	Infections (not neutropenic sepsis)		1	4	Possibly
	FCM-miniR	Fever		3	4	Possibly
	FCM-miniR	Nausea		2	5	Almost certainly
	FCM-miniR	Fatigue		2	5	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	Almost certainly	18 January 2010	Yes	18 January 2010	0
Unrelated	Unrelated	Unrelated	29 January 2010	Yes	30 January 2010	1
Possibly	Possibly	Unlikely	11 February 2010	Yes	12 February 2010	1
Unlikely	Unlikely	Unlikely	24 February 2010	Yes	11 March 2010	15
Possibly	Possibly	Unlikely	8 April 2010	No		
Unlikely	Almost certainly	Unlikely	7 May 2010	No		
Possibly	Almost certainly	Unlikely		Yes	7 May 2010	
Possibly	Possibly	Unlikely	6 May 2010	No		
Possibly	Possibly	Possibly	17 May 2010	Yes	3 June 2010	17
Probably	Probably	Possibly	1 July 2010	Yes	13 January 2011	196
Unrelated	Unrelated	Probably	24 February 2010	Yes	24 February 2010	0
Unrelated	Possibly	Probably	24 February 2010	Yes	25 February 2010	1
Unrelated	Probably	Probably	24 February 2010	Yes	24 February 2010	0
Probably	Probably	Possibly	24 February 2010	Yes	3 March 2010	7
Unlikely	Unlikely	Possibly	24 March 2010	Yes	24 March 2010	0
Unlikely	Unlikely	Probably	21 April 2010	Yes	21 April 2010	0
Almost certainly	Almost certainly	Possibly	19 May 2010	Yes	5 June 2010	17
Probably	Probably	Possibly	14 July 2010	Yes	19 July 2010	5
Probably	Probably	Possibly	14 July 2010	Yes	4 August 2010	21
Probably	Probably	Unlikely	5 March 2010	Yes	7 March 2010	2
Probably	Probably	Unlikely	5 March 2010	No		
Probably	Probably	Unrelated	18 February 2010	Yes	26 February 2010	8
Possibly	Possibly	Missing		No		
Possibly	Possibly	Missing		No		
Probably	Probably	Missing	18 March 2010	Yes	23 March 2010	5
Almost certainly	Probably	Missing	16 April 2010	Yes	20 April 2010	4
Almost certainly	Probably	Missing	17 April 2010	Yes	17 April 2010	0
Almost certainly	Almost certainly	Missing	22 April 2010	Yes	26 April 2010	4
Almost certainly	Almost certainly	Missing	15 May 2010	Yes	19 May 2010	4
Possibly	Possibly	Missing	17 May 2010	Yes	21 May 2010	4
Possibly	Possibly	Missing	19 May 2010	Yes	21 May 2010	2
Almost certainly	Almost certainly	Missing	9 June 2010	Yes	12 June 2010	3
Possibly	Almost certainly	Missing	10 June 2010	Yes	18 June 2010	8

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Vomiting		2	5	Almost certainly
	FCM-miniR	Hypotension		3	6	Unrelated
	FCM-miniR	Fatigue		2	6	Almost certainly
	FCM-miniR	Nausea		1	6	Almost certainly
	FCM-miniR	Vomiting		1	6	Almost certainly
	FCM-miniR	Anaemia		2	6	Almost certainly
	FCM-miniR	Neutropenia		3	6	Probably
	FCM-miniR	Thrombocytopenia		1	6	Probably
	FCM-miniR	Neutropenia		3	6	Almost certainly
6	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Constipation		4	2	Possibly
	FCM-miniR	Vomiting		1	3	Probably
10	FCM-miniR	Anaemia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		3	1	Almost certainly
	FCM-miniR	Anaemia		3	2	Probably
	FCM-miniR	Rash/flushing		1	2	Unrelated
	FCM-miniR	Abnormal electrolytes		3	4	Unlikely
12	FCM-miniR	Rigors		1	1	Unrelated
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Thrombocytopenia		2	1	Probably
	FCM-miniR	Neutropenia		2	1	Probably
14	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Diarrhoea		1	6	Possibly
	FCM-miniR	Thrombocytopenia		3	6	Almost certainly
15	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Vomiting		2	1	Almost certainly
	FCM-miniR	Diarrhoea		1	1	Almost certainly
	FCM-miniR	Constipation		1	1	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		1	1	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Missing	9 June 2010	Yes	10 June 2010	1
Unrelated	Unrelated	Missing	7 July 2010	Yes	7 July 2010	0
Almost certainly	Almost certainly	Missing	12 July 2010	Yes	18 July 2010	6
Almost certainly	Almost certainly	Missing	7 July 2010	Yes	11 July 2010	4
Almost certainly	Almost certainly	Missing	8 July 2010	Yes	8 July 2010	0
Possibly	Possibly	Missing	4 August 2010	No		
Almost certainly	Probably	Missing	4 August 2010	No		
Probably	Almost certainly	Missing	4 August 2010	No		
Almost certainly	Almost certainly	Missing	11 August 2010	No		
Probably	Probably	Probably	16 March 2010	Yes	30 March 2010	14
Possibly	Possibly	Possibly	2 March 2010	Yes	9 March 2010	7
Probably	Probably	Probably	21 April 2010	Yes	27 April 2010	6
Almost certainly	Almost certainly	Almost certainly	22 March 2010	No		
Almost certainly	Almost certainly	Almost certainly	8 April 2010	No		
Probably	Probably	Probably	8 April 2010	Yes	7 May 2010	29
Unrelated	Unrelated	Unrelated	10 May 2010	Yes	17 June 2010	38
Unlikely	Unlikely	Unlikely	1 July 2010	Yes	5 July 2010	4
Unrelated	Unrelated	Probably	27 April 2010	Yes	27 April 2010	0
Probably	Probably	Unlikely	28 April 2010	Yes	9 May 2010	11
Probably	Probably	Probably	10 May 2010	No		
Probably	Probably	Probably	26 April 2010	No		
Almost certainly	Almost certainly	Almost certainly	30 August 2010	Yes	12 September 2010	13
Possibly	Possibly	Possibly		Yes		
Almost certainly	Almost certainly	Almost certainly	10 October 2010	No		
Almost certainly	Almost certainly	Almost certainly	1 May 2010	Yes	7 May 2010	6
Almost certainly	Almost certainly	Almost certainly	1 May 2010	Yes	7 May 2010	6
Almost certainly	Almost certainly	Almost certainly	1 May 2010	Yes	7 May 2010	6
Almost certainly	Almost certainly	Almost certainly		No		
Almost certainly	Almost certainly	Almost certainly	30 April 2010	Yes	7 May 2010	7

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Thrombocytopenia		3	1	Almost certainly
	FCM-miniR	Nausea		2	2	Almost certainly
	FCM-miniR	Vomiting		1	2	Almost certainly
	FCM-miniR	Fatigue		2	2	Almost certainly
	FCM-miniR	Thrombocytopenia		1	2	Almost certainly
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Vomiting		1	3	Almost certainly
	FCM-miniR	Fatigue		2	3	Almost certainly
	FCM-miniR	Nausea		2	4	Almost certainly
	FCM-miniR	Vomiting		2	4	Almost certainly
	FCM-miniR	Fatigue		2	4	Almost certainly
	FCM-miniR	Nausea		2	5	Almost certainly
	FCM-miniR	Fatigue		2	5	Almost certainly
	FCM-miniR	Alopecia		2	5	Almost certainly
	FCM-miniR	Nausea		2	6	Almost certainly
	FCM-miniR	Fatigue		2	6	Almost certainly
16	FCM-miniR	Infusional reaction		2	1	Unrelated
	FCM-miniR	Headache		1	2	Unrelated
	FCM-miniR	Nausea		1	2	Almost certainly
	FCM-miniR	Myalgias		2	3	Unlikely
	FCM-miniR	Fever		3	6	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	29 April 2010	No		
Almost certainly	Almost certainly	Almost certainly	10 May 2010	Yes	21 June 2010	42
Almost certainly	Almost certainly	Almost certainly	29 April 2010	Yes	19 July 2010	81
Almost certainly	Almost certainly	Almost certainly	29 May 2010	Yes	5 June 2010	7
Almost certainly	Almost certainly	Almost certainly	29 May 2010	Yes	31 May 2010	2
Almost certainly	Almost certainly	Almost certainly	27 May 2010	No		
Almost certainly	Almost certainly	Almost certainly	21 June 2010	Yes	19 July 2010	28
Almost certainly	Almost certainly	Almost certainly	26 June 2010	Yes	30 June 2010	4
Almost certainly	Almost certainly	Almost certainly	26 June 2010	Yes	30 June 2010	4
Almost certainly	Almost certainly	Almost certainly	24 June 2010	No		
Almost certainly	Almost certainly	Almost certainly	22 July 2010	Yes	29 July 2010	7
Almost certainly	Almost certainly	Almost certainly	24 July 2010	Yes	29 July 2010	5
Almost certainly	Almost certainly	Almost certainly	22 July 2010	No		
Almost certainly	Almost certainly	Almost certainly	21 August 2010	Yes	28 August 2010	7
Almost certainly	Almost certainly	Almost certainly	19 August 2010	No		
Almost certainly	Almost certainly	Almost certainly	19 August 2010	No		
Almost certainly	Almost certainly	Almost certainly	3 October 2010	Yes	13 October 2010	10
Almost certainly	Almost certainly	Almost certainly	30 September 2010	No		
Unrelated	Unrelated	Almost certainly	5 May 2010	Yes	5 May 2010	0
Unrelated	Unrelated	Unrelated		Yes	3 June 2010	
Almost certainly	Almost certainly	Almost certainly	3 June 2010	Yes	3 June 2010	0
Unlikely	Unlikely	Unlikely	17 June 2010	Yes	1 July 2010	14
Almost certainly	Almost certainly	Almost certainly	27 August 2010	Yes	8 September 2010	12

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Anaemia		3	6	Almost certainly
	FCM-miniR	Neutropenia		4	6	Unlikely
20	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Vomiting		2	1	Almost certainly
	FCM-miniR	Infections (not neutropenic sepsis)		1	4	Unrelated
	FCM-miniR	Rash/flushing		1	4	Unrelated
	FCM-miniR	Nausea		1	6	Almost certainly
	FCM-miniR	Cough		1	6	Almost certainly
	FCM-miniR	Fatigue		1	6	Almost certainly
	FCM-miniR	Rigors		1	6	Almost certainly
21	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Vomiting			1	Almost certainly
	FCM-miniR	Renal impairment		3	1	Almost certainly
	FCM-miniR	Other AE description	Acidosis	4	1	Almost certainly
	FCM-miniR	Abnormal electrolytes		4	1	Almost certainly
	FCM-miniR	Abnormal electrolytes			1	Almost certainly
	FCM-miniR	Diarrhoea			1	Almost certainly
22	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Fatigue		2	1	Almost certainly
	FCM-miniR	Fatigue		1	2	Unlikely
	FCM-miniR	Neutropenia		1	3	Probably
	FCM-miniR	Thrombocytopenia		1	3	Unrelated
	FCM-miniR	Fatigue		1	3	Probably
	FCM-miniR	Neutropenia		1	4	Almost certainly
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Neutropenia		3	5	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	2 September 2010	Yes	6 September 2010	4
Almost certainly	Almost certainly	Almost certainly	31 August 2010	Yes	6 September 2010	6
Possibly	Possibly	Unrelated	1 July 2010	Yes	5 July 2010	4
Possibly	Possibly	Unrelated	1 July 2010	Yes	5 July 2010	4
Unrelated	Unrelated	Unrelated	25 September 2010	Yes	4 October 2010	9
Unrelated	Unrelated	Unrelated	11 October 2010	Yes	8 November 2010	28
Possibly	Possibly	Almost certainly	11 December 2010	Yes	13 December 2010	2
Unlikely	Unlikely	Unlikely	30 December 2010	Yes	4 January 2011	5
Unlikely	Unlikely	Unlikely	11 December 2010	No		
Unlikely	Unlikely	Almost certainly	8 December 2010	Yes	4 January 2011	27
Almost certainly	Almost certainly	Almost certainly	30 June 2010	Yes	4 July 2010	4
Almost certainly	Almost certainly	Almost certainly	30 June 2010	Yes	4 July 2010	4
Almost certainly	Almost certainly	Almost certainly	2 July 2010	Yes	20 July 2010	18
Almost certainly	Almost certainly	Almost certainly	2 July 2010	Yes	10 July 2010	8
Almost certainly	Almost certainly	Almost certainly	2 July 2010	Yes	5 July 2010	3
Almost certainly	Almost certainly	Almost certainly	3 July 2010	Yes	30 July 2010	27
Almost certainly	Almost certainly	Almost certainly	30 June 2010	Yes	5 July 2010	5
Almost certainly	Almost certainly	Almost certainly	20 July 2010	Yes	3 August 2010	14
Almost certainly	Almost certainly	Almost certainly	17 July 2010	Yes	21 July 2010	4
Unlikely	Unlikely	Unlikely	3 August 2010	Yes	7 August 2010	4
Probably	Probably	Probably	17 August 2010	Yes	31 August 2010	14
Unrelated	Unrelated	Unrelated	31 August 2010	No		
Probably	Probably	Probably	31 August 2010	Yes	4 September 2010	4
Almost certainly	Almost certainly	Almost certainly	12 October 2010	Yes	25 October 2010	13
Almost certainly	Almost certainly	Almost certainly	25 October 2010	No		
Almost certainly	Almost certainly	Almost certainly	9 November 2010	Yes	22 November 2010	13

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Neutropenia		3	6	Almost certainly
	FCM-miniR	Thrombocytopenia		1	6	Almost certainly
23	FCM-miniR	Neutropenia		4	2	Almost certainly
	FCM-miniR	Nausea		1	2	Almost certainly
	FCM-miniR	Neutropenia		1	3	Almost certainly
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Anaemia		1	4	Probably
	FCM-miniR	Neutropenia		1	4	Probably
	FCM-miniR	Anaemia		1	5	Almost certainly
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Leucocytosis/ lymphocytosis		4	5	Almost certainly
	FCM-miniR	Anaemia		1	6	Almost certainly
	FCM-miniR	Thrombocytopenia		2	6	Almost certainly
	FCM-miniR	Neutropenia		4	6	Almost certainly
27	FCM-miniR	Neutropenia		2	1	Almost certainly
	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Vomiting		1	1	Almost certainly
	FCM-miniR	Vomiting		2	2	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		1	2	Possibly
	FCM-miniR	Fatigue		1	2	Probably
	FCM-miniR	Neuropathy (sensory)		1	2	Possibly
	FCM-miniR	Neutropenia		2	2	Almost certainly
	FCM-miniR	Thrombocytopenia		1	2	Almost certainly
	FCM-miniR	Infections (not neutropenic sepsis)		1	3	Possibly
	FCM-miniR	Diarrhoea		2	3	Unlikely
	FCM-miniR	Neuropathy (sensory)		1	3	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	22 November 2010	No		
Almost certainly	Almost certainly	Almost certainly	7 December 2010	No		
Almost certainly	Almost certainly	Almost certainly	7 December 2010	No		
Almost certainly	Almost certainly	Almost certainly	28 July 2010	Yes	9 August 2010	12
Almost certainly	Almost certainly	Almost certainly	28 July 2010	Yes	18 August 2010	21
Almost certainly	Almost certainly	Almost certainly	17 August 2010	Yes	6 September 2010	20
Almost certainly	Almost certainly	Almost certainly	7 September 2010	No		
Probably	Probably	Probably	20 September 2010	Yes	28 September 2010	8
Probably	Probably	Probably	20 September 2010	Yes	28 September 2010	8
Almost certainly	Almost certainly	Almost certainly	16 November 2010	Yes	29 November 2010	13
Almost certainly	Almost certainly	Almost certainly	16 November 2010	No		
Almost certainly	Almost certainly	Almost certainly	16 November 2010	Yes	29 November 2010	13
Almost certainly	Almost certainly	Almost certainly	14 October 2010	No		
Almost certainly	Almost certainly	Almost certainly	14 December 2010	No		
Almost certainly	Almost certainly	Almost certainly	14 December 2010	No		
Almost certainly	Almost certainly	Possibly	12 August 2010	No		
Almost certainly	Almost certainly	Unrelated	27 July 2010	Yes	30 July 2010	3
Almost certainly	Almost certainly	Unrelated	28 July 2010	Yes	29 July 2010	1
Almost certainly	Almost certainly	Possibly		Yes	16 September 2010	
Possibly	Possibly	Possibly		Yes	16 September 2010	
Probably	Probably	Probably		Yes	16 September 2010	
Possibly	Probably	Possibly		Yes	16 September 2010	
Almost certainly	Almost certainly	Possibly	14 September 2010	No		
Almost certainly	Unlikely	Probably	14 September 2010	No		
Possibly	Possibly	Possibly	1 October 2010	Yes	18 October 2010	17
Unlikely	Unlikely	Unlikely	29 September 2010	Yes	17 October 2010	18
Possibly	Probably	Possibly	3 October 2010	Yes	3 October 2010	0

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Abdominal pain/ bloating		1	3	Possibly
	FCM-miniR	Anaemia		2	3	Probably
	FCM-miniR	Neutropenia		4	3	Almost certainly
	FCM-miniR	Neutropenia		3	3	Almost certainly
	FCM-miniR	Nausea		1	4	Almost certainly
	FCM-miniR	Dry skin/erythema		1	4	Possibly
	FCM-miniR	Neutropenia		2	4	Almost certainly
	FCM-miniR	Mucositis/thrush		2	4	Probably
	FCM-miniR	Anaemia		1	4	Probably
	FCM-miniR	Cystitis		1	5	Possibly
	FCM-miniR	Neutropenia		3	5	Almost certainly
	FCM-miniR	Neutropenia		2	5	Almost certainly
	FCM-miniR	Common cold		1	5	Unlikely
	FCM-miniR	Neutropenic sepsis		3	6	Almost certainly
	FCM-miniR	Diarrhoea		1	6	Possibly
	FCM-miniR	Neutropenia		4	6	Almost certainly
	FCM-miniR	Thrombocytopenia		1	6	Possibly
30	FCM-miniR	Anaemia		4	1	Almost certainly
31	FCM-miniR	Rigors		1	1	Unlikely
	FCM-miniR	Other AE description	Hypertension	2	1	Unlikely
	FCM-miniR	Fever		1	1	Unlikely
	FCM-miniR	Back pain		3	2	Unrelated
	FCM-miniR	Neutropenia		4	2	Probably
	FCM-miniR	Diarrhoea		1	3	Possibly
	FCM-miniR	Thrombocytopenia		4	5	Almost certainly
	FCM-miniR	Neutropenia		4	5	Almost certainly
	FCM-miniR	Anaemia		4	5	Almost certainly
34	FCM-miniR	Infusional reaction		2	1	Unrelated
	FCM-miniR	Nausea		1	3	Almost certainly
36	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Neutropenia		1	1	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	Possibly	4 October 2010	Yes	4 October 2010	0
Probably	Probably	Probably	19 October 2010	No		
Probably	Probably	Probably	29 September 2010	Yes	19 October 2010	20
Probably	Probably	Probably	19 October 2010	No		
Almost certainly	Almost certainly	Possibly		No		
Possibly	Possibly	Possibly		No		
Almost certainly	Almost certainly	Possibly	28 October 2010	Yes	25 November 2010	28
Possibly	Probably	Possibly	1 October 2010	Yes	1 November 2010	31
Probably	Probably	Probably	25 October 2010	Yes	25 November 2010	31
Possibly	Possibly	Possibly		Yes	29 November 2010	
Almost certainly	Almost certainly	Possibly	29 December 2010	Yes	4 January 2011	6
Probably	Probably	Probably	25 October 2010	Yes	4 January 2011	71
Unlikely	Unlikely	Unlikely	23 December 2010	Yes	5 January 2011	13
Almost certainly	Almost certainly	Possibly	21 February 2011	Yes	25 February 2011	4
Possibly	Possibly	Possibly	21 February 2011	Yes	24 February 2011	3
Probably	Probably	Probably	22 February 2011	Yes	24 February 2011	2
Possibly	Possibly	Possibly	22 February 2011	No		
Possibly	Possibly	Possibly	22 August 2010	Yes	31 August 2010	9
Unlikely	Unlikely	Probably	18 August 2010	Yes	18 August 2010	0
Unlikely	Unlikely	Probably	18 August 2010	Yes	18 August 2010	0
Unlikely	Unlikely	Probably	18 August 2010	Yes	18 August 2010	0
Unrelated	Unrelated	Unrelated	8 October 2010	No		
Probably	Probably	Probably	1 September 2010	Yes	11 October 2010	40
Possibly	Possibly	Unlikely	13 October 2010	Yes	15 October 2010	2
Almost certainly	Almost certainly	Almost certainly	4 January 2011	No		
Almost certainly	Almost certainly	Almost certainly	4 January 2011	No		
Almost certainly	Almost certainly	Almost certainly	4 January 2011	No		
Unrelated	Unrelated	Almost certainly	17 September 2010	Yes	17 September 2010	0
Almost certainly	Almost certainly	Almost certainly	13 November 2010	Yes	17 November 2010	4
Almost certainly	Almost certainly	Almost certainly	27 September 2010	No		
Almost certainly	Almost certainly	Probably	25 October 2010	No		
Almost certainly	Almost certainly	Possibly	21 October 2010	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Cystitis		1	2	Possibly
	FCM-miniR	Neutropenia		3	2	Almost certainly
	FCM-miniR	Lymphopenia		3	2	Possibly
	FCM-miniR	Anaemia		1	2	Probably
	FCM-miniR	Constipation		2	3	Possibly
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Cough		1	3	Possibly
	FCM-miniR	Anorexia/cachexia		1	4	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		1	4	Probably
	FCM-miniR	Anorexia/cachexia		3	4	Almost certainly
	FCM-miniR	Oedema		1	4	Possibly
	FCM-miniR	Neutropenia		2	4	Almost certainly
	FCM-miniR	Lymphopenia		3	4	Possibly
37	FCM-miniR	Mucositis/thrush		1	5	Probably
	FCM-miniR	Anorexia/cachexia		1	5	Probably
	FCM-miniR	Fatigue		1	5	Probably
	FCM-miniR	Nausea		1	5	Probably
	FCM-miniR	Nausea		1	6	Probably
39	FCM-miniR	Vomiting		1	1	Probably
	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Thrombocytopenia		2	1	Possibly
	FCM-miniR	Anaemia		1	1	Probably
	FCM-miniR	Nausea		1	2	Almost certainly
	FCM-miniR	Vomiting		1	2	Almost certainly
	FCM-miniR	Neuropathy (sensory)		1	2	Almost certainly
	FCM-miniR	Vomiting		2	3	Almost certainly
	FCM-miniR	Fatigue		2	3	Almost certainly
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Neutropenia		1	4	Missing
	FCM-miniR	Vomiting		2	4	Missing
	FCM-miniR	Diarrhoea		1	4	Missing
	FCM-miniR	Neutropenia		1	5	Missing
	FCM-miniR	Anaemia		2	6	Almost certainly
	FCM-miniR	Neutropenia		2	6	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	Missing	30 October 2010	Yes	18 November 2010	19
Probably	Probably	Missing	3 November 2010	Yes	18 November 2010	15
Possibly	Possibly	Missing	3 November 2010	Yes	25 November 2010	22
Probably	Probably	Missing	3 November 2010	No		
Possibly	Possibly	Missing	10 November 2010	Yes	23 December 2010	43
Almost certainly	Almost certainly	Missing	29 November 2010	Yes	23 December 2010	24
Possibly	Possibly	Missing	27 October 2010	Yes	23 December 2010	57
Probably	Probably	Missing		Yes	10 February 2011	
Probably	Probably	Missing		No		
Almost certainly	Almost certainly	Missing	5 January 2011	Yes	10 February 2011	36
Possibly	Possibly	Missing	27 January 2011	Yes	10 February 2011	14
Almost certainly	Almost certainly	Missing	23 December 2010	Yes	10 February 2011	49
Possibly	Possibly	Missing	23 December 2010	Yes	10 February 2011	49
Probably	Probably	Unlikely		Yes		
Probably	Probably	Unlikely		Yes		
Probably	Probably	Unlikely		Yes		
Probably	Probably	Unlikely	2 February 2011	Yes	4 February 2011	2
Probably	Probably	Unlikely	2 March 2011	Yes	4 March 2011	2
Probably	Probably	Unlikely	8 November 2010	Yes	9 November 2010	1
Unrelated	Unrelated	Unrelated	6 November 2010	Yes	12 November 2010	6
Probably	Probably	Possibly	15 November 2010	Yes	30 December 2010	45
Possibly	Possibly	Possibly	4 November 2010	Yes	16 December 2010	42
Probably	Probably	Possibly	15 November 2010	Yes	30 December 2010	45
Almost certainly	Almost certainly	Unlikely	3 December 2010	Yes	7 December 2010	4
Almost certainly	Almost certainly	Unlikely	3 December 2010	Yes	4 December 2010	1
Almost certainly	Almost certainly	Unlikely	3 December 2010	No		
Almost certainly	Almost certainly	Unrelated	4 January 2011	Yes	6 January 2011	2
Unrelated	Unrelated	Unrelated	31 December 2010	No		
Almost certainly	Almost certainly	Unrelated	4 January 2011	Yes	6 January 2011	2
Missing	Missing	Missing	11 February 2011	Yes	15 February 2011	4
Missing	Missing	Missing	11 February 2011	Yes	13 February 2011	2
Missing	Missing	Missing	11 February 2011	Yes	12 February 2011	1
Missing	Missing	Missing	9 March 2011	Yes	24 March 2011	15
Almost certainly	Almost certainly	Unlikely	5 April 2011	No		
Almost certainly	Almost certainly	Unlikely	5 April 2011	Yes	19 April 2011	14

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
40	FCM-miniR	Anaemia		3	1	Possibly
	FCM-miniR	Infusional reaction		1	2	Unrelated
	FCM-miniR	Neutropenia		3	2	Probably
	FCM-miniR	Renal impairment		1	2	Possibly
	FCM-miniR	Allergic reaction		2	3	Unrelated
	FCM-miniR	Neutropenia		2	3	Almost certainly
	FCM-miniR	Thrombocytopenia		1	3	Almost certainly
	FCM-miniR	Anaemia		3	3	Almost certainly
	FCM-miniR	Bone pain		4	4	Unlikely
	FCM-miniR	Pruritus		3	4	Unrelated
	FCM-miniR	Neutropenia		3	4	Almost certainly
	FCM-miniR	Thrombocytopenia		4	4	Almost certainly
	FCM-miniR	Renal impairment		1	4	Possibly
	FCM-miniR	Anaemia		3	4	Almost certainly
45	FCM-miniR	Vomiting		3	1	Probably
	FCM-miniR	Anaemia		1	1	Possibly
	FCM-miniR	Thrombocytopenia		1	1	Possibly
	FCM-miniR	Neutropenia		1	1	Probably
	FCM-miniR	Infusional reaction		2	1	Unrelated
	FCM-miniR	Infections (not neutropenic sepsis)		2	2	Possibly
	FCM-miniR	Constipation		2	2	Possibly
	FCM-miniR	Dizziness		1	2	Possibly
	FCM-miniR	Neutropenia		4	3	Almost certainly
	FCM-miniR	Thrombocytopenia		3	3	Almost certainly
	FCM-miniR	Vomiting		1	3	Almost certainly
46	FCM-miniR	Rigors		1	1	Unlikely
	FCM-miniR	Hypotension		2	1	Unlikely
	FCM-miniR	Arrhythmias/ palpitation		2	1	Unlikely
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Sore throat		2	2	Unlikely
	FCM-miniR	Vomiting		2	2	Probably

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	Unlikely	16 November 2010	No		
Unrelated	Unrelated	Almost certainly	17 November 2010	Yes	17 November 2010	0
Probably	Probably	Unlikely		No		
Possibly	Possibly	Possibly	16 November 2010	Yes	14 December 2010	28
Unrelated	Unrelated	Almost certainly	22 December 2010	Yes	22 December 2010	0
Almost certainly	Almost certainly	Possibly	17 January 2011	Yes	23 January 2011	6
Almost certainly	Almost certainly	Possibly	22 November 2010	Yes	23 January 2011	62
Almost certainly	Almost certainly	Possibly	17 January 2011	Yes	23 January 2011	6
Unlikely	Unlikely	Unlikely	7 March 2011	No		
Unrelated	Unrelated	Unrelated	19 January 2011	Yes	26 January 2011	7
Almost certainly	Almost certainly	Possibly	28 February 2011	No		
Almost certainly	Almost certainly	Possibly	7 March 2011	No		
Possibly	Possibly	Possibly	17 January 2011	Yes	15 February 2011	29
Almost certainly	Almost certainly	Possibly	15 February 2011	No		
Probably	Probably	Possibly		Yes		
Possibly	Possibly	Possibly	13 December 2010	No		
Possibly	Possibly	Possibly	1 February 2010	No		
Probably	Probably	Possibly	13 December 2010	No		
Unrelated	Unrelated	Almost certainly	17 November 2010	Yes	17 November 2010	0
Possibly	Possibly	Possibly		Yes	9 January 2011	
Possibly	Possibly	Possibly	18 November 2010	Yes	12 January 2011	55
Possibly	Possibly	Possibly	21 December 2010	Yes	21 December 2010	0
Almost certainly	Almost certainly	Unlikely	7 February 2011	Yes	21 February 2011	14
Almost certainly	Almost certainly	Unlikely	7 February 2011	No		
Almost certainly	Almost certainly	Unlikely	15 January 2011	Yes	16 January 2011	1
Unlikely	Unlikely	Probably	11 November 2010	Yes	11 November 2010	0
Unlikely	Unlikely	Probably	11 November 2010	Yes	11 November 2010	0
Unlikely	Unlikely	Probably	11 November 2010	Yes	11 November 2010	0
Probably	Probably	Unlikely		Yes		
Probably	Probably	Probably	22 November 2010	Yes	6 December 2010	14
Probably	Probably	Unlikely	9 December 2010	Yes	10 December 2010	1
Unlikely	Unlikely	Unlikely	20 December 2010	Yes		
Probably	Probably	Unlikely	31 December 2010	Yes	5 January 2011	5

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Diarrhoea		2	2	Probably
	FCM-miniR	Nausea		1	3	Probably
	FCM-miniR	Diarrhoea		3	5	Unlikely
	FCM-miniR	Abdominal pain/ bloating		2	5	Unlikely
	FCM-miniR	Diarrhoea		3	6	Unlikely
47	FCM-miniR	Cough		2	1	Possibly
	FCM-miniR	Hypotension		1	1	Unrelated
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Neutropenia		2	2	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		2	2	Probably
	FCM-miniR	Fatigue		1	3	Possibly
	FCM-miniR	Diarrhoea		1	3	Probably
	FCM-miniR	Vomiting		1	3	Probably
	FCM-miniR	Neutropenia		4	3	Probably
	FCM-miniR	Neutropenia		4	5	Probably
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Cough		2	6	Possibly
49	FCM-miniR	Gout/hyperuricemia		2	1	Probably
	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		3	1	Almost certainly
	FCM-miniR	Anaemia		3	1	Almost certainly
	FCM-miniR	Renal impairment		1	1	Unlikely
	FCM-miniR	Neutropenia		4	2	Almost certainly
	FCM-miniR	Thrombocytopenia		2	2	Almost certainly
	FCM-miniR	Anaemia		2	2	Almost certainly
	FCM-miniR	Neutropenia		2	3	Almost certainly
	FCM-miniR	Thrombocytopenia		3	3	Almost certainly
	FCM-miniR	Anaemia		3	3	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Unlikely	31 December 2010	Yes	5 January 2011	5
Probably	Probably	Unlikely	6 January 2011	Yes		
Unlikely	Unlikely	Unlikely	6 January 2011	Yes	4 April 2011	88
Unlikely	Unlikely	Unlikely		No		
Unlikely	Unlikely	Unlikely		Yes	28 April 2011	
Possibly	Possibly	Possibly	6 December 2010	Yes	14 January 2010	–326
Unrelated	Unrelated	Possibly	26 November 2010	Yes	26 November 2010	0
Probably	Probably	Unrelated	26 November 2010	Yes	26 November 2010	0
Probably	Probably	Unrelated	14 January 2011	Yes	26 January 2011	12
Probably	Probably	Probably	7 January 2011	Yes	2 February 2011	26
Possibly	Possibly	Possibly	23 February 2011	No		
Probably	Probably	Unrelated	26 February 2011	Yes	4 March 2011	6
Probably	Probably	Unrelated	1 March 2011	Yes	3 March 2011	2
Probably	Probably	Unrelated	7 March 2011	Yes	14 March 2011	7
Probably	Probably	Unrelated	21 March 2011	Yes	13 April 2011	23
Probably	Probably	Possibly	18 April 2011	Yes	16 May 2011	28
Probably	Probably	Possibly	26 May 2011	No		
Possibly	Possibly	Possibly	6 May 2011	Yes	10 June 2011	35
Probably	Probably	Probably	13 April 2011	Yes	24 April 2011	11
Almost certainly	Almost certainly	Almost certainly	14 April 2011	Yes	21 April 2011	7
Almost certainly	Almost certainly	Almost certainly	14 April 2011	Yes	27 April 2011	13
Almost certainly	Almost certainly	Almost certainly	14 April 2011	No		
Unlikely	Unlikely	Unlikely		Yes	11 July 2011	
Almost certainly	Almost certainly	Almost certainly	10 May 2011	Yes	17 May 2011	7
Almost certainly	Almost certainly	Almost certainly	10 May 2011	Yes	13 July 2011	64
Almost certainly	Almost certainly	Almost certainly	10 May 2011	No		
Almost certainly	Almost certainly	Almost certainly	2 June 2011	Yes	21 June 2011	19
Almost certainly	Almost certainly	Almost certainly	24 May 2011	Yes	13 July 2011	50
Almost certainly	Almost certainly	Almost certainly	10 June 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
52	FCM-miniR	Nausea		1	1	Unrelated
	FCM-miniR	Vomiting		2	1	Probably
	FCM-miniR	Rash/flushing		2	1	Unrelated
	FCM-miniR	Rash/flushing		2	2	Unrelated
	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Allergic reaction		1	2	Unrelated
	FCM-miniR	Vomiting		2	3	Probably
	FCM-miniR	Nausea		1	4	Probably
	FCM-miniR	Cough		2	5	Probably
	FCM-miniR	Neutropenia		1	5	Almost certainly
53	FCM-miniR	Dyspnoea		2	1	Unrelated
	FCM-miniR	Vomiting		3	1	Almost certainly
	FCM-miniR	Urinary symptoms		1	2	Unlikely
	FCM-miniR	Infections (not neutropenic sepsis)		2	2	Possibly
	FCM-miniR	Abnormal electrolytes		3	2	Unrelated
	FCM-miniR	Rash/flushing		2	3	Unrelated
	FCM-miniR	Infections (not neutropenic sepsis)		2	6	Possibly
54	FCM-miniR	Vomiting		2	1	Missing
	FCM-miniR	Nausea		2	1	Missing
	FCM-miniR	Neutropenic sepsis		4	1	Missing
	FCM-miniR	Vomiting		2	2	Unrelated
	FCM-miniR	Vomiting		2	3	Probably
	FCM-miniR	Thrombocytopenia		1	3	Probably
	FCM-miniR	Nausea		1	4	Probably
	FCM-miniR	Fatigue		1	5	Probably
	FCM-miniR	Vomiting		1	5	Probably
	FCM-miniR	Thrombocytopenia		2	5	Probably
	FCM-miniR	Anaemia		1	5	Probably
57	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Insomnia		1	1	Unrelated
	FCM-miniR	Neutropenia		3	1	Probably
	FCM-miniR	Mucositis/thrush		1	1	Probably
	FCM-miniR	Headache		1	1	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	Almost certainly	21 December 2010	Yes	27 December 2010	6
Probably	Probably	Probably	26 December 2010	Yes	27 December 2010	1
Unrelated	Unrelated	Almost certainly	20 December 2010	Yes	20 December 2010	0
Unrelated	Unrelated	Almost certainly	17 January 2011	Yes	17 January 2011	0
Probably	Probably	Probably	20 January 2011	Yes	24 January 2011	4
Unrelated	Unrelated	Almost certainly	17 January 2011	Yes	17 January 2011	0
Probably	Probably	Probably	15 February 2011	Yes	17 February 2011	2
Probably	Probably	Probably	14 March 2011	Yes	20 March 2011	6
Probably	Probably	Unlikely	7 May 2011	No		
Almost certainly	Almost certainly	Possibly	9 May 2011	No		
Unrelated	Unrelated	Unrelated	23 January 2011	Yes		
Almost certainly	Almost certainly	Unrelated		Yes	8 February 2011	
Unlikely	Unlikely	Unlikely		Yes	22 March 2011	
Possibly	Possibly	Possibly		Yes	22 March 2011	
Unrelated	Unrelated	Unrelated	11 January 2011	No		
Unrelated	Unrelated	Unrelated	8 March 2011	Yes	19 April 2011	42
Possibly	Possibly	Possibly	7 June 2011	Yes	27 July 2011	50
Missing	Missing	Missing	23 January 2011	Yes	24 January 2011	1
Missing	Missing	Missing	22 January 2011	Yes	28 January 2011	6
Missing	Missing	Missing	16 February 2011	Yes		
Probably	Probably	Unrelated	18 February 2011	Yes	23 February 2011	5
Probably	Probably	Unlikely	17 March 2011	Yes	27 March 2011	10
Probably	Probably	Possibly	13 April 2011	No		
Probably	Probably	Unlikely	27 April 2011	Yes	7 May 2011	10
Probably	Probably	Unrelated	25 May 2011	No		
Probably	Probably	Unrelated	26 May 2011	Yes	4 June 2011	9
Probably	Probably	Unrelated	22 June 2011	No		
Probably	Probably	Unrelated	22 June 2011	Yes	6 July 2011	14
Probably	Probably	Unlikely	13 January 2011	Yes	25 January 2011	12
Unrelated	Unrelated	Unrelated	13 January 2011	No		
Probably	Probably	Unlikely	25 January 2011	Yes	8 February 2011	14
Probably	Probably	Unlikely	25 January 2011	No		
Possibly	Possibly	Missing	5 February 2011	Yes	8 February 2011	3

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Insomnia		1	2	Unrelated
	FCM-miniR	Neutropenia		3	2	Probably
	FCM-miniR	Fatigue		1	2	Probably
	FCM-miniR	Nausea		1	3	Probably
	FCM-miniR	Insomnia		1	3	Unrelated
	FCM-miniR	Neutropenia		4	3	Probably
	FCM-miniR	Fatigue		1	3	Probably
	FCM-miniR	Nausea		1	4	Probably
	FCM-miniR	Insomnia		1	4	Unrelated
	FCM-miniR	Neutropenia		4	4	Probably
	FCM-miniR	Fatigue		1	4	Probably
	FCM-miniR	Nausea		1	5	Probably
	FCM-miniR	Insomnia		1	5	Unrelated
	FCM-miniR	Neutropenia		4	5	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		1	5	Probably
	FCM-miniR	Fatigue		1	5	Probably
	FCM-miniR	Nausea		1	6	Probably
	FCM-miniR	Insomnia		1	6	Unrelated
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Fatigue		1	6	Probably
58	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Headache		1	1	Possibly
	FCM-miniR	Vomiting		1	1	Probably
	FCM-miniR	Dry skin/erythema		1	1	Possibly
	FCM-miniR	Back pain		2	1	Unlikely
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Vomiting		1	2	Probably
	FCM-miniR	Headache		1	2	Possibly
	FCM-miniR	Cough		1	2	Possibly
	FCM-miniR	Fatigue		2	2	Possibly
	FCM-miniR	Fatigue		1	2	Possibly
	FCM-miniR	Nausea		1	3	Probably
	FCM-miniR	Fatigue		2	3	Probably
	FCM-miniR	Headache		1	3	Possibly
	FCM-miniR	Cough		1	3	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Unlikely	8 February 2011	Yes	12 February 2011	4
Unrelated	Unrelated	Unrelated	8 February 2011	No		
Probably	Probably	Unlikely	22 February 2011	Yes	8 March 2011	14
Probably	Probably	Unlikely	22 February 2011	No		
Probably	Probably	Unlikely	8 March 2011	Yes	14 March 2011	6
Unrelated	Unrelated	Unrelated	8 March 2011	No		
Probably	Probably	Probably	14 March 2011	No		
Probably	Probably	Unlikely	8 March 2011	No		
Probably	Probably	Unlikely	5 April 2011	Yes	11 April 2011	6
Unrelated	Unrelated	Unrelated	5 April 2011	No		
Probably	Probably	Probably	18 April 2011	No		
Probably	Probably	Unlikely	5 April 2011	No		
Probably	Probably	Unlikely	3 May 2011	Yes	9 May 2011	6
Unrelated	Unrelated	Unrelated	3 May 2011	No		
Probably	Probably	Unlikely	16 May 2011	No		
Probably	Probably	Unlikely		Yes	31 May 2011	
Probably	Probably	Unlikely	3 May 2011	No		
Probably	Probably	Unlikely	31 May 2011	Yes	6 June 2011	6
Unrelated	Unrelated	Probably	31 May 2011	No		
Probably	Probably	Unlikely	31 May 2011	Yes	27 June 2011	27
Probably	Probably	Unlikely	31 May 2011	No		
Probably	Probably	Possibly	26 January 2011	Yes	5 February 2011	10
Possibly	Possibly	Unlikely	29 January 2011	Yes	5 February 2011	7
Probably	Probably	Unrelated	29 January 2011	Yes	30 January 2011	1
Possibly	Possibly	Unrelated	27 January 2011	No		
Unlikely	Unlikely	Unlikely	31 January 2011	Yes	5 February 2011	5
Probably	Probably	Possibly	25 February 2011	Yes	3 March 2011	6
Probably	Probably	Unrelated	28 February 2011	Yes	1 March 2011	1
Possibly	Possibly	Unlikely	25 February 2011	Yes	28 February 2011	3
Possibly	Possibly	Unlikely	8 March 2011	Yes	14 March 2011	6
Possibly	Possibly	Probably	27 January 2011	Yes	28 February 2011	32
Possibly	Possibly	Probably	1 March 2011	Yes	26 March 2011	25
Probably	Probably	Possibly	25 March 2011	Yes	29 March 2011	4
Probably	Probably	Possibly	27 March 2011	No		
Possibly	Possibly	Unlikely	2 April 2011	No		
Possibly	Possibly	Unlikely	5 April 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Neutropenia		2	3	Possibly
	FCM-miniR	Neuropathy (sensory)		1	3	Possibly
	FCM-miniR	Nausea		1	4	Probably
	FCM-miniR	Cough		1	4	Possibly
	FCM-miniR	Neutropenia		4	4	Almost certainly
	FCM-miniR	Headache		2	4	Unlikely
	FCM-miniR	Constipation		2	4	Possibly
	FCM-miniR	Vomiting		1	4	Probably
	FCM-miniR	Nausea		1	5	Probably
	FCM-miniR	Headache		2	5	Unlikely
	FCM-miniR	Vomiting		1	5	Probably
	FCM-miniR	Neutropenia		3	5	Probably
	FCM-miniR	Nausea		1	6	Probably
	FCM-miniR	Headache		1	6	Unlikely
	FCM-miniR	Vomiting		1	6	Probably
	FCM-miniR	Dizziness		2	6	Possibly
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Thrombocytopenia		4	6	Probably
	FCM-miniR	Mucositis/thrush		2	6	Probably
	FCM-miniR	Other AE description	Loss of sense of smell	1	6	Possibly
	FCM-miniR	Dry skin/erythema		1	6	Possibly
63	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Thrombocytopenia		1	1	Almost certainly
	FCM-miniR	Neutropenia		3	2	Almost certainly
	FCM-miniR	Anaemia		2	4	Almost certainly
	FCM-miniR	Neutropenia		3	4	Almost certainly
	FCM-miniR	Neutropenia		1	6	Almost certainly
64	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Nausea		2	2	Almost certainly
	FCM-miniR	Other AE description	Restlessness	2	2	Unrelated
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Nausea		2	5	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	Probably	15 April 2011	No		
Unlikely	Probably	Unrelated	24 March 2011	Yes	27 March 2011	3
Probably	Probably	Possibly	22 April 2011	Yes	24 May 2011	32
Possibly	Possibly	Possibly	21 April 2011	Yes	13 May 2011	22
Almost certainly	Almost certainly	Unlikely	27 April 2011	Yes	16 May 2011	19
Unlikely	Unlikely	Unlikely	13 May 2011	Yes	27 May 2011	14
Possibly	Possibly	Unlikely	27 January 2011	Yes	20 April 2011	83
Probably	Probably	Unlikely	22 May 2011	Yes	24 May 2011	2
Probably	Probably	Possibly	3 June 2011	Yes	25 June 2011	22
Unlikely	Unlikely	Unlikely	11 June 2011	Yes	25 June 2011	14
Probably	Probably	Unlikely	7 June 2011	Yes	21 June 2011	14
Probably	Probably	Possibly	8 June 2011	Yes	28 June 2011	20
Probably	Probably	Possibly	29 June 2011	Yes	10 July 2011	11
Unlikely	Unlikely	Unlikely	30 June 2011	Yes	14 July 2011	14
Probably	Probably	Unlikely	1 July 2011	Yes	1 July 2011	0
Possibly	Probably	Unlikely	2 July 2011	Yes	19 July 2011	17
Probably	Probably	Possibly	6 July 2011	Yes	13 July 2011	7
Probably	Probably	Possibly	6 July 2011	No		
Probably	Probably	Possibly	9 July 2011	No		
Possibly	Possibly	Possibly	7 July 2011	No		
Possibly	Possibly	Probably	17 July 2011	No		
Almost certainly	Almost certainly	Almost certainly	30 September 2011	No		
Almost certainly	Almost certainly	Almost certainly	30 September 2011	No		
Almost certainly	Almost certainly	Almost certainly	30 September 2011	Yes	7 October 2011	7
Almost certainly	Almost certainly	Almost certainly	9 January 2012	No		
Almost certainly	Almost certainly	Almost certainly	11 January 2012	No		
Almost certainly	Almost certainly	Almost certainly	9 December 2011	Yes	12 March 2012	94
Almost certainly	Almost certainly	Unrelated	12 February 2011	Yes	18 February 2011	6
Almost certainly	Almost certainly	Unrelated	9 March 2011	Yes	15 March 2011	6
Unrelated	Unrelated	Unrelated	9 March 2011	Yes	15 March 2011	6
Almost certainly	Almost certainly	Unlikely	8 April 2011	Yes		
Almost certainly	Almost certainly	Unlikely	1 June 2011	Yes	28 July 2011	57

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
65	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Anaemia		3	1	Possibly
	FCM-miniR	Dry skin/erythema		1	3	Unlikely
	FCM-miniR	Nausea		1	4	Possibly
	FCM-miniR	Neutropenia		2	4	Almost certainly
	FCM-miniR	Nausea		1	5	Possibly
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Anaemia		2	5	Possibly
	FCM-miniR	Neutropenia		3	6	Almost certainly
	FCM-miniR	Anaemia		4	6	Probably
69	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Thrombocytopenia		1	1	Almost certainly
	FCM-miniR	Diarrhoea		1	1	Unlikely
	FCM-miniR	Diarrhoea		1	3	Possibly
	FCM-miniR	Neutropenia		2	4	Probably
	FCM-miniR	Fatigue		1	4	Probably
	FCM-miniR	Neutropenia		3	5	Probably
71	FCM-miniR	Fatigue		1	1	Unrelated
	FCM-miniR	Cough		1	1	Unlikely
	FCM-miniR	Anaemia		1	1	Unrelated
	FCM-miniR	Vomiting		1	3	Almost certainly
	FCM-miniR	Diarrhoea		2	3	Possibly
	FCM-miniR	Nausea		3	4	Almost certainly
	FCM-miniR	Vomiting		1	4	Almost certainly
	FCM-miniR	Alopecia		1	5	Possibly
	FCM-miniR	Nausea		1	6	Almost certainly
	FCM-miniR	Diarrhoea		1	6	Possibly
73	FCM-miniR	Neutropenia		3	1	Possibly
	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Vomiting		1	1	Probably
	FCM-miniR	Neutropenia		3	3	Possibly
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Neutropenia		1	4	Almost certainly
	FCM-miniR	Neutropenia		4	5	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Unlikely	23 February 2011	Yes	3 March 2011	8
Possibly	Possibly	Unlikely	28 February 2011	Yes	18 March 2011	18
Unlikely	Unlikely	Unlikely	22 April 2011	No		
Possibly	Possibly	Unlikely	15 April 2011	Yes	17 May 2011	32
Almost certainly	Almost certainly	Unlikely	12 May 2011	No		
Possibly	Possibly	Unlikely	10 June 2011	Yes	15 June 2011	5
Almost certainly	Almost certainly	Unlikely	10 June 2011	Yes	11 July 2011	31
Possibly	Possibly	Unlikely	8 July 2011	Yes	11 July 2011	3
Almost certainly	Almost certainly	Unlikely	20 June 2011	Yes	15 July 2011	25
Probably	Probably	Unlikely	22 August 2011	No		
Almost certainly	Almost certainly	Almost certainly	10 May 2011	Yes	16 May 2011	6
Almost certainly	Almost certainly	Almost certainly	11 May 2011	Yes	16 May 2011	5
Unlikely	Unlikely	Unlikely	7 May 2011	Yes	16 May 2011	9
Possibly	Possibly	Possibly	2 July 2011	Yes	7 July 2011	5
Probably	Probably	Probably	19 July 2011	Yes	12 September 2011	55
Probably	Probably	Probably	7 June 2011	Yes	20 July 2011	43
Probably	Probably	Probably	16 August 2011	Yes	9 September 2011	24
Unrelated	Unrelated	Unrelated		No		
Unlikely	Unlikely	Unlikely		No		
Unrelated	Unrelated	Unrelated	11 August 2010	No		
Almost certainly	Almost certainly	Unlikely		Yes	5 May 2011	
Possibly	Possibly	Possibly	1 May 2011	Yes	5 May 2011	4
Almost certainly	Almost certainly	Unlikely	22 May 2011	Yes	16 June 2011	25
Almost certainly	Almost certainly	Unlikely	22 May 2011	Yes	16 June 2011	25
Possibly	Possibly	Unlikely		No		
Almost certainly	Almost certainly	Unlikely		Yes	11 August 2011	
Possibly	Possibly	Possibly		Yes	11 August 2011	
Possibly	Almost certainly	Possibly	4 April 2011	Yes	13 April 2011	9
Probably	Almost certainly	Unlikely	21 March 2011	Yes	25 March 2011	4
Probably	Almost certainly	Unlikely	21 March 2011	Yes	22 March 2011	1
Almost certainly	Possibly	Possibly	26 May 2011	Yes	3 June 2011	8
Possibly	Possibly	Possibly	19 May 2011	Yes	22 May 2011	3
Almost certainly	Probably	Probably	11 July 2011	No		
Almost certainly	Probably	Probably	19 July 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Nausea		2	5	Probably
	FCM-miniR	Rigors		1	5	Probably
	FCM-miniR	Anorexia/cachexia		2	5	Almost certainly
75	FCM-miniR	Rash/flushing		1	1	Unlikely
	FCM-miniR	Pruritus		2	1	Unlikely
	FCM-miniR	Neutropenia		4	2	Probably
	FCM-miniR	Anaemia		2	2	Probably
	FCM-miniR	Thrombocytopenia		1	2	Possibly
	FCM-miniR	Anaemia		3	3	Probably
	FCM-miniR	Mucositis/thrush		1	4	Probably
	FCM-miniR	Pruritus		1	4	Unlikely
	FCM-miniR	Anaemia		2	4	Probably
	FCM-miniR	Neutropenia		4	4	Probably
	FCM-miniR	Anaemia		2	5	Probably
	FCM-miniR	Fever		1	6	Unrelated
	FCM-miniR	Anaemia		2	6	Probably
	FCM-miniR	Thrombocytopenia		1	6	Possibly
	FCM-miniR	Neutropenia		2	6	Probably
77	FCM-miniR	Vomiting		1	1	Possibly
	FCM-miniR	Abdominal pain/ bloating		1	1	Unlikely
	FCM-miniR	Nausea		1	2	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		1	3	Possibly
	FCM-miniR	Nausea		3	3	Almost certainly
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Dehydration		2	3	Almost certainly
	FCM-miniR	Vomiting		2	3	Almost certainly
	FCM-miniR	Thrombocytopenia		1	3	Almost certainly
	FCM-miniR	Neutropenia		1	4	Almost certainly
	FCM-miniR	Thrombocytopenia		2	4	Almost certainly
	FCM-miniR	Fatigue		2	5	Possibly
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Almost certainly	19 July 2011	Yes	22 July 2011	3
Probably	Probably	Probably	19 July 2011	Yes	22 July 2011	3
Almost certainly	Almost certainly	Almost certainly	11 July 2011	No		
Unlikely	Unlikely	Unlikely	8 April 2011	Yes	11 April 2011	3
Unlikely	Unlikely	Unlikely	11 April 2011	Yes	12 April 2011	1
Probably	Probably	Possibly	26 April 2011	Yes	2 May 2011	6
Probably	Probably	Possibly	20 April 2011	Yes	3 May 2011	13
Possibly	Possibly	Possibly	1 May 2011	Yes	5 May 2011	4
Missing	Probably	Missing	4 May 2011	No		
Probably	Unlikely	Unlikely	13 June 2011	Yes	28 June 2011	15
Unlikely	Unlikely	Unlikely	24 May 2011	Yes	17 June 2011	24
Probably	Probably	Possibly	27 June 2011	Yes	11 July 2011	14
Probably	Probably	Possibly	20 June 2011	Yes	7 July 2011	17
Probably	Probably	Unrelated	27 July 2011	Yes	3 August 2011	7
Unrelated	Unrelated	Unrelated	16 August 2011	Yes	24 August 2011	8
Probably	Probably	Possibly	17 August 2011	No		
Possibly	Possibly	Probably	10 August 2011	No		
Probably	Probably	Possibly	31 August 2011	No		
Possibly	Possibly	Unlikely	20 April 2011	Yes	23 April 2011	3
Unlikely	Unlikely	Unlikely	24 April 2011	Yes	25 April 2011	1
Almost certainly	Almost certainly	Unlikely	21 May 2011	Yes	23 May 2011	2
Possibly	Possibly	Unlikely	22 May 2011	Yes	13 June 2011	22
Almost certainly	Almost certainly	Unlikely	18 June 2011	Yes	21 June 2011	3
Almost certainly	Almost certainly	Unlikely	22 June 2011	No		
Almost certainly	Almost certainly	Unlikely	18 June 2011	Yes	22 June 2011	4
Almost certainly	Almost certainly	Unlikely	19 June 2011	Yes	22 June 2011	3
Almost certainly	Almost certainly	Unlikely	13 June 2011	No		
Almost certainly	Almost certainly	Unlikely	1 September 2011	Yes	7 September 2011	6
Almost certainly	Almost certainly	Unlikely	13 July 2011	No		
Possibly	Possibly	Unlikely	26 August 2011	Yes	7 September 2011	12
Almost certainly	Almost certainly	Unlikely	10 August 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
79	FCM-miniR	Pruritus		1	3	Unlikely
	FCM-miniR	Pruritus		1	3	Unlikely
	FCM-miniR	Neutropenia		3	3	Unlikely
	FCM-miniR	Neutropenia		3	3	Unlikely
	FCM-miniR	Neutropenia		3	4	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		2	4	Probably
	FCM-miniR	Neutropenia		3	5	Almost certainly
80	FCM-miniR	Infections (not neutropenic sepsis)		3	1	Probably
	FCM-miniR	Fatigue		1	1	Probably
	FCM-miniR	Neutropenia		4	2	Probably
	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Alopecia		1	2	Probably
	FCM-miniR	Anorexia/cachexia		1	2	Probably
	FCM-miniR	Nausea		2	3	Probably
	FCM-miniR	Fatigue		2	3	Probably
	FCM-miniR	Anxiety/depression		1	3	Unlikely
	FCM-miniR	Pruritus		1	3	Possibly
	FCM-miniR	Rash/flushing		2	3	Possibly
	FCM-miniR	Fever		1	3	Unlikely
	FCM-miniR	Neutropenia		3	4	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		3	4	Probably
	FCM-miniR	Nausea		2	4	Probably
	FCM-miniR	Vomiting		1	4	Probably
	FCM-miniR	Fatigue		1	4	Probably
	FCM-miniR	Anxiety/depression		1	4	Unrelated
	FCM-miniR	Rash/flushing		2	4	Probably
	FCM-miniR	Neutropenia		1	6	Probably
	FCM-miniR	Anxiety/depression		2	6	Unrelated
81	FCM-miniR	Neutropenia		3	1	Possibly
	FCM-miniR	Anaemia		3	1	Possibly
	FCM-miniR	Vomiting		2	1	Almost certainly
	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Thrombocytopenia		1	1	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	Unlikely	2 July 2011	Yes	9 July 2011	7
Unlikely	Unrelated	Unlikely	13 July 2011	Yes	20 July 2011	7
Unlikely	Unrelated	Unlikely	23 June 2011	Yes	6 July 2011	13
Unlikely	Unrelated	Unlikely	6 July 2011	Yes	20 July 2011	14
Probably	Probably	Probably	17 August 2011	Yes	31 August 2011	14
Probably	Probably	Probably	17 August 2011	Yes	31 August 2011	14
Almost certainly	Almost certainly	Unrelated	28 September 2011	Yes	5 October 2011	7
Probably	Probably	Probably	5 July 2011	Yes	18 July 2011	13
Probably	Probably	Probably	17 July 2011	No		
Probably	Probably	Probably	2 August 2011	Yes	16 August 2011	14
Probably	Probably	Probably	21 July 2011	Yes	24 July 2011	3
Probably	Probably	Probably	21 July 2011	Yes	24 July 2011	3
Probably	Probably	Probably	24 July 2011	No		
Probably	Probably	Probably	21 July 2011	Yes	24 July 2011	3
Probably	Probably	Probably	21 August 2011	Yes	28 August 2011	7
Probably	Probably	Probably	22 August 2011	Yes	2 September 2011	11
Unlikely	Unlikely	Unlikely	28 August 2011	Yes	2 September 2011	5
Unrelated	Unrelated	Unrelated	31 August 2011	Yes	14 September 2011	14
Unrelated	Unrelated	Unrelated	31 August 2011	Yes	1 September 2011	1
Unlikely	Unlikely	Unlikely	31 August 2011	Yes	1 September 2011	1
Probably	Probably	Probably	4 October 2011	Yes	5 October 2011	1
Probably	Probably	Probably	1 October 2011	Yes	6 October 2011	5
Probably	Unrelated	Unrelated	20 September 2011	Yes	22 September 2011	2
Probably	Unrelated	Unrelated	20 September 2011	Yes	20 September 2011	0
Probably	Probably	Probably	20 September 2011	Yes	6 October 2011	16
Unrelated	Unrelated	Unrelated	1 October 2011	No		
Unlikely	Unlikely	Unlikely	1 October 2011	Yes	2 October 2011	1
Probably	Probably	Probably	7 December 2011	No		
Unrelated	Unrelated	Unrelated	7 December 2011	No		
Probably	Possibly	Possibly	24 May 2011	Yes	6 June 2011	13
Probably	Possibly	Possibly	3 June 2011	Yes	7 June 2011	4
Possibly	Possibly	Possibly	13 May 2011	Yes	16 May 2011	3
Possibly	Possibly	Possibly	13 May 2011	Yes	16 May 2011	3
Probably	Almost certainly	Unlikely	24 May 2011	Yes	9 June 2011	16

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Anaemia		2	1	Possibly
	FCM-miniR	Anaemia		3	2	Possibly
	FCM-miniR	Neutropenia		4	2	Possibly
	FCM-miniR	Neutropenia		4	3	Probably
	FCM-miniR	Nausea		2	3	Possibly
	FCM-miniR	Anaemia		3	3	Possibly
	FCM-miniR	Thrombocytopenia		1	3	Almost certainly
	FCM-miniR	Anaemia		2	3	Possibly
	FCM-miniR	Neutropenia		4	4	Probably
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Thrombocytopenia		2	4	Almost certainly
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Anaemia		2	4	Possibly
	FCM-miniR	Anaemia		2	4	Possibly
83	FCM-miniR	Vomiting		1	1	Probably
	FCM-miniR	Headache		1	1	Possibly
	FCM-miniR	Neutropenia		4	2	Almost certainly
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Vomiting		2	3	Almost certainly
	FCM-miniR	Infusional reaction		1	3	Unlikely
	FCM-miniR	Vomiting		2	4	Almost certainly
	FCM-miniR	Rash/flushing		2	4	Unlikely
	FCM-miniR	Nausea		2	4	Almost certainly
	FCM-miniR	Vomiting		2	5	Almost certainly
	FCM-miniR	Fatigue		2	5	Unlikely
	FCM-miniR	Dyspnoea		1	5	Unlikely
	FCM-miniR	Nausea		2	5	Almost certainly
	FCM-miniR	Constipation		1	5	Unlikely
	FCM-miniR	Diarrhoea		1	6	Probably
85	FCM-miniR	Thrombocytopenia		2	1	Possibly
	FCM-miniR	Anaemia		2	2	Possibly
	FCM-miniR	Neutropenia		3	2	Possibly
	FCM-miniR	Anaemia		1	3	Possibly
	FCM-miniR	Thrombocytopenia		1	3	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Possibly	Possibly	7 June 2011	Yes	9 June 2011	2
Probably	Possibly	Possibly	29 June 2011	Yes	7 July 2011	8
Probably	Possibly	Possibly	29 June 2011	Yes	7 July 2011	8
Almost certainly	Probably	Probably	14 July 2011	Yes	21 July 2011	7
Possibly	Possibly	Almost certainly	7 July 2011	Yes	21 July 2011	14
Probably	Possibly	Possibly	21 July 2011	Yes	2 August 2011	12
Probably	Almost certainly	Unlikely	29 June 2011	Yes	14 July 2011	15
Probably	Possibly	Possibly	7 July 2011	Yes	21 July 2011	14
Almost certainly	Probably	Probably	15 August 2011	Yes	24 August 2011	9
Probably	Almost certainly	Unlikely	15 August 2011	Yes	20 August 2011	5
Probably	Almost certainly	Unlikely	20 August 2011	Yes	21 August 2011	1
Probably	Almost certainly	Unlikely	21 August 2011	Yes	8 September 2011	18
Probably	Possibly	Possibly	2 August 2011	Yes	18 August 2011	16
Probably	Possibly	Possibly	19 August 2011	Yes	8 September 2011	20
Probably	Probably	Unlikely	15 May 2011	Yes	15 May 2011	0
Possibly	Possibly	Unlikely	15 May 2011	Yes	15 May 2011	0
Almost certainly	Almost certainly	Probably	20 June 2011	Yes	4 July 2011	14
Almost certainly	Almost certainly	Unlikely	6 July 2011	Yes	9 July 2011	3
Almost certainly	Almost certainly	Unlikely	6 July 2011	Yes	9 July 2011	3
Unlikely	Unlikely	Unlikely	1 August 2011	No		
Almost certainly	Almost certainly	Almost certainly	2 August 2011	Yes		
Unlikely	Unlikely	Unlikely	1 August 2011	No		
Almost certainly	Almost certainly	Almost certainly	2 August 2011	Yes		
Almost certainly	Almost certainly	Unlikely	9 September 2011	Yes	11 September 2011	2
Unlikely	Unlikely	Unlikely		No		
Unlikely	Unlikely	Unlikely		No		
Almost certainly	Almost certainly	Unlikely	9 September 2011	Yes		
Unlikely	Unlikely	Unlikely	11 September 2011	Yes		
Probably	Probably	Unlikely		No		
Possibly	Possibly	Unlikely	23 June 2011	No		
Possibly	Possibly	Unlikely	23 June 2011	Yes	18 August 2011	56
Possibly	Possibly	Unlikely	23 June 2011	Yes	18 July 2011	25
Possibly	Possibly	Unlikely	18 July 2011	No		
Possibly	Possibly	Unlikely	18 July 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Neutropenia		1	3	Possibly
	FCM-miniR	Fatigue		2	5	Possibly
	FCM-miniR	Abnormal electrolytes		1	5	Unlikely
	FCM-miniR	Neutropenia		3	6	Almost certainly
	FCM-miniR	Neutropenia		2	6	Almost certainly
	FCM-miniR	Fatigue		1	6	Possibly
86	FCM-miniR	Thrombocytopenia		2	1	Unlikely
	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Anaemia		1	2	Almost certainly
	FCM-miniR	Neutropenia		4	2	Almost certainly
	FCM-miniR	Vomiting		1	2	Almost certainly
	FCM-miniR	Neutropenia		1	3	Almost certainly
	FCM-miniR	Anaemia		2	3	Almost certainly
	FCM-miniR	Fatigue		1	3	Almost certainly
	FCM-miniR	Neutropenia		4	4	Possibly
	FCM-miniR	Arrhythmias/ palpitation		1	4	Unlikely
	FCM-miniR	Fatigue		2	5	Probably
	FCM-miniR	Anaemia		2	5	Probably
	FCM-miniR	Thrombocytopenia		2	5	Possibly
	FCM-miniR	Neutropenia		4	5	Almost certainly
	FCM-miniR	Nausea		1	5	Almost certainly
	FCM-miniR	Anaemia		1	5	Unlikely
	FCM-miniR	Thrombocytopenia		2	6	Possibly
	FCM-miniR	Fatigue		2	6	Almost certainly
90	FCM-miniR	Neutropenia		3	5	Probably
	FCM-miniR	Neutropenia		2	6	Probably

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Possibly	Possibly	Unlikely	18 July 2011	No		
Possibly	Possibly	Unlikely	18 August 2011	Yes	29 September 2011	42
Unlikely	Unlikely	Unlikely	15 September 2011	Yes	13 October 2011	28
Almost certainly	Almost certainly	Unlikely	13 October 2011	Yes	20 October 2011	7
Almost certainly	Almost certainly	Unlikely	20 October 2011	Yes	10 November 2011	21
Possibly	Possibly	Unlikely	20 October 2011	Yes	10 November 2011	21
Unlikely	Unlikely	Unlikely		No		
Almost certainly	Almost certainly	Almost certainly	31 May 2011	No		
Almost certainly	Almost certainly	Almost certainly	15 June 2011	No		
Almost certainly	Almost certainly	Almost certainly	13 July 2011	No		
Almost certainly	Almost certainly	Almost certainly	13 July 2011	Yes	25 July 2011	12
Almost certainly	Almost certainly	Almost certainly	30 June 2011	Yes	30 June 2011	0
Almost certainly	Almost certainly	Almost certainly	17 August 2011	Yes	19 August 2011	2
Almost certainly	Almost certainly	Almost certainly	17 August 2011	No		
Almost certainly	Almost certainly	Almost certainly	19 August 2011	No		
Possibly	Possibly	Possibly	22 August 2011	Yes	23 September 2011	32
Unlikely	Unlikely	Unlikely	21 September 2011	Yes	22 September 2011	1
Probably	Probably	Probably	4 October 2011	No		
Probably	Probably	Probably	24 May 2011	No		
Possibly	Possibly	Possibly	21 September 2011	No		
Almost certainly	Almost certainly	Almost certainly	19 October 2011	No		
Almost certainly	Almost certainly	Almost certainly	5 October 2011	Yes	19 October 2011	14
Unlikely	Unlikely	Unlikely	19 October 2011	No		
Possibly	Possibly	Possibly	1 September 2011	No		
Almost certainly	Almost certainly	Almost certainly	1 November 2011	No		
Probably	Probably	Probably	6 October 2011	No		
Probably	Probably	Probably	8 November 2011	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
94	FCM-miniR	Thrombocytopenia		1	1	Almost certainly
	FCM-miniR	Anaemia		3	1	Possibly
	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Vomiting		1	1	Possibly
	FCM-miniR	Thrombocytopenia		1	2	Almost certainly
	FCM-miniR	Rash/flushing		1	2	Unlikely
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Vomiting		1	3	Probably
	FCM-miniR	Anaemia		2	3	Almost certainly
	FCM-miniR	Thrombocytopenia		1	3	Almost certainly
	FCM-miniR	Thrombocytopenia		3	4	Probably
	FCM-miniR	Nausea		1	4	Almost certainly
	FCM-miniR	Vomiting		1	4	Almost certainly
	FCM-miniR	Rash/flushing		1	4	Possibly
	FCM-miniR	Neutropenia		4	4	Almost certainly
95	FCM-miniR	Nausea		1	1	Possibly
	FCM-miniR	Fatigue		1	1	Unlikely
	FCM-miniR	Fatigue		1	2	Unlikely
	FCM-miniR	Other AE description	Weight gain	1	2	Unlikely
	FCM-miniR	Infusional reaction		3	2	Almost certainly
	FCM-miniR	Fatigue		2	4	Unlikely
	FCM-miniR	Dry skin/erythema		1	5	Possibly
	FCM-miniR	Thrombocytopenia		3	6	Probably
	FCM-miniR	Lymphopenia		4	6	Probably
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Anaemia		3	6	Probably
	FCM-miniR	Haematuria		1	6	Probably
	FCM-miniR	Fever		1	6	Probably

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	22 August 2011	No		
Possibly	Possibly	Possibly		No		
Almost certainly	Almost certainly	Almost certainly	13 August 2011	Yes	13 August 2011	0
Possibly	Possibly	Possibly	5 September 2011	Yes	5 September 2011	0
Almost certainly	Almost certainly	Almost certainly	26 September 2011	Yes	10 October 2011	14
Unlikely	Unlikely	Unlikely	28 September 2011	Yes	28 September 2011	0
Almost certainly	Almost certainly	Almost certainly	12 October 2011	Yes	12 October 2011	0
Probably	Probably	Unlikely	12 October 2011	Yes	12 October 2011	0
Almost certainly	Almost certainly	Almost certainly	28 September 2011	No		
Almost certainly	Almost certainly	Almost certainly	24 October 2011	No		
Probably	Probably	Probably	31 October 2011	No		
Almost certainly	Almost certainly	Almost certainly	12 November 2011	Yes	13 November 2011	1
Almost certainly	Almost certainly	Almost certainly	12 November 2011	Yes	13 November 2011	1
Possibly	Possibly	Possibly	11 November 2011	Yes	20 November 2011	9
Almost certainly	Almost certainly	Almost certainly		Yes	5 December 2011	
Possibly	Possibly	Unlikely	27 July 2011	Yes	29 July 2011	2
Unlikely	Unlikely	Unlikely	27 July 2011	Yes	27 July 2011	0
Unlikely	Unlikely	Unlikely	24 August 2011	No		
Unlikely	Unlikely	Unlikely		Yes		
Almost certainly	Almost certainly	Almost certainly	8 August 2011	No		
Unlikely	Unlikely	Unlikely		No		
Possibly	Possibly	Unlikely		No		
Probably	Probably	Probably	16 January 2012	No		
Probably	Probably	Probably	8 August 2011	No		
Probably	Probably	Probably	1 January 2012	Yes	16 January 2012	15
Probably	Probably	Probably	1 January 2012	Yes	4 January 2012	3
Probably	Probably	Probably		Yes		
Probably	Probably	Probably	31 December 2011	Yes	1 January 2012	1

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
96	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Fatigue		1	1	Probably
	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Thrombocytopenia		3	1	Almost certainly
	FCM-miniR	Anaemia		2	1	Almost certainly
	FCM-miniR	Diarrhoea		3	2	Almost certainly
97	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Vomiting		2	1	Almost certainly
	FCM-miniR	Diarrhoea		1	1	Almost certainly
	FCM-miniR	Fatigue		2	1	Possibly
	FCM-miniR	Cystitis		2	2	Unlikely
	FCM-miniR	Infections (not neutropenic sepsis)		2	2	Unlikely
	FCM-miniR	Vomiting		1	2	Almost certainly
	FCM-miniR	Nausea		2	2	Almost certainly
	FCM-miniR	Diarrhoea		1	2	Almost certainly
	FCM-miniR	Infusional reaction		2	2	Unrelated
	FCM-miniR	Thrombocytopenia		1	2	Unlikely
	FCM-miniR	Thrombocytopenia		2	3	Possibly
	FCM-miniR	Vomiting		1	3	Probably
	FCM-miniR	Nausea		1	3	Probably
	FCM-miniR	Constipation		1	3	Probably
	FCM-miniR	Constipation		1	3	Probably
	FCM-miniR	Ophthalmic infections		1	3	Unlikely
	FCM-miniR	Fatigue		2	4	Possibly
	FCM-miniR	Constipation		1	4	Probably
	FCM-miniR	Constipation		1	5	Probably
	FCM-miniR	Vomiting		1	5	Probably
	FCM-miniR	Ophthalmic infections		1	5	Unlikely
	FCM-miniR	Constipation		1	6	Probably
99	FCM-miniR	Allergic reaction		3	1	Unrelated
	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Thrombocytopenia		2	1	Almost certainly
	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Neutropenia		1	2	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Possibly	3 August 2011	Yes	12 August 2011	9
Possibly	Possibly	Possibly	18 August 2011	No		
Possibly	Almost certainly	Possibly	25 August 2011	No		
Possibly	Possibly	Possibly	25 August 2011	No		
Almost certainly	Possibly	Possibly	25 August 2011	No		
Almost certainly	Almost certainly	Probably	15 October 2011	No		
Almost certainly	Almost certainly	Unlikely	18 August 2011	Yes	26 August 2011	8
Almost certainly	Almost certainly	Unlikely	18 August 2011	Yes	24 August 2011	6
Possibly	Possibly	Unlikely	18 August 2011	Yes	25 August 2011	7
Possibly	Possibly	Unlikely	18 August 2011	Yes	31 August 2011	13
Unlikely	Unlikely	Unlikely	8 October 2011	Yes	13 October 2011	5
Unlikely	Unlikely	Unlikely	8 October 2011	Yes	13 October 2011	5
Unlikely	Probably	Unlikely	22 September 2011	Yes	26 September 2011	4
Unlikely	Probably	Unlikely	22 September 2011	Yes	26 September 2011	4
Unlikely	Unlikely	Unlikely	25 September 2011	Yes	25 September 2011	0
Unrelated	Unrelated	Almost certainly	20 September 2011	Yes	20 September 2011	0
Unlikely	Unlikely	Unlikely	3 March 2010	No		
Possibly	Possibly	Possibly	17 October 2011	No		
Probably	Probably	Probably	28 October 2011	Yes	30 October 2011	2
Probably	Probably	Probably	27 October 2011	Yes	1 November 2011	5
Probably	Probably	Probably	29 October 2011	Yes	31 October 2011	2
Probably	Probably	Probably	15 November 2011	Yes	17 November 2011	2
Unlikely	Unlikely	Unlikely	10 November 2011	Yes	15 November 2011	5
Possibly	Possibly	Unlikely	10 December 2011	Yes	12 December 2011	2
Probably	Probably	Probably	1 December 2011	Yes	2 December 2011	1
Probably	Probably	Probably	29 January 2012	Yes	31 January 2012	2
Probably	Probably	Probably	26 January 2012	Yes	27 January 2012	1
Unlikely	Unlikely	Unlikely	9 February 2012	Yes	12 February 2012	3
Probably	Probably	Probably	23 February 2012	Yes	24 February 2012	1
Unrelated	Possibly	Probably	10 August 2011	Yes	10 August 2011	0
Almost certainly	Almost certainly	Possibly	10 June 2011	No		
Almost certainly	Almost certainly	Possibly	5 September 2011	No		
Probably	Unlikely	Unlikely	16 September 2011	Yes	19 September 2011	3
Probably	Unlikely	Unlikely	16 September 2011	Yes	19 September 2011	3
Almost certainly	Almost certainly	Possibly	14 September 2011	Yes	12 October 2011	28

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Neutropenia		1	2	Almost certainly
	FCM-miniR	Vomiting		2	3	Almost certainly
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Neutropenia		2	3	Almost certainly
	FCM-miniR	Nausea		1	4	Probably
	FCM-miniR	Fatigue		1	4	Probably
	FCM-miniR	Mucositis/thrush		1	4	Probably
	FCM-miniR	Neutropenia		3	4	Almost certainly
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Vomiting		1	4	Probably
	FCM-miniR	Nausea		2	5	Probably
	FCM-miniR	Vomiting		2	5	Probably
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Dyspnoea		1	5	Almost certainly
	FCM-miniR	Thrombocytopenia		2	5	Almost certainly
	FCM-miniR	Anaemia		2	5	Almost certainly
100	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Nausea		2	3	Unlikely
	FCM-miniR	Back pain		2	3	Unrelated
	FCM-miniR	Fever		1	4	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		2	4	Possibly
103	FCM-miniR	Anorexia/cachexia		1	1	Possibly
	FCM-miniR	Fatigue		1	1	Probably
	FCM-miniR	Anorexia/cachexia		1	1	Possibly
	FCM-miniR	Anaemia		1	2	Probably
	FCM-miniR	Rash/flushing		2	4	Unrelated
	FCM-miniR	Infections (not neutropenic sepsis)		2	6	Possibly
106	FCM-miniR	Neutropenia		3	1	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		1	5	Unlikely
	FCM-miniR	Sore throat		1	6	Unlikely
	FCM-miniR	Neutropenia		3	6	Possibly
	FCM-miniR	Cough		1	6	Unlikely

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Unrelated	5 September 2011	Yes	12 October 2011	37
Almost certainly	Almost certainly	Unlikely	14 October 2011	Yes	17 October 2011	3
Almost certainly	Almost certainly	Unlikely	14 October 2011	Yes	18 October 2011	4
Almost certainly	Almost certainly	Unrelated	7 November 2011	No		
Probably	Probably	Unrelated	10 November 2011	Yes	15 November 2011	5
Probably	Probably	Unrelated	7 December 2011	No		
Probably	Probably	Unrelated	7 December 2011	No		
Almost certainly	Almost certainly	Unrelated	7 December 2011	No		
Almost certainly	Almost certainly	Unrelated	10 September 2011	No		
Probably	Probably	Unrelated	9 November 2011	Yes	13 November 2011	4
Probably	Probably	Unrelated	7 December 2011	Yes	13 December 2011	6
Probably	Probably	Unrelated	7 December 2011	Yes	13 December 2011	6
Almost certainly	Almost certainly	Possibly		No		
Almost certainly	Almost certainly	Possibly		No		
Almost certainly	Almost certainly	Possibly	3 January 2012	No		
Almost certainly	Almost certainly	Possibly	3 January 2012	No		
Probably	Unrelated	Probably	15 September 2011	Yes	19 September 2011	4
Probably	Unrelated	Probably	15 September 2011	Yes	19 September 2011	4
Unlikely	Unlikely	Unlikely	21 October 2011	Yes	10 November 2011	20
Unrelated	Unrelated	Unrelated	5 November 2011	Yes	12 November 2011	7
Possibly	Possibly	Possibly	2 December 2011	Yes	18 December 2011	16
Possibly	Possibly	Possibly	2 December 2011	Yes	18 December 2011	16
Possibly	Possibly	Unlikely	19 September 2011	No		
Probably	Possibly	Unlikely	26 August 2011	Yes	27 August 2011	1
Possibly	Possibly	Unlikely		No		
Probably	Probably	Probably	19 September 2011	Yes	17 October 2011	28
Unrelated	Possibly	Unrelated	4 December 2011	No		
Possibly	Possibly	Possibly	18 January 2012	No		
Possibly	Possibly	Possibly	9 September 2011	Yes	27 September 2011	18
Unlikely	Unlikely	Unlikely	28 January 2012	Yes	7 February 2012	10
Unlikely	Unlikely	Unlikely	12 March 2012	Yes	19 March 2012	7
Possibly	Possibly	Possibly	5 April 2012	Yes	8 May 2012	33
Unlikely	Unlikely	Unlikely	12 March 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
108	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		1	1	Unrelated
	FCM-miniR	Anaemia		1	1	Probably
	FCM-miniR	Nausea		1	2	Possibly
	FCM-miniR	Vomiting		1	2	Possibly
	FCM-miniR	Neutropenia		4	2	Possibly
	FCM-miniR	Neutropenia		2	3	Possibly
	FCM-miniR	Neutropenia		4	4	Possibly
	FCM-miniR	Thrombocytopenia		1	4	Possibly
	FCM-miniR	Thrombocytopenia		1	5	Possibly
	FCM-miniR	Mucositis/thrush		1	6	Probably
	FCM-miniR	Dyspnoea		2	6	Unlikely
109	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Headache		1	2	Unlikely
	FCM-miniR	Rash/flushing		1	2	Possibly
	FCM-miniR	Neutropenia		3	3	Almost certainly
	FCM-miniR	Nausea		2	4	Missing
	FCM-miniR	Vomiting		2	4	Missing
	FCM-miniR	Fatigue		1	5	Missing
	FCM-miniR	Nausea		1	6	Missing
	FCM-miniR	Fatigue		1	6	Missing
113	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Neutropenia		1	2	Almost certainly
	FCM-miniR	Anaemia		1	3	Almost certainly
	FCM-miniR	Mucositis/thrush		2	4	Possibly
	FCM-miniR	Gout/hyperuricemia		3	4	Unlikely
	FCM-miniR	Anaemia		1	4	Almost certainly
	FCM-miniR	Neutropenia		4	4	Almost certainly
	FCM-miniR	Gout/Hyperuricemia		2	5	Possibly
	FCM-miniR	Gout/Hyperuricemia		2	6	Unlikely
114	FCM-miniR	Anaemia		3	1	Possibly
	FCM-miniR	Thrombocytopenia		1	1	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Possibly	Unlikely	24 September 2011	Yes	2 October 2011	8
Unrelated	Unrelated	Unrelated	15 July 2011	Yes	2 October 2011	79
Probably	Possibly	Unrelated	9 September 2011	Yes	16 November 2011	68
Possibly	Possibly	Possibly		Yes	16 November 2011	
Possibly	Possibly	Possibly		Yes	16 November 2011	
Possibly	Possibly	Possibly		No		
Possibly	Possibly	Possibly	21 December 2011	No		
Possibly	Possibly	Possibly	8 January 2012	No		
Possibly	Possibly	Possibly	3 January 2012	Yes	12 January 2012	9
Possibly	Possibly	Possibly	15 February 2012	No		
Probably	Probably	Probably	3 April 2012	Yes	7 May 2012	34
Unlikely	Unlikely	Unlikely	10 April 2012	Yes	17 April 2012	7
Probably	Probably	Unlikely	21 October 2011	Yes	1 December 2011	41
Probably	Probably	Unlikely	21 October 2011	Yes	1 December 2011	41
Unlikely	Unlikely	Unlikely	21 October 2011	Yes	26 November 2011	36
Possibly	Possibly	Possibly	11 November 2011	Yes	12 November 2011	1
Almost certainly	Almost certainly	Possibly	17 November 2011	Yes	21 December 2011	34
Probably	Probably	Unlikely	22 December 2011	Yes	31 December 2011	9
Probably	Probably	Unlikely	22 December 2011	Yes	31 December 2011	9
Probably	Probably	Unlikely		Yes	19 January 2012	
Probably	Probably	Unlikely	18 February 2012	Yes	22 February 2012	4
Probably	Probably	Unlikely	18 February 2012	Yes	23 February 2012	5
Almost certainly	Almost certainly	Possibly	30 November 2011	Yes	5 December 2011	5
Almost certainly	Almost certainly	Possibly	30 November 2011	Yes	5 December 2011	5
Almost certainly	Almost certainly	Possibly	28 December 2011	No		
Almost certainly	Almost certainly	Possibly	28 December 2011	Yes	1 February 2012	35
Possibly	Possibly	Unlikely	18 February 2012	Yes	22 February 2012	4
Unlikely	Unlikely	Unlikely	22 February 2012	Yes	27 February 2012	5
Almost certainly	Almost certainly	Possibly	29 February 2012	No		
Almost certainly	Almost certainly	Possibly	20 February 2012	Yes	29 February 2012	9
Possibly	Possibly	Unlikely	22 March 2012	Yes	28 March 2012	6
Unlikely	Unlikely	Unlikely	21 April 2012	Yes	24 April 2012	3
Possibly	Possibly	Unrelated	5 December 2011	Yes	4 January 2012	30
Possibly	Possibly	Unrelated	5 December 2011	Yes	2 April 2012	119

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
115	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Constipation		1	1	Probably
	FCM-miniR	Fatigue		1	1	Probably
	FCM-miniR	Abdominal pain/ bloating		2	2	Probably
	FCM-miniR	Neutropenia		1	2	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		3	3	Probably
	FCM-miniR	Constipation		1	3	Probably
	FCM-miniR	Diarrhoea		2	3	Possibly
	FCM-miniR	Abdominal pain/ bloating		1	3	Probably
	FCM-miniR	Cystitis		1	3	Unlikely
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		2	4	Possibly
	FCM-miniR	Abnormal electrolytes		2	5	Unlikely
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Abdominal pain/ bloating		2	6	Possibly
	FCM-miniR	Constipation		1	6	Possibly
	FCM-miniR	Anorexia/cachexia		2	6	Possibly
	FCM-miniR	Neutropenia		1	6	Almost certainly
117	FCM-miniR	Anaemia		4	1	Unrelated
	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Thrombocytopenia		1	2	Probably
	FCM-miniR	Nausea		3	5	Almost certainly
	FCM-miniR	Vomiting		3	5	Almost certainly
	FCM-miniR	Neutropenia		4	5	Almost certainly
	FCM-miniR	Thrombocytopenia		1	5	Almost certainly
	FCM-miniR	Anaemia		2	5	Almost certainly
	FCM-miniR	Nausea		1	6	Almost certainly
	FCM-miniR	Neutropenia		3	6	Almost certainly
	FCM-miniR	Thrombocytopenia		2	6	Almost certainly
	FCM-miniR	Anaemia		3	6	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	5 November 2011	Yes	19 November 2011	14
Probably	Probably	Unlikely		Yes		
Probably	Probably	Unlikely		Yes		
Probably	Probably	Unlikely	3 November 2011	Yes	11 November 2011	8
Almost certainly	Almost certainly	Possibly	28 November 2011	Yes	25 January 2012	58
Probably	Probably	Unlikely	30 December 2011	Yes	7 January 2012	8
Probably	Probably	Unlikely	7 January 2012	Yes	10 January 2012	3
Possibly	Probably	Unlikely	11 January 2012	Yes	12 January 2012	1
Probably	Possibly	Unlikely	18 January 2012	No		
Unlikely	Unlikely	Unlikely	18 January 2012	Yes	25 January 2012	7
Almost certainly	Almost certainly	Possibly	28 December 2011	Yes	22 February 2012	56
Possibly	Possibly	Unlikely	26 January 2012	Yes	30 January 2012	4
Unlikely	Unlikely	Unlikely	23 February 2012	Yes	23 February 2012	0
Almost certainly	Almost certainly	Possibly	28 March 2012	No		
Possibly	Possibly	Unlikely	3 April 2012	Yes	8 April 2012	5
Possibly	Possibly	Unlikely	6 April 2012	Yes	10 April 2012	4
Possibly	Possibly	Possibly	3 April 2012	Yes	8 April 2012	5
Almost certainly	Almost certainly	Possibly	27 April 2012	No		
Unrelated	Probably	Unlikely	16 November 2011	No		
Probably	Probably	Unlikely	1 November 2011	No		
Probably	Probably	Unlikely	1 November 2011	Yes	28 December 2011	57
Almost certainly	Almost certainly	Possibly	8 March 2012	Yes	12 March 2012	4
Almost certainly	Almost certainly	Possibly	8 March 2012	Yes	12 March 2012	4
Almost certainly	Almost certainly	Possibly	15 March 2012	No		
Almost certainly	Almost certainly	Possibly	15 March 2012	Yes	28 March 2012	13
Almost certainly	Almost certainly	Possibly	15 March 2012	No		
Almost certainly	Almost certainly	Possibly	8 April 2012	Yes	12 April 2012	4
Almost certainly	Almost certainly	Possibly	11 April 2012	No		
Almost certainly	Almost certainly	Possibly	11 April 2012	No		
Almost certainly	Almost certainly	Possibly	11 April 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
118	FCM-miniR	Fatigue		1	1	Unrelated
	FCM-miniR	Non-specific pain		1	1	Unrelated
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Diarrhoea		1	4	Possibly
	FCM-miniR	Nausea		1	4	Possibly
	FCM-miniR	Fatigue		1	5	Possibly
	FCM-miniR	Nausea		2	5	Possibly
	FCM-miniR	Vomiting		2	5	Possibly
	FCM-miniR	Nausea		2	6	Possibly
	FCM-miniR	Fatigue		1	6	Possibly
119	FCM-miniR	Fatigue		2	1	Unlikely
	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Constipation		1	1	Unlikely
	FCM-miniR	Anaemia		1	1	Unlikely
	FCM-miniR	Thrombocytopenia		1	1	Unlikely
	FCM-miniR	Anaemia		1	2	Probably
	FCM-miniR	Thrombocytopenia		2	2	Unlikely
	FCM-miniR	Non-specific pain		2	2	Unlikely
124	FCM-miniR	Nausea		2	1	Almost certainly
	FCM-miniR	Constipation		1	1	Unlikely
	FCM-miniR	Neutropenia		3	6	Probably
126	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Thrombocytopenia		4	1	Unlikely
	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Neutropenia		4	2	Almost certainly
	FCM-miniR	Neutropenia		1	3	Almost certainly
	FCM-miniR	Anaemia		1	4	Possibly
	FCM-miniR	Neutropenia		3	5	Almost certainly
	FCM-miniR	Neutropenia		1	6	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	Unrelated	3 August 2011	No		
Unrelated	Unrelated	Unrelated		Yes	20 November 2011	
Probably	Probably	Possibly	4 December 2011	Yes	7 December 2011	3
Possibly	Possibly	Unlikely	16 January 2012	Yes	16 January 2012	0
Possibly	Possibly	Unlikely	31 December 2011	Yes	3 January 2012	3
Possibly	Possibly	Possibly	26 January 2012	Yes	31 January 2012	5
Possibly	Possibly	Unlikely	29 January 2012	Yes	2 February 2012	4
Possibly	Possibly	Unlikely	29 January 2012	Yes	2 February 2012	4
Possibly	Possibly	Unlikely	26 February 2012	Yes	2 March 2012	5
Possibly	Possibly	Possibly	26 February 2012	Yes	28 February 2012	2
Almost certainly	Unlikely	Unlikely	11 November 2011	No		
Almost certainly	Almost certainly	Unlikely	2 December 2011	Yes	7 December 2011	5
Unlikely	Unlikely	Unlikely	12 November 2011	Yes	20 November 2011	8
Almost certainly	Unlikely	Unlikely	21 November 2011	No		
Probably	Unlikely	Unlikely	21 November 2011	No		
Almost certainly	Unlikely	Unlikely	9 December 2011	No		
Probably	Unlikely	Unlikely	9 December 2011	No		
Unlikely	Unlikely	Unlikely	1 December 2011	No		
Almost certainly	Unlikely	Unlikely	6 December 2011	Yes	12 December 2011	6
Unlikely	Unlikely	Unlikely	6 December 2011	Yes	15 December 2011	9
Probably	Probably	Unlikely	2 May 2012	Yes	15 May 2012	13
Almost certainly	Almost certainly	Almost certainly	10 January 2012	Yes	11 January 2012	1
Almost certainly	Almost certainly	Almost certainly	10 January 2012	Yes	23 January 2012	13
Unlikely	Unlikely	Unlikely		No		
Almost certainly	Almost certainly	Almost certainly	16 January 2012	Yes	6 February 2012	21
Almost certainly	Almost certainly	Almost certainly	21 February 2012	Yes	29 February 2012	8
Almost certainly	Almost certainly	Almost certainly	14 February 2012	No		
Possibly	Possibly	Possibly		Yes	8 August 2012	
Almost certainly	Almost certainly	Almost certainly	1 May 2012	No		
Almost certainly	Almost certainly	Almost certainly	29 May 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
127	FCM-miniR	Infusional reaction		2	1	Unrelated
	FCM-miniR	Fatigue		2	1	Possibly
	FCM-miniR	Dyspnoea		2	1	Possibly
	FCM-miniR	Other AE description	Pulmonary embolism	3	1	Unlikely
	FCM-miniR	Other AE description	Pleural effusion	3	1	Unlikely
	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Constipation		1	2	Unlikely
	FCM-miniR	Fatigue		2	2	Possibly
	FCM-miniR	Rash/flushing		1	2	Unlikely
	FCM-miniR	Neutropenia		2	2	Almost certainly
	FCM-miniR	Lymphopenia		4	2	Almost certainly
	FCM-miniR	Nausea		1	3	Almost certainly
	FCM-miniR	Vomiting		1	3	Almost certainly
	FCM-miniR	Constipation		1	3	Possibly
	FCM-miniR	Neutropenia		2	3	Almost certainly
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Neutropenia		3	6	Almost certainly
	FCM-miniR	Fatigue		2	6	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		2	6	Probably
128	FCM-miniR	Neutropenia		3	1	Possibly
	FCM-miniR	Thrombocytopenia		1	1	Possibly
	FCM-miniR	Thrombocytopenia		1	3	Possibly
132	FCM-miniR	Rigors		1	1	Unrelated
	FCM-miniR	Constipation		1	1	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		2	3	Unrelated
	FCM-miniR	Neutropenic sepsis		3	4	Almost certainly
	FCM-miniR	Neutropenia		4	4	Probably
	FCM-miniR	Diarrhoea		2	4	Unrelated
	FCM-miniR	Infections (not neutropenic sepsis)		3	4	Probably
	FCM-miniR	Other AE description	Confusion	3	4	Unlikely
	FCM-miniR	Neutropenia		4	4	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	Almost certainly	20 December 2011	Yes	20 December 2011	0
Possibly	Possibly	Unlikely	22 December 2011	Yes	27 December 2011	5
Possibly	Possibly	Unlikely	26 December 2011	Yes	23 February 2012	59
Possibly	Unlikely	Unlikely	3 January 2012	Yes	11 January 2012	8
Possibly	Unlikely	Unlikely	3 January 2012	Yes	23 February 2012	51
Almost certainly	Almost certainly	Unlikely	31 December 2011	Yes	5 January 2012	5
Unlikely	Unlikely	Unlikely	29 January 2012	Yes	31 January 2012	2
Possibly	Possibly	Unlikely	21 January 2012	Yes	2 February 2012	12
Unlikely	Unlikely	Unlikely	30 January 2012	Yes	9 February 2012	10
Almost certainly	Almost certainly	Unlikely	25 January 2012	Yes	23 February 2012	29
Almost certainly	Almost certainly	Almost certainly	25 January 2012	Yes	13 November 2012	293
Almost certainly	Almost certainly	Unlikely	24 February 2012	Yes	1 March 2012	6
Almost certainly	Almost certainly	Unlikely	24 February 2012	Yes	1 March 2012	6
Possibly	Possibly	Unlikely	24 February 2012	Yes	8 March 2012	13
Almost certainly	Almost certainly	Unlikely	22 March 2012	No		
Almost certainly	Almost certainly	Unlikely	26 April 2012	Yes	28 February 2013	308
Almost certainly	Almost certainly	Possibly	24 May 2012	Yes	23 August 2012	91
Possibly	Possibly	Possibly	1 June 2012	Yes	21 June 2012	20
Probably	Probably	Possibly	21 June 2012	Yes	28 February 2013	252
Possibly	Possibly	Possibly	20 January 2012	Yes	30 January 2012	10
Possibly	Possibly	Possibly	11 January 2012	Yes	30 January 2012	19
Possibly	Possibly	Possibly	6 February 2012	Yes	10 April 2012	64
Unrelated	Unrelated	Almost certainly	1 February 2012	Yes	1 February 2012	0
Possibly	Possibly	Unlikely	8 February 2012	Yes	10 February 2012	2
Unrelated	Unrelated	Unrelated	11 April 2012	Yes	13 April 2012	2
Almost certainly	Almost certainly	Unrelated	7 May 2012	Yes	16 May 2012	9
Probably	Probably	Unlikely	8 May 2012	Yes	12 May 2012	4
Unrelated	Unrelated	Unrelated	1 June 2012	Yes	7 June 2012	6
Probably	Probably	Unlikely	8 May 2012	Yes	14 May 2012	6
Unlikely	Unlikely	Unlikely	8 May 2012	Yes	13 May 2012	5
Unlikely	Unlikely	Unlikely	3 June 2012	Yes	20 June 2012	17

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Anaemia		2	5	Probably
	FCM-miniR	Infections (not neutropenic sepsis)		2	6	Possibly
	FCM-miniR	Haematuria		1	6	Possibly
	FCM-miniR	Neutropenia		4	6	Probably
	FCM-miniR	Anaemia		2	6	Probably
	FCM-miniR	Thrombocytopenia		3	6	Probably
133	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Diarrhoea		1	1	Almost certainly
	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		1	1	Almost certainly
	FCM-miniR	Thrombocytopenia		2	2	Almost certainly
	FCM-miniR	Fatigue		1	2	Possibly
	FCM-miniR	Thrombocytopenia		1	3	Almost certainly
	FCM-miniR	Constipation		1	5	Unrelated
	FCM-miniR	Vomiting		1	5	Probably
	FCM-miniR	Neutropenia		1	6	Probably
	FCM-miniR	Anaemia		1	6	Probably
135	FCM-miniR	Nausea		1	1	Probably
	FCM-miniR	Vomiting		1	1	Unlikely
	FCM-miniR	Rash/flushing		1	1	Unrelated
	FCM-miniR	Anaemia		1	1	Possibly
	FCM-miniR	Neutropenia		4	1	Possibly
	FCM-miniR	Thrombocytopenia		3	1	Possibly
	FCM-miniR	Rash/flushing		2	2	Unrelated
	FCM-miniR	Nausea		1	2	Probably
	FCM-miniR	Fatigue		1	2	Possibly
	FCM-miniR	Anaemia		1	2	Possibly
	FCM-miniR	Thrombocytopenia		3	2	Possibly
	FCM-miniR	Neutropenia		4	2	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		2	3	Possibly
	FCM-miniR	Anaemia		1	3	Possibly
	FCM-miniR	Thrombocytopenia		3	3	Possibly
	FCM-miniR	Neutropenia		4	3	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Unrelated	7 June 2012	Yes	18 July 2012	41
Possibly	Possibly	Possibly	29 July 2012	Yes	5 August 2012	7
Possibly	Possibly	Possibly	29 July 2012	No		
Probably	Probably	Unlikely	22 August 2012	No		
Probably	Probably	Unlikely	22 August 2012	No		
Probably	Probably	Unlikely	22 August 2012	No		
Almost certainly	Almost certainly	Unlikely		Yes		
Almost certainly	Almost certainly	Unlikely		Yes		
Almost certainly	Almost certainly	Almost certainly	27 February 2012	Yes	12 March 2012	14
Almost certainly	Almost certainly	Almost certainly	12 March 2012	No		
Almost certainly	Almost certainly	Almost certainly	11 April 2012	No		
Possibly	Possibly	Possibly		Yes		
Almost certainly	Almost certainly	Almost certainly	14 May 2012	No		
Unrelated	Unrelated	Unrelated		Yes		
Probably	Probably	Unrelated	15 June 2012	Yes	15 June 2012	0
Probably	Probably	Unrelated	6 August 2012	No		
Probably	Probably	Unrelated	9 July 2012	No		
Probably	Probably	Unlikely	16 March 2012	Yes	23 March 2012	7
Unlikely	Unlikely	Unlikely	23 March 2012	Yes	23 March 2012	0
Unrelated	Unrelated	Unrelated	5 April 2012	No		
Possibly	Possibly	Unlikely	14 March 2012	No		
Possibly	Possibly	Unlikely	30 March 2012	No		
Possibly	Possibly	Unlikely	23 March 2012	No		
Unrelated	Unrelated	Unrelated	13 April 2012	No		
Probably	Probably	Unlikely	15 April 2012	Yes	18 April 2012	3
Possibly	Possibly	Unlikely	14 April 2012	Yes	26 April 2012	12
Possibly	Possibly	Unlikely	13 April 2012	No		
Possibly	Possibly	Unlikely	26 April 2012	No		
Possibly	Possibly	Unlikely	26 April 2012	No		
Possibly	Possibly	Unlikely	31 May 2012	Yes	4 June 2012	4
Possibly	Possibly	Unlikely	1 June 2012	No		
Possibly	Possibly	Unlikely	17 May 2012	No		
Possibly	Possibly	Unlikely	23 May 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
139	FCM-miniR	Anaemia		3	1	Probably
	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Thrombocytopenia		3	1	Probably
142	FCM-miniR	Neutropenia		4	1	Almost certainly
	FCM-miniR	Anaemia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		2	1	Almost certainly
144	FCM-miniR	Nausea		1	1	Almost certainly
	FCM-miniR	Fatigue		1	1	Almost certainly
	FCM-miniR	Neuropathy (sensory)		1	1	Almost certainly
	FCM-miniR	Back pain		1	1	Unrelated
	FCM-miniR	Nausea		1	2	Almost certainly
	FCM-miniR	Fatigue		1	2	Unlikely
	FCM-miniR	Constipation		1	2	Possibly
	FCM-miniR	Infections (not neutropenic sepsis)		1	2	Unlikely
	FCM-miniR	Neutropenia		1	2	Almost certainly
	FCM-miniR	Nausea		2	3	Almost certainly
	FCM-miniR	Vomiting		2	3	Almost certainly
	FCM-miniR	Mucositis/thrush		1	3	Almost certainly
	FCM-miniR	Neutropenia		3	4	Almost certainly
	FCM-miniR	Anaemia		1	5	Almost certainly
	FCM-miniR	Neutropenia		2	6	Almost certainly
	FCM-miniR	Thrombocytopenia		1	6	Almost certainly
	FCM-miniR	Anaemia		1	6	Almost certainly
	FCM-miniR	Anaemia		2	6	Almost certainly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Probably	Probably	9 May 2012	No		
Probably	Probably	Probably	9 May 2012	Yes	11 July 2012	63
Probably	Probably	Probably	9 May 2012	No		
Almost certainly	Almost certainly	Almost certainly	30 May 2012	Yes	4 June 2012	5
Almost certainly	Almost certainly	Almost certainly	24 May 2012	Yes	30 May 2012	6
Almost certainly	Almost certainly	Almost certainly	24 May 2012	Yes	4 June 2012	11
Almost certainly	Almost certainly	Almost certainly	3 May 2012	Yes	7 May 2012	4
Unlikely	Unlikely	Unlikely	3 May 2012	Yes	10 May 2012	7
Almost certainly	Almost certainly	Almost certainly		No		
Unrelated	Unrelated	Unrelated		Yes		
Almost certainly	Almost certainly	Almost certainly	31 May 2012	No		
Unlikely	Unlikely	Unlikely		No		
Possibly	Possibly	Possibly		Yes		
Unlikely	Unlikely	Unlikely		Yes		
Almost certainly	Almost certainly	Almost certainly	26 June 2012	Yes	17 July 2012	21
Almost certainly	Almost certainly	Almost certainly		No		
Almost certainly	Almost certainly	Almost certainly		Yes	26 July 2012	
Almost certainly	Almost certainly	Almost certainly		No		
Almost certainly	Almost certainly	Almost certainly	17 July 2012	Yes	21 August 2012	35
Almost certainly	Almost certainly	Almost certainly	17 July 2012	Yes	24 July 2012	7
Almost certainly	Almost certainly	Almost certainly	21 August 2012	Yes	23 October 2012	63
Almost certainly	Almost certainly	Almost certainly	29 May 2012	Yes	23 October 2012	147
Almost certainly	Almost certainly	Almost certainly	18 September 2012	Yes	23 October 2012	35
Almost certainly	Almost certainly	Almost certainly	23 October 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
	FCM-miniR	Thrombocytopenia		2	6	Almost certainly
	FCM-miniR	Neutropenia		3	6	Almost certainly
149	FCM-miniR	Nausea		2	1	Probably
	FCM-miniR	Alopecia		2	1	Probably
	FCM-miniR	Diarrhoea		1	1	Probably
	FCM-miniR	Mucositis/thrush		1	1	Possibly
	FCM-miniR	Taste alteration		4	1	Probably
	FCM-miniR	Fatigue		2	1	Probably
	FCM-miniR	Fatigue		2	2	Probably
	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Constipation		2	2	Probably
	FCM-miniR	Diarrhoea		2	2	Probably
	FCM-miniR	Neutropenia		3	2	Unlikely
	FCM-miniR	Non-specific pain		1	2	Unlikely
	FCM-miniR	Neutropenia		3	3	Probably
	FCM-miniR	Nausea		2	3	Probably
150	FCM-miniR	Anaemia		3	2	Possibly
	FCM-miniR	Neutropenia		4	3	Probably
	FCM-miniR	Anaemia		2	3	Probably
	FCM-miniR	Neutropenia		1	4	Probably
	FCM-miniR	Neutropenia		1	5	Probably
	FCM-miniR	Lymphopenia		2	5	Probably
	FCM-miniR	Neutropenia		2	6	Probably
	FCM-miniR	Lymphopenia		3	6	Probably
154	FCM-miniR	Neutropenia		4	1	Probably
	FCM-miniR	Thrombocytopenia		3	1	Probably
	FCM-miniR	Anaemia		2	1	Probably
165	FCM-miniR	Neutropenia		3	1	Almost certainly
	FCM-miniR	Thrombocytopenia		3	1	Possibly
	FCM-miniR	Anaemia		2	2	Unlikely
	FCM-miniR	Raised GGT/bilirubin		1	3	Possibly

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Almost certainly	Almost certainly	23 October 2012	No		
Almost certainly	Almost certainly	Almost certainly	23 October 2012	No		
Probably	Probably	Unrelated	21 May 2012	Yes	28 May 2012	7
Probably	Unlikely	Unlikely	11 June 2012	No		
Unlikely	Possibly	Unlikely	28 May 2012	Yes	12 June 2012	15
Possibly	Probably	Unrelated	28 May 2012	Yes	19 June 2012	22
Probably	Probably	Unlikely	28 May 2012	Yes	28 May 2012	0
Probably	Probably	Unlikely	15 May 2012	No		
Probably	Probably	Unlikely	18 June 2012	No		
Probably	Probably	Unrelated	19 July 2012	No		
Unlikely	Possibly	Unlikely	19 July 2012	No		
Unlikely	Possibly	Unlikely	19 July 2012	Yes	24 July 2012	5
Unlikely	Unlikely	Unlikely	18 June 2012	Yes	16 July 2012	28
Unlikely	Unlikely	Unlikely	18 June 2012	Yes	16 July 2012	28
Probably	Probably	Unlikely	24 August 2012	Yes	3 September 2012	10
Probably	Probably	Unrelated	24 August 2012	Yes	3 September 2012	10
Possibly	Possibly	Possibly	1 June 2012	Yes	3 June 2012	2
Probably	Probably	Probably	25 June 2012	Yes	15 August 2012	51
Probably	Probably	Probably	3 June 2012	Yes	9 July 2012	36
Probably	Probably	Probably	10 October 2012	No		
Probably	Probably	Probably	10 September 2012	No		
Probably	Probably	Probably	10 September 2012	No		
Probably	Probably	Probably	8 October 2012	Yes	14 January 2013	98
Probably	Probably	Probably	5 November 2012	Yes	3 December 2012	28
Probably	Probably	Probably	11 June 2012	No		
Probably	Probably	Probably	11 June 2012	No		
Probably	Probably	Probably	11 June 2012	No		
Almost certainly	Almost certainly	Unlikely	13 July 2012	Yes	2 August 2012	20
Possibly	Possibly	Unlikely	13 July 2012	Yes	23 July 2012	10
Unlikely	Unlikely	Unrelated	13 July 2012	Yes	31 August 2012	49
Possibly	Possibly	Possibly	30 August 2012	No		

continued

TABLE 85 Adverse events in participants receiving FCM-miniR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to fludarabine?
180	FCM-miniR	Constipation		2	1	Almost certainly
	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Vomiting		2	2	Almost certainly
	FCM-miniR	Lymphopenia		3	2	Almost certainly
	FCM-miniR	Urinary symptoms		2	3	Unlikely
	FCM-miniR	Nausea		2	4	Unlikely
	FCM-miniR	Constipation		2	4	Unlikely
	FCM-miniR	Thrombocytopenia		1	4	Almost certainly
	FCM-miniR	Infections (not neutropenic sepsis)		1	5	Probably
	FCM-miniR	Sore throat		1	6	Possibly
	FCM-miniR	Pruritus		1	6	Unrelated
	FCM-miniR	Dry skin/erythema		1	6	Unrelated
	FCM-miniR	Anaemia		1	6	Almost certainly
	FCM-miniR	Thrombocytopenia		1	6	Almost certainly
184	FCM-miniR	Thrombocytopenia		2	1	Almost certainly
	FCM-miniR	Anaemia		1	1	Almost certainly
	FCM-miniR	Nausea		2	1	Probably
	FCM-miniR	Vomiting		1	1	Probably
	FCM-miniR	Fatigue		2	1	Probably
	FCM-miniR	Anaemia		2	2	Almost certainly
	FCM-miniR	Nausea		2	2	Probably
	FCM-miniR	Vomiting		2	2	Probably
	FCM-miniR	Nausea		2	2	Possibly
	FCM-miniR	Vomiting		2	2	Possibly
	FCM-miniR	Other AE description	Small bowel obstruction	3	2	Unrelated
	FCM-miniR	Other AE description	Femoral hernia	3	2	Unrelated

GGT, gamma-glutamyl transpeptidase.
Duration of AE: days from date of onset to date of recovery (if known).

Related to cyclophosphamide?	Related to mitoxantrone?	Related to low-dose rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Almost certainly	Missing	Missing	2 August 2012	Yes	7 August 2012	5
Almost certainly	Missing	Missing	14 August 2012	Yes	19 October 2012	66
Almost certainly	Missing	Missing		Yes		
Almost certainly	Missing	Missing	5 September 2012	No		
Unlikely	Missing	Missing		Yes	15 October 2012	
Probably	Missing	Missing		Yes	23 November 2012	
Unlikely	Missing	Missing		Yes	14 November 2012	
Almost certainly	Missing	Missing	19 October 2012	Yes	14 November 2012	26
Probably	Missing	Missing		Yes	14 December 2012	
Possibly	Missing	Missing		Yes		
Unrelated	Missing	Missing		Yes		
Unrelated	Missing	Missing	11 January 2013	Yes		
Almost certainly	Missing	Missing	22 December 2012	Yes	1 March 2013	69
Almost certainly	Missing	Missing	14 December 2012	Yes	1 March 2013	77
Almost certainly	Almost certainly	Probably	13 September 2012	No		
Almost certainly	Almost certainly	Probably	13 September 2012	No		
Probably	Probably	Probably	23 August 2012	Yes	20 September 2012	28
Probably	Probably	Probably	28 August 2012	Yes	20 September 2012	23
Possibly	Probably	Possibly	23 August 2012	No		
Almost certainly	Almost certainly	Probably	19 October 2012	No		
Probably	Probably	Probably	30 September 2012	Yes	6 October 2012	6
Probably	Probably	Probably	30 September 2012	Yes	6 October 2012	6
Possibly	Possibly	Possibly	13 October 2012	No		
Possibly	Possibly	Possibly	13 October 2012	No		
Unrelated	Unrelated	Unrelated	14 October 2012	No		
Unrelated	Unrelated	Unrelated	14 October 2012	No		

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
145	FCM-miniR/FCR	Constipation		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Fatigue		1	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		4	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		1	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Allergic reaction		3	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nausea		3	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anorexia/cachexia		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		4	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Raised aminotransferases		1	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Cutaneous herpes/ shingles		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		3	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Diarrhoea		2	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Diarrhoea		1	6	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nausea		2	6	Almost certainly	Almost certainly
148	FCM-miniR/FCR	Neutropenic sepsis		4	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		3	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		3	2	Almost certainly	Almost certainly
152	FCM-miniR/FCR	Diarrhoea		1	2	Unrelated	Unrelated
	FCM-miniR/FCR	Neutropenia		4	3	Probably	Probably
	FCM-miniR/FCR	Diarrhoea		1	3	Unrelated	Unrelated
153	FCM-miniR/FCR	Abnormal electrolytes		1	1	Probably	Probably
	FCM-miniR/FCR	Anorexia/cachexia		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nausea		2	4	Unlikely	Unlikely

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	Missing	31 May 2012	Yes		
Almost certainly	Almost certainly	Missing	31 May 2012	Yes	3 June 2012	3
Almost certainly	Almost certainly	Missing	31 May 2012	Yes	12 June 2012	12
Almost certainly	Almost certainly	Missing	31 May 2012	Yes	3 June 2012	3
Almost certainly	Almost certainly	Missing	17 May 2012	Yes	17 May 2012	0
Almost certainly	Almost certainly	Missing	16 June 2012	Yes	21 June 2012	5
Almost certainly	Almost certainly	Missing	17 May 2012	No		
Almost certainly	Almost certainly	Missing	20 June 2012	Yes	28 June 2012	8
Almost certainly	Almost certainly	Missing	28 June 2012	Yes	29 June 2012	1
Almost certainly	Almost certainly	Missing	9 July 2012	Yes	11 July 2012	2
Almost certainly	Almost certainly	Missing	25 June 2012	Yes	30 June 2012	5
Almost certainly	Almost certainly	Missing	22 August 2012	Yes	3 September 2012	12
Almost certainly	Almost certainly	Missing	11 September 2012	Yes	4 October 2012	23
Missing	Missing	Almost certainly	12 October 2012	No		
Missing	Missing	Almost certainly	11 October 2012	Yes	15 October 2012	4
Almost certainly	Possibly	Missing	27 May 2012	Yes	31 May 2012	4
Almost certainly	Unrelated	Missing	28 May 2012	Yes	28 May 2012	0
Almost certainly	Unrelated	Missing	16 June 2012	Yes	16 June 2012	0
Probably	Possibly	Missing	25 July 2012	Yes	7 August 2012	13
Probably	Unlikely	Missing	3 August 2012	Yes	28 August 2012	25
Probably	Possibly	Missing	4 August 2012	Yes	6 August 2012	2
Possibly	Probably	Missing	1 June 2012	Yes	3 June 2012	2
Unrelated	Almost certainly	Missing	2 July 2012	No		
Unrelated	Almost certainly	Missing	25 June 2012	Yes	16 July 2012	21
Possibly	Unlikely	Missing	17 September 2012	No		

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
	FCM-miniR/FCR	Neutropenia		2	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		2	6	Almost certainly	Almost certainly
160	FCM-miniR/FCR	Hypotension		2	1	Unrelated	Unrelated
	FCM-miniR/FCR	Dyspnoea		3	1	Unrelated	Unrelated
	FCM-miniR/FCR	Infections (not neutropenic sepsis)		2	1	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		2	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Abdominal pain/ bloating		2	2	Possibly	Possibly
	FCM-miniR/FCR	Thrombocytopenia		1	2	Almost certainly	Probably
	FCM-miniR/FCR	Nausea		1	3	Probably	Probably
	FCM-miniR/FCR	Nausea		2	4	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		3	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Dyspnoea		1	5	Unrelated	Unrelated
	FCM-miniR/FCR	Anaemia		2	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		1	5	Almost certainly	Probably
	FCM-miniR/FCR	Neutropenia		2	6	Almost certainly	Almost certainly
162	FCM-miniR/FCR	Nausea		1	1	Probably	Probably
	FCM-miniR/FCR	Neutropenia		4	3	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		1	3	Almost certainly	Almost certainly
	FCM-miniR/FCR	Mucositis/thrush		1	3	Almost certainly	Almost certainly
	FCM-miniR/FCR	Rash/flushing		2	3	Unlikely	Unlikely
	FCM-miniR/FCR	Thrombocytopenia		1	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		2	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		3	5	Almost certainly	Almost certainly
164	FCM-miniR/FCR	Fever		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Neutropenia		4	1	Possibly	Possibly
	FCM-miniR/FCR	Vomiting		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Fever		1	1	Unlikely	Unlikely

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Missing	Missing	Almost certainly	15 October 2012	No		
Missing	Missing	Almost certainly	12 November 2012	No		
Unrelated	Almost certainly	Missing	19 June 2012	Yes	19 June 2012	0
Unrelated	Almost certainly	Missing	19 June 2012	Yes	19 June 2012	0
Unrelated	Unrelated	Missing	12 July 2012	Yes	17 July 2012	5
Probably	Probably	Missing	13 July 2012	No		
Possibly	Possibly	Missing	20 August 2012	Yes	24 August 2012	4
Probably	Probably	Missing	20 August 2012	Yes	30 August 2012	10
Probably	Probably	Missing	30 July 2012	No		
Missing	Missing	Unrelated	8 October 2012	Yes		
Missing	Missing	Almost certainly	31 October 2012	No		
Missing	Missing	Possibly	8 November 2012	No		
Missing	Missing	Almost certainly	26 November 2012	No		
Missing	Missing	Unlikely	5 November 2012	Yes	26 November 2012	21
Missing	Missing	Unlikely		Yes	22 March 2013	
Probably	Possibly	Missing	27 June 2012	Yes	30 June 2012	3
Almost certainly	Possibly	Missing	4 July 2012	Yes	15 September 2012	73
Almost certainly	Possibly	Missing	14 August 2012	Yes	5 September 2012	22
Almost certainly	Possibly	Missing	2 August 2012	Yes	20 August 2012	18
Unlikely	Unlikely	Missing	5 September 2012	Yes	12 September 2012	7
Almost certainly	Possibly	Missing	24 September 2012	Yes	24 October 2012	30
Missing	Missing	Possibly	4 October 2012	Yes	1 November 2012	28
Missing	Missing	Possibly	15 November 2012	No		
Probably	Probably	Missing	13 July 2012	Yes	16 July 2012	3
Possibly	Unlikely	Missing	23 July 2012	Yes	14 August 2012	22
Unlikely	Possibly	Missing	13 July 2012	Yes	16 July 2012	3
Probably	Probably	Missing	4 August 2012	Yes	8 August 2012	4

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
	FCM-miniR/FCR	Rash/flushing		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Cough		1	2	Possibly	Possibly
	FCM-miniR/FCR	Vomiting		1	2	Unlikely	Unlikely
	FCM-miniR/FCR	Rash/flushing		1	2	Unlikely	Unlikely
	FCM-miniR/FCR	Fever		1	3	Unlikely	Unlikely
	FCM-miniR/FCR	Nausea		1	3	Possibly	Possibly
	FCM-miniR/FCR	Fatigue		1	3	Possibly	Possibly
	FCM-miniR/FCR	Nausea		2	4	Possibly	Possibly
	FCM-miniR/FCR	Anorexia/cachexia		1	4	Possibly	Possibly
	FCM-miniR/FCR	Fatigue		1	4	Possibly	Possibly
	FCM-miniR/FCR	Nausea		1	5	Possibly	Possibly
	FCM-miniR/FCR	Fatigue		1	5	Possibly	Possibly
	FCM-miniR/FCR	Nausea		1	6	Possibly	Possibly
	FCM-miniR/FCR	Fatigue		1	6	Possibly	Possibly
169	FCM-miniR/FCR	Neutropenia		4	5	Probably	Probably
170	FCM-miniR/FCR	Anaemia		1	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		1	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		2	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Allergic reaction		1	1	Unrelated	Unrelated
	FCM-miniR/FCR	Neutropenia		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		1	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anaemia		1	3	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		3	3	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nausea		1	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Fatigue		1	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Anorexia/cachexia		1	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nausea		1	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Nasal symptoms		1	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Fatigue		1	6	Almost certainly	Almost certainly

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Possibly	Missing	6 August 2012	Yes	14 August 2012	8
Possibly	Unlikely	Missing	10 July 2012	Yes	14 August 2012	35
Unlikely	Possibly	Missing	14 August 2012	Yes	17 August 2012	3
Unlikely	Possibly	Missing	14 August 2012	Yes	21 August 2012	7
Unrelated	Probably	Missing	19 September 2012	Yes	19 September 2012	0
Possibly	Possibly	Missing	18 September 2012	Yes	23 September 2012	5
Unlikely	Unlikely	Missing	18 September 2012	Yes	23 September 2012	5
Missing	Missing	Missing	16 October 2012	Yes	20 October 2012	4
Missing	Missing	Missing	16 October 2012	Yes	20 October 2012	4
Missing	Missing	Missing	16 October 2012	No		
Missing	Missing	Missing	13 November 2012	Yes	20 November 2012	7
Missing	Missing	Missing	13 November 2012	Yes	4 December 2012	21
Missing	Missing	Missing	11 December 2012	Yes	18 December 2012	7
Missing	Missing	Missing	11 December 2012	No		
Missing	Missing	Probably	28 November 2012	Yes	10 December 2012	12
Almost certainly	Almost certainly	Missing	15 August 2012	Yes	28 August 2012	13
Almost certainly	Almost certainly	Missing	13 June 2012	No		
Almost certainly	Almost certainly	Missing	15 August 2012	Yes	28 August 2012	13
Unrelated	Almost certainly	Missing	31 July 2012	Yes	31 July 2012	0
Almost certainly	Almost certainly	Missing	12 September 2012	Yes	24 September 2012	12
Almost certainly	Almost certainly	Missing	12 September 2012	Yes	24 September 2012	12
Almost certainly	Almost certainly	Missing	10 October 2012	Yes	19 October 2012	9
Almost certainly	Almost certainly	Missing	10 October 2012	Yes	19 October 2012	9
Missing	Missing	Almost certainly	23 October 2012	Yes	27 October 2012	4
Missing	Missing	Almost certainly	23 October 2012	Yes	27 October 2012	4
Missing	Missing	Almost certainly	23 October 2012	Yes	23 October 2012	0
Missing	Missing	Almost certainly	24 November 2012	Yes	1 December 2012	7
Missing	Missing	Almost certainly	24 November 2012	Yes	1 December 2012	7
Missing	Missing	Almost certainly	18 December 2012	No		

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
173	FCM-miniR/FCR	Constipation		2	1	Possibly	Unlikely
	FCM-miniR/FCR	Renal impairment		1	1	Probably	Probably
	FCM-miniR/FCR	Anaemia		2	1	Unrelated	Unrelated
	FCM-miniR/FCR	Constipation		2	2	Possibly	Unlikely
176	FCM-miniR/FCR	Neutropenia		4	1	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		2	1	Almost certainly	Probably
	FCM-miniR/FCR	Rash/flushing		2	1	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		3	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Thrombocytopenia		2	2	Almost certainly	Probably
	FCM-miniR/FCR	Infections (not neutropenic sepsis)		2	6	Possibly	Possibly
177	FCM-miniR/FCR	Rash/flushing		2	3	Unrelated	Unrelated
	FCM-miniR/FCR	Fever		2	3	Probably	Probably
	FCM-miniR/FCR	Neutropenia		3	3	Probably	Probably
	FCM-miniR/FCR	Neutropenia		3	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Neutropenia		3	5	Almost certainly	Almost certainly
	FCM-miniR/FCR	Bone pain		1	5	Unrelated	Unrelated
	FCM-miniR/FCR	Neutropenia		4	6	Almost certainly	Almost certainly
183	FCM-miniR/FCR	Nausea		1	1	Probably	Probably
	FCM-miniR/FCR	Vomiting		1	1	Probably	Probably
	FCM-miniR/FCR	Constipation		1	1	Probably	Probably
	FCM-miniR/FCR	Fatigue		1	1	Possibly	Probably
	FCM-miniR/FCR	Taste alteration		1	1	Possibly	Possibly
	FCM-miniR/FCR	Vomiting		1	2	Probably	Probably
	FCM-miniR/FCR	Diarrhoea		1	2	Probably	Probably
	FCM-miniR/FCR	Vomiting		1	3	Probably	Probably
186	FCM-miniR/FCR	Infections (not neutropenic sepsis)		2	1	Unrelated	Unrelated
	FCM-miniR/FCR	Otalgia		3	1	Unrelated	Unrelated
	FCM-miniR/FCR	Nausea		1	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Constipation		1	2	Unlikely	Unlikely
	FCM-miniR/FCR	Pruritus		1	3	Unrelated	Unrelated
	FCM-miniR/FCR	Neutropenia		2	3	Almost certainly	Almost certainly

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unlikely	Unlikely	Missing	14 July 2012	Yes	17 July 2012	3
Probably	Probably	Missing	7 August 2012	Yes	5 September 2012	29
Unrelated	Unrelated	Missing	7 August 2012	Yes	5 September 2012	29
Unlikely	Unlikely	Missing	11 August 2012	Yes	13 August 2012	2
Almost certainly	Probably	Missing	15 August 2012	Yes	3 September 2012	19
Probably	Probably	Missing	15 August 2012	Yes	3 September 2012	19
Possibly	Possibly	Missing	21 August 2012	Yes	29 August 2012	8
Almost certainly	Probably	Missing	3 October 2012	Yes	16 October 2012	13
Probably	Probably	Missing	9 October 2012	Yes	16 October 2012	7
Missing	Missing	Possibly	1 January 2013	Yes	20 January 2013	19
Possibly	Unrelated	Missing	20 August 2012	Yes	31 August 2012	11
Possibly	Probably	Missing	20 August 2012	Yes	31 August 2012	11
Possibly	Probably	Missing	5 September 2012	Yes	19 September 2012	14
Missing	Missing	Almost certainly	16 October 2012	Yes	23 October 2012	7
Missing	Missing	Almost certainly	20 November 2012	Yes	27 November 2012	7
Missing	Missing	Unrelated	27 November 2012	Yes	27 December 2012	30
Missing	Missing	Unlikely	27 December 2012	Yes	3 January 2013	7
Probably	Probably	Missing	8 August 2012	No		
Probably	Probably	Missing	9 August 2012	Yes	9 August 2012	0
Probably	Probably	Missing	8 August 2012	Yes	5 September 2012	28
Probably	Probably	Missing	8 August 2012	No		
Possibly	Probably	Missing	8 August 2012	No		
Probably	Probably	Missing	5 September 2012	Yes	7 September 2012	2
Probably	Probably	Missing	5 September 2012	Yes	10 October 2012	35
Missing	Missing	Probably	3 October 2012	Yes	3 October 2012	0
Unrelated	Unrelated	Missing	6 August 2012	Yes	12 September 2012	37
Unrelated	Unrelated	Missing	15 August 2012	Yes	12 September 2012	28
Almost certainly	Almost certainly	Missing	22 August 2012	Yes	10 October 2012	49
Unrelated	Unlikely	Missing	22 August 2012	No		
Missing	Missing	Almost certainly	10 October 2012	Yes	6 November 2012	27
Missing	Missing	Almost certainly	10 October 2012	Yes	6 November 2012	27

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
188	FCM-miniR/FCR	Nausea		1	1	Probably	Probably
	FCM-miniR/FCR	Vomiting		2	1	Unlikely	Unlikely
	FCM-miniR/FCR	Headache		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Fatigue		2	1	Probably	Unlikely
	FCM-miniR/FCR	Alopecia		1	1	Unlikely	Almost certainly
	FCM-miniR/FCR	Nausea		1	2	Probably	Probably
	FCM-miniR/FCR	Abdominal pain/ bloating		2	2	Unlikely	Unlikely
	FCM-miniR/FCR	Fatigue		2	2	Probably	Unlikely
	FCM-miniR/FCR	Non-specific pain		1	2	Unlikely	Unlikely
	FCM-miniR/FCR	Nausea		1	3	Probably	Probably
	FCM-miniR/FCR	Fatigue		2	3	Probably	Unlikely
	FCM-miniR/FCR	Non-specific pain		1	3	Unlikely	Unlikely
	FCM-miniR/FCR	Abdominal pain/ bloating		2	3	Unlikely	Unlikely
	FCM-miniR/FCR	Nausea		2	4	Probably	Probably
	FCM-miniR/FCR	Non-specific pain		1	4	Unlikely	Unlikely
	FCM-miniR/FCR	Abdominal pain/ bloating		1	4	Unlikely	Unlikely
	FCM-miniR/FCR	Nausea		2	5	Probably	Probably
	FCM-miniR/FCR	Mucositis/thrush		2	5	Probably	Unlikely
189	FCM-miniR/FCR	Vomiting		3	1	Probably	Possibly
	FCM-miniR/FCR	Fatigue		1	1	Possibly	Possibly
	FCM-miniR/FCR	Myalgias		1	1	Possibly	Possibly
	FCM-miniR/FCR	Anaemia		2	1	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		4	1	Probably	Possibly
	FCM-miniR/FCR	Abdominal pain/ bloating		1	2	Possibly	Possibly
	FCM-miniR/FCR	Fatigue		2	4	Probably	Probably
	FCM-miniR/FCR	Arthralgias		1	4	Unlikely	Unlikely
	FCM-miniR/FCR	Neutropenia		1	4	Probably	Probably
	FCM-miniR/FCR	Fatigue		2	5	Probably	Probably
	FCM-miniR/FCR	Arthralgias		1	5	Unlikely	Unlikely
	FCM-miniR/FCR	Neutropenia		3	5	Probably	Probably

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Probably	Possibly	Missing	1 September 2012	Yes	4 September 2012	3
Unlikely	Unlikely	Missing	3 September 2012	Yes	5 September 2012	2
Unlikely	Almost certainly	Missing	30 August 2012	Yes	31 August 2012	1
Probably	Possibly	Missing	4 September 2012	Yes	22 September 2012	18
Unlikely	Probably	Missing	21 September 2012	No		
Probably	Possibly	Missing	27 September 2012	Yes	30 September 2012	3
Possibly	Possibly	Missing	30 September 2012	Yes	6 October 2012	6
Probably	Possibly	Missing	3 October 2012	Yes	11 October 2012	8
Unlikely	Possibly	Missing	13 October 2012	Yes	18 October 2012	5
Missing	Missing	Possibly	26 October 2012	Yes	2 November 2012	7
Missing	Missing	Possibly	27 October 2012	No		
Missing	Missing	Possibly	15 October 2012	Yes	19 October 2012	4
Missing	Missing	Possibly	15 October 2012	Yes	19 October 2012	4
Missing	Missing	Possibly	23 November 2012	Yes	16 December 2012	23
Missing	Missing	Possibly	29 November 2012	Yes	30 November 2012	1
Missing	Missing	Possibly	29 November 2012	Yes	30 November 2012	1
Missing	Missing	Possibly	24 December 2012	Yes	7 January 2013	14
Missing	Missing	Probably	7 January 2013	Yes	11 January 2013	4
Possibly	Unlikely	Missing	10 September 2012	Yes	17 September 2012	7
Possibly	Possibly	Missing	2 October 2012	No		
Possibly	Possibly	Missing	2 October 2012	No		
Possibly	Unlikely	Missing	12 September 2012	No		
Probably	Possibly	Missing	17 September 2012	Yes	2 October 2012	15
Missing	Missing	Possibly	3 October 2012	Yes	23 October 2012	20
Missing	Missing	Unlikely	28 November 2012	Yes	7 December 2012	9
Missing	Missing	Unlikely	5 December 2012	Yes	7 December 2012	2
Missing	Missing	Unlikely	24 December 2012	No		
Missing	Missing	Unlikely	27 January 2013	No		
Missing	Missing	Possibly	27 January 2013	No		
Missing	Missing	Possibly	8 January 2013	Yes	11 January 2013	3

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
	FCM-miniR/FCR	Anaemia		1	5	Probably	Probably
	FCM-miniR/FCR	Neutropenia		2	5	Probably	Probably
	FCM-miniR/FCR	Fatigue		2	6	Probably	Probably
	FCM-miniR/FCR	Arthralgias		1	6	Unlikely	Unlikely
	FCM-miniR/FCR	Headache		1	6	Unlikely	Unlikely
	FCM-miniR/FCR	Thrombocytopenia		1	6	Probably	Probably
	FCM-miniR/FCR	Neutropenia		3	6	Probably	Probably
190	FCM-miniR/FCR	Nausea		1	1	Probably	Probably
	FCM-miniR/FCR	Vomiting		1	1	Probably	Probably
	FCM-miniR/FCR	Neuropathy (sensory)		1	1	Unlikely	Unlikely
	FCM-miniR/FCR	Abdominal pain/ bloating		1	1	Probably	Probably
	FCM-miniR/FCR	Nausea		1	2	Probably	Probably
	FCM-miniR/FCR	Nausea		1	4	Possibly	Almost certainly
	FCM-miniR/FCR	Vomiting		1	6	Possibly	Possibly
196	FCM-miniR/FCR	Fatigue		1	2	Probably	Probably
	FCM-miniR/FCR	Back pain		2	2	Unlikely	Unlikely
	FCM-miniR/FCR	Nausea		2	2	Almost certainly	Almost certainly
	FCM-miniR/FCR	Oedema		1	2	Unlikely	Unlikely
	FCM-miniR/FCR	Bone pain		2	3	Unlikely	Unlikely
	FCM-miniR/FCR	Anorexia/cachexia		1	4	Probably	Probably
	FCM-miniR/FCR	Nausea		2	4	Almost certainly	Almost certainly
	FCM-miniR/FCR	Constipation		1	4	Unrelated	Unrelated
	FCM-miniR/FCR	Back pain		2	4	Unlikely	Unlikely
	FCM-miniR/FCR	Constipation		1	6	Unrelated	Unrelated

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Missing	Missing	Unlikely	13 January 2013	No		
Missing	Missing	Possibly	13 January 2013	Yes	22 January 2013	9
Missing	Missing	Unlikely	24 January 2013	Yes	12 February 2013	19
Missing	Missing	Unlikely		Yes	12 February 2013	
Missing	Missing	Unlikely		Yes	12 February 2013	
Missing	Missing	Unlikely	31 January 2013	Yes	12 February 2013	12
Missing	Missing	Unlikely	31 January 2013	Yes	5 March 2013	33
Probably	Unlikely	Missing	8 September 2012	Yes	9 September 2012	1
Probably	Unlikely	Missing	8 September 2012	Yes	9 September 2012	1
Unlikely	Unlikely	Missing	9 September 2012	Yes	10 September 2012	1
Probably	Unlikely	Missing	9 September 2012	No		
Probably	Unlikely	Missing	5 October 2012	Yes	8 October 2012	3
Missing	Missing	Missing	28 November 2012	Yes	3 December 2012	5
Missing	Missing	Missing	5 February 2013	Yes	7 February 2013	2
Missing	Missing	Unlikely	20 September 2012	No		
Missing	Missing	Unlikely	17 September 2012	No		
Missing	Missing	Unlikely	20 September 2012	Yes		
Missing	Missing	Unlikely	2 October 2012	Yes	5 October 2012	3
Missing	Missing	Unrelated	29 October 2012	No		
Missing	Missing	Unrelated	21 November 2012	No		
Missing	Missing	Unrelated	21 November 2012	No		
Missing	Missing	Unrelated	12 December 2012	Yes	13 December 2012	1
Missing	Missing	Unrelated	29 October 2012	No		
Missing	Missing	Unrelated	7 February 2013	No		

continued

TABLE 86 Adverse events in participants receiving FCM-miniR followed by FCR (*continued*)

Patient number	Treatment received	AE description	Other AE description	Maximum CTCAE grade	Treatment cycle AE started	Related to Fludarabine?	Related to Cyclophosphamide?
197	FCM-miniR/FCR	Fatigue		1	1	Unrelated	Unrelated
	FCM-miniR/FCR	Myalgias		1	1	Unrelated	Unrelated
	FCM-miniR/FCR	Oedema		1	2	Possibly	Possibly
	FCM-miniR/FCR	Insomnia		1	2	Possibly	Possibly
	FCM-miniR/FCR	Anaemia		2	2	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		2	2	Possibly	Possibly
	FCM-miniR/FCR	Abdominal pain/ bloating		1	2	Possibly	Possibly
	FCM-miniR/FCR	Neutropenia		2	3	Probably	Probably
	FCM-miniR/FCR	Lymphopenia		2	3	Probably	Probably
	FCM-miniR/FCR	Dry skin/erythema		1	4	Unlikely	Unlikely
	FCM-miniR/FCR	Non-specific pain		1	4	Unlikely	Unlikely
	FCM-miniR/FCR	Lymphopenia		2	4	Probably	Probably
	FCM-miniR/FCR	Other AE description	Cold hands	1	5	Possibly	Possibly
	FCM-miniR/FCR	Dyspnoea		1	5	Possibly	Possibly
	FCM-miniR/FCR	Infections (not neutropenic sepsis)		1	5	Unlikely	Unlikely
	FCM-miniR/FCR	Other AE description	R pulmonary effusion	1	5	Unlikely	Unlikely
	FCM-miniR/FCR	Rash/flushing		1	6	Possibly	Possibly

Related to Mitoxantrone?	Related to low-dose Rituximab?	Related to Rituximab?	Date of onset	Recovered?	Date of recovery	Duration of AE (days)
Unrelated	Unrelated	Missing	11 September 2012	No		
Unrelated	Unrelated	Missing		Yes	23 October 2012	
Missing	Missing	Possibly	16 October 2012	No		
Missing	Missing	Possibly	2 October 2012	No		
Missing	Missing	Possibly	22 October 2012	No		
Missing	Missing	Possibly	22 October 2012	No		
Missing	Missing	Possibly	24 October 2012	No		
Missing	Missing	Unlikely	19 November 2012	No		
Missing	Missing	Unlikely	19 November 2012	No		
Missing	Missing	Possibly	27 November 2012	No		
Missing	Missing	Unlikely	13 December 2012	Yes		
Missing	Missing	Unlikely	17 December 2012	No		
Missing	Missing	Possibly	17 December 2012	No		
Missing	Missing	Possibly	19 October 2012	Yes	24 January 2013	97
Missing	Missing	Unlikely	26 December 2012	Yes	24 January 2013	29
Missing	Missing	Unlikely	26 December 2012	No		
Missing	Missing	Possibly	6 February 2013	No		

Appendix 3 Baseline patient health economics questionnaire booklet

Baseline

ARCTIC

Patient Health Economics Questionnaire Booklet

For Hospital Use

To be completed at baseline
(Prior to the patient being informed of their randomisation allocation)

Patient initials

Patient date of birth Day Month Year

Hospital name

Today's date Day Month Year

Information

We need to ask you some questions about your general health and your employment. Some questions will seem more relevant to you than others, but please try to answer all the questions. The responses are confidential and will not be seen by the doctors or nurses.

When you have completed the questionnaire booklet, please place it in the envelope provided and return the sealed envelope to the nurse.

Thank you

ARCTIC

Baseline
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

Employment status before diagnosis

This section is about how your diagnosis has affected your work.

1. Please tick one box for the category that describes your employment status in the <u>month before</u> your diagnosis.

Employment status:

- Full time employee (more than 30 hours a week) ☐
- Part time employee (less than 30 hours a week) ☐
- Self-employed ☐
- Full or part time training or education ☐
- Employee on sick leave ☐
- Not in paid employment due to long standing illness or disability ☐
- Retired and not in paid employment ☐

2. Please state approximately how many <u>years</u> had you been in this employment status, before your diagnosis?

Years ☐

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ARCTIC

Baseline
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

General health

3. For each of the five sets of statements below, please tick the one box that best describes your own health state today.

(i) Mobility

I have no problems in walking about..... ☐
I have some problems in walking about ..... ☐
I am confined to bed ..... ☐

(ii) Self-care

I have no problems with self-care..... ☐
I have some problems washing and dressing myself..... ☐
I am unable to wash or dress myself..... ☐

(iii) Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities..... ☐
I have some problems with performing my usual activities.... ☐
I am unable to perform my usual activities..... ☐

(iv) Pain/discomfort

I have no pain or discomfort..... ☐
I have moderate pain or discomfort..... ☐
I have extreme pain or discomfort..... ☐

(v) Anxiety/depression

I am not anxious or depressed..... ☐
I am moderately anxious or depressed..... ☐
I am extremely anxious or depressed..... ☐

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ARCTIC

Baseline
Patient Health Economics Questionnaire Booklet

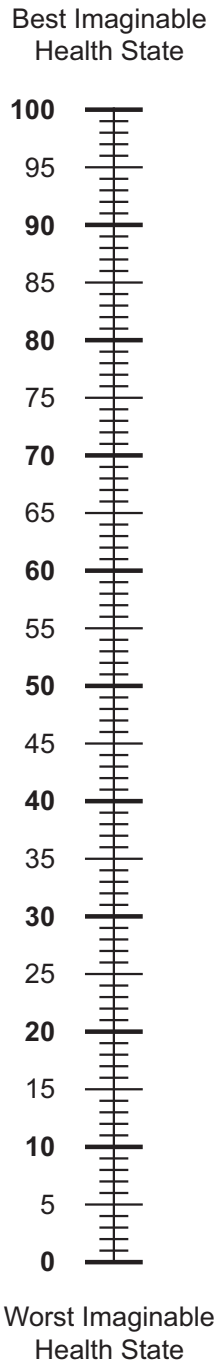
Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(vi) Health State Scale

To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad you think your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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Baseline
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

General health

4. Finally, some questions about your health in general.

(i) In general, how would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

(ii) The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
b Climbing **several** flights of stairs	☐	☐	☐

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ARCTIC

Baseline
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(iii) During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	**Accomplished less** than you would like	☐	☐	☐	☐	☐
b	Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐

(iv) During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	**Accomplished less** than you would like	☐	☐	☐	☐	☐
b	Did work or other activities **less carefully than usual**	☐	☐	☐	☐	☐

(v) During the past **4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

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ARCTIC

Baseline
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(vi) These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b	Did you have a lot of energy?	☐	☐	☐	☐	☐
c	Have you felt downhearted and low?	☐	☐	☐	☐	☐

(vii) During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Thank you for completing this questionnaire.

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Appendix 4 Follow-up patient health economics questionnaire booklet

Follow-up

ARCTIC

Patient Health Economics Questionnaire Booklet

For Hospital Use

To be completed 3 months after the end of therapy and 6, 9, 12, 15, 18, 21 and 24 months post-randomisation.

Patient initials

Patient date of birth Day Month Year

Hospital name

Today's date Day Month Year

Timepoint:

- ☐ 3 months after the end of therapy
- ☐ 6 months post-randomisation
- ☐ 9 months post-randomisation
- ☐ 12 months post-randomisation
- ☐ 15 months post-randomisation
- ☐ 18 months post-randomisation
- ☐ 21 months post-randomisation
- ☐ 24 months post-randomisation

Information

We need to ask you some questions about the health care services you have used and anything you have had to buy because of your diagnosis during the last 3 months. We are doing this to find out the costs of the different approaches to treatment.

Some questions will seem more relevant to you than others, but please try to answer all the questions so that we can compare the costs of the treatments fairly. The responses are confidential and will not be seen by the doctors or nurses.

When you have completed the questionnaire booklet, please place it in the envelope provided and return the sealed envelope to the nurse.

Thank you

ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

Use of health and social services

1. Please record information on the health and social services that you have used during the last 3 months.

Type of service	Which services have you used since during the last 3 months?	Total number of face to face contacts you have had during the last 3 months	Total number of contacts you had by telephone or e-mail during the last 3 months
GP surgery visit	Yes ☐ No ☐		
GP home visit	Yes ☐ No ☐		
District nurse	Yes ☐ No ☐		
Health visitor	Yes ☐ No ☐		
Community-based Occupational Therapist	Yes ☐ No ☐		
Community-based Physiotherapist	Yes ☐ No ☐		
Macmillan social worker	Yes ☐ No ☐		
Palliative care social worker	Yes ☐ No ☐		
Counsellor	Yes ☐ No ☐		
Home help or care worker	Yes ☐ No ☐		
Citizens advice or welfare rights advisor	Yes ☐ No ☐		
Psychiatrist or psychologist	Yes ☐ No ☐		
Food, medicine or laundry delivery service	Yes ☐ No ☐		
Family or patient support or self help groups	Yes ☐ No ☐		
Other services: Please specify in the boxes and for each service also provide the total number of contacts.	1.	1.	1.
	2.	2.	2.
	3.	3.	3.

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

Use of hospital-based care services

2. Please tick the hospital-based care services that you have used during the last 3 months because of your diagnosis. If you have used any of the services then please also provide the hospital name and address and tell us about the number of visits or stays you have had at the hospital.

Type of service	Which services have you used during the last 3 months?	Name and town of hospital	Total number of days' stay during the last 3 months	Total number of visits during the last 3 months
Hospital inpatient stay	Yes ☐ No ☐	Hospital: Town:		
Hospital day centre	Yes ☐ No ☐	Hospital: Town:		
Hospital outpatient clinic	Yes ☐ No ☐	Hospital: Town:		
Hospital accident and emergency department	Yes ☐ No ☐	Hospital: Town:		
Convalescent home	Yes ☐ No ☐			
Nursing home	Yes ☐ No ☐			

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

Travel costs & additional expenses

This section is about expenses which you may have had to meet during the last 3 months because of your diagnosis.

3. During the last 3 months, how much do you think you have spent on travel because of your diagnosis?

If you have not spent anything on travel please tick the box: ☐

Type of service	Your spending on travel during the last 3 months. (Fares for public transport, taxis and car park fees.)	If you have used your own car, approximate number of miles travelled during the last 3 months.
GP, surgery visit	£	
District nurse, health visitor or member of community health team	£	
Social worker	£	
Physiotherapy	£	
Occupational therapy	£	
Counsellor	£	
Citizens advice or welfare rights advisor	£	
Psychiatrist or psychologist	£	
Hospital	£	
Day centre	£	
Lunch or social club	£	
Family or patient support or self help groups	£	
Other (please specify):	£	

For office use only	computerised Date Initials	verified/checked Date Initials

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

4. Have had to meet any major expenses of £50 or more during the last 3 months because of your diagnosis? (Please tick Yes or No.)

Yes ☐ **No** ☐

5. If you have ticked 'Yes' to Question 4, please also describe the expenses that you have had to meet in the table below.

Brief description of item	Cost to you during the last 3 months
	£
	£
	£
	£

6. We are interested in how much you have spent on medicines as a result of your diagnosis. This might be prescribed medicines, over the counter medicines or homeopathic or herbal remedies.

During the last 3 months, what medicines have you used as a result of your diagnosis and what was the cost?

Medicine (Copy name from the bottle/packet)	**Cost to you**

For office use only	computerised Date Initials	verified/checked Date Initials

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

Employment and usual activities

This section is about how your diagnosis has affected your work and usual activities that you do on a regular basis.

7. Please tick the box or boxes for your employment status(es) during the last 3 months. You may tick more than one box, for example you may be in full time employment but have had time off work (sick leave).

Please also tell us which employment status you are currently in.

Employment status	**Which employment status have you been during the last 3 months?**	**Current employment status** *(Please tick one box only)*
Full time employee (more than 30 hours a week)	Yes ☐ No ☐	☐
Part time employee (less than 30 hours a week)	Yes ☐ No ☐	☐
Self-employed	Yes ☐ No ☐	☐
Full or part time training or education	Yes ☐ No ☐	☐
Employee on sick leave	Yes ☐ No ☐	☐
Not in paid employment due to long standing illness or disability	Yes ☐ No ☐	☐
Retired and not in paid employment	Yes ☐ No ☐	☐

8. Have you lost any earnings because of your diagnosis? (Please tick Yes or No.)

Yes ☐ **No** ☐

Please also provide an estimate of your gross amount lost during the last 3 months. (Gross amount refers to money lost before tax and national insurance has been deducted.)

Gross amount lost **£** ☐

For office use only	computerised Date Initials	verified/checked Date Initials

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

This section is about your general health following your diagnosis.

9. For each of the five sets of statements below, please tick the one box that best describes your own health state today.

(i) Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

(ii) Self-care

- I have no problems with self-care ☐
- I have some problems washing and dressing myself ☐
- I am unable to wash or dress myself ☐

(iii) Usual activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

(iv) Pain/discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

(v) Anxiety/depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

For office use only	computerised Date Initials	verified/checked Date Initials

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ARCTIC

Follow-up
Patient Health Economics
Questionnaire Booklet

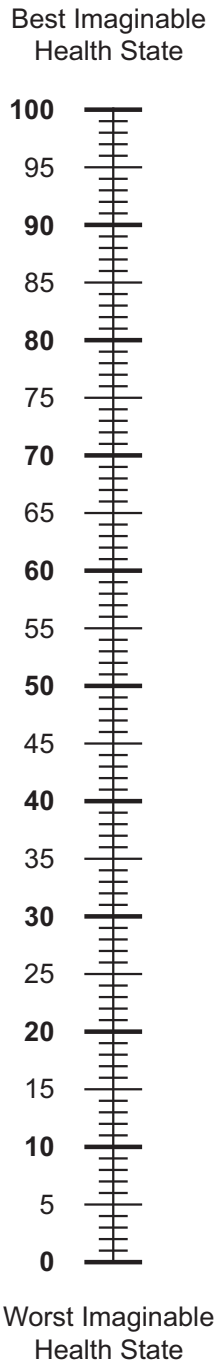
Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(vi) Health State Scale

To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad you think your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



For office use only	computerised Date	Initials	verified/checked Date	Initials

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

General health

10. Finally, some questions about your health in general.

(i) In general, how would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

(ii) The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
b Climbing **several** flights of stairs	☐	☐	☐

For office use only	computerised Date Initials	verified/checked Date Initials

Version 3.0 13/10/2009

ARCTIC

Follow-up
Patient Health Economics
Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(iii) During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	**Accomplished less** than you would like	☐	☐	☐	☐	☐
b	Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐

(iv) During the past **4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	**Accomplished less** than you would like	☐	☐	☐	☐	☐
b	Did work or other activities **less carefully than usual**	☐	☐	☐	☐	☐

(v) During the past **4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

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ARCTIC

Follow-up
Patient Health Economics Questionnaire Booklet

Patient Initials		Date of Birth	Day Month Year	Patient ID	Centre No	Trial No

(vi) These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Have you felt calm and peaceful?	☐	☐	☐	☐	☐
b	Did you have a lot of energy?	☐	☐	☐	☐	☐
c	Have you felt downhearted and low?	☐	☐	☐	☐	☐

(vii) During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Thank you for completing this questionnaire.

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Appendix 5 Participant Information Sheet

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ARCTIC Trial

Attenuated dose Rituximab with ChemoTherapy In CLL:

A randomised, phase IIB trial in previously untreated patients with Chronic Lymphocytic Leukaemia (CLL) to compare fludarabine, cyclophosphamide and rituximab (FCR) with FC, mitoxantrone and low dose rituximab (FCM-miniR)

PATIENT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

A large-print version of this sheet is available on request.

You have been invited to take part in a research study called "ARCTIC". Before you decide whether to accept, we would like to explain why the research is being done and what it will involve. Please read this information carefully, and discuss it with others if you wish. Ask us if anything is unclear, or if you would like more information.

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Take time to decide whether or not you wish to take part.

Thank you for reading this information sheet.

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Part 1

What is the purpose of the study?

You are invited to take part in a research study known as a clinical trial. The study is looking at two combinations of drugs, one called fludarabine, cyclophosphamide and rituximab (FCR for short) and one called fludarabine, cyclophosphamide, mitoxantrone and reduced dose rituximab (FCM-miniR for short). This is a variation on established treatments and we wish to find out if they will be effective in treating patients with chronic lymphocytic leukaemia (CLL) who have not yet received any treatment for their disease and whether or not they cause a better response than other treatments.

A total of 206 patients with CLL will be invited to take part in this study. Half of the patients will be randomly selected (by computer) to receive FCR and the other half will be randomly selected to receive FCM-miniR. You will receive up to 6 cycles of treatment, with each cycle being given every 4 weeks and this is the same for all patients. This means that the total duration of your treatment will be approximately 24 weeks (6 months).

This study is being carried out at approximately 20 hospitals in the UK. It is expected that the study will take approximately 1.5 years to complete.

Why have I been chosen?

You have been invited to participate because you have been diagnosed with CLL which now requires treatment and your doctor believes that treatment with either FCR or FCM-miniR is appropriate at this time.

Do I have to take part?

No, ARCTIC is entirely voluntary. If you decide to take part you will be given this information sheet to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, your specialist will be happy to talk through alternative options with you and your treatment and care will not be affected in any way.

What will happen to me if I take part?

The best way of finding out whether one treatment is as effective as another treatment is in a randomised study. 'Randomised' means that a computer will allocate you randomly (as if by the roll of dice) to receive either FCR or FCM-miniR. Neither your doctor nor you will choose which treatment you receive. In this way, a fair comparison can be made.

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Before going onto the study you will have a number of blood tests, a heart trace (ECG) and a CT scan (a type of X-ray). You will be examined thoroughly by your study doctor. If you are a woman, and capable of having children, a pregnancy test will be done before starting treatment to make sure you are not pregnant. This is to make sure that it is safe for you to receive the drugs in the trial. Only after we have completed all these tests will we be able to confirm that you may go ahead with the study.

Your treatment will be similar to the treatments usually used in CLL. You will receive up to a total of 6 cycles of treatment. Each cycle lasts 5 days and will be repeated every 4 weeks. You will be required to attend the day unit/ward in your hospital on the first day of each cycle of treatment to receive intravenous chemotherapy and the first day of your oral chemotherapy. The remaining 4 days of your oral chemotherapy will be taken at home.

During the study we will also need to take some blood and bone marrow samples at some of your routine visits to the hospital. Most of the blood tests and other investigations, such as bone marrow tests or CT-scans, are routine and would be performed to assess the safety of and response to your treatment whether or not you are taking part in the study; however, you should be aware that the bone marrow test may cause you some discomfort. At the initial visit, prior to commencing the first cycle of therapy, some extra tubes of blood (4 to 10 teaspoonfuls) will be taken to study your CLL in more detail, but this will not require an extra needle puncture. This is part of the study that we hope will allow us to identify which patients will respond the best to the treatments. Similar tests will be performed on samples of your bone marrow taken prior to the first cycle of therapy. In addition, a blood sample will be taken after your third cycle of treatment and blood and bone marrow samples will be taken 3 months after your final cycle of treatment to assess the response of your disease to the treatment. A CT scan will also be performed at this time. You should be aware that by receiving a CT scan you will be exposed to additional radiation although the health risks associated with this are low and are considered to be justified.

We will follow your progress for 2 years and this will involve at least 3 visits after the end of your therapy, usually on a 6 monthly basis. Depending on the results of the previous tests, we may need to take additional blood samples at these visits. If your doctor feels that it is appropriate, and depending upon the response of your disease, you may also need to have another CT scan at these time points. Once you have reached the 2 year post randomisation time point we would then like to follow you annually for the rest of your life in order to assess your long term progress after taking part in the trial.

The study also involves a health economics assessment which will help to find out the costs of the different approaches to treatment. This will involve you completing a questionnaire which

will ask you questions about your health and wellbeing and any health care services you have used. You will be asked to complete this questionnaire during your clinic visits at regular time points during the study.

If you are unable to travel to the hospital at any time during the study you should contact your haematology unit. If you need to see your own GP during the course of the study then he or she will already have been informed of your participation in the study.

What is the standard treatment?

The standard treatment for many patients with CLL who have not received any previous treatment in the United Kingdom is fludarabine, cyclophosphamide and rituximab (FCR).

What are the new treatments?

It is believed that adding mitoxantrone to FCR (FCM-R) may result in an improvement in response rates and that using a reduced dose of rituximab (miniR) may be just as effective as using the full dose. This study will therefore test whether FCM-miniR is as effective as FCR at improving response rates for previously untreated patients with CLL.

How long does treatment go on?

You will receive 6 cycles of treatment with either FCR or FCM-miniR. Each cycle is repeated every 28 days meaning that you can expect to receive treatment for approximately 6 months. If you experience any side effects it may be the case that your doctor wishes to delay some or all of your treatment cycles; side effects, which are common to all chemotherapy treatments, are further discussed later in this information sheet.

Your doctor will assess your progress after you have received 3 cycles of treatment and will make the decision for you to receive the next three cycles. If you are unable to tolerate treatment with FCR or FCM-miniR or are not responding to treatment your doctor may decide to stop your treatment before you have received 6 cycles.

What if the treatment doesn't help?

If your CLL levels start to increase then your doctor may decide to offer you a different treatment; details of this will be discussed with you at that time.

Unwanted effects of treatment

It is important to remember that all drugs have side effects. All chemotherapy can cause nausea, though this is usually well controlled with anti-sickness tablets. Chemotherapy for CLL with FCR and FCM-miniR is frequently associated with effects on the bone marrow. This can show itself in any of the following ways:

- Lower white blood cells which can increase the risk of infection.
- Lower red blood cells (called anaemia) which may give you shortness of breath, weakness and fatigue.
- Lower platelets (blood cells which make your blood clot) which may cause easy bruising or bleeding

In addition the following side effects may also occur:

Fludarabine has very commonly (that is, in over 10% of patients), been associated with increased coughing, vomiting, diarrhoea, fever; feeling tired, weakness, bruising, bleeding and infections (some serious) including infections of the lungs (*pneumonia*) with possible symptoms such as breathing difficulties. Fludarabine has commonly (that is around 10% of patients) been associated pins and needles, disturbed vision, mouth ulcers / sore mouth, skin rash, swelling due to increased fluid retention, chills and loss of appetite leading to weight loss. Cyclophosphamide has commonly (that is, around 10% of patients) been associated with irregular or absent menstrual periods in women, blood in the urine, hair loss (generally reversible), mouth ulcers / sore mouth, abnormal colouring of the skin usually affecting the palms of the hands, soles of the feet or nails, changes to the way food and drink tastes and loss of appetite leading to weight loss.

Cyclophosphamide may reduce the level of normal blood cells and make you more likely to get infections, anaemia or to excessive bleeding. These are monitored by blood tests but if they occur unexpectedly you should contact the hospital immediately. Rarely (less than 5% of patients) patients may become anaemic enough to need a blood transfusion.

Mitoxantrone has commonly (that is, around 10% of patients) been associated with pins and needles, confusion, sleepiness, anxiety, abnormal colouring of the skin usually affecting the palms of the hands, soles of the feet or nails, loosening of nails, sore mouth, skin rash, conjunctivitis (inflammation of the eye), constipation, black stools or blood in your urine or stools, stomach pain, changes to the way food and drink tastes and loss of appetite leading to weight loss

Mitoxantrone has rarely (that is less 5% of patients) been associated with blue/green discolouration to whites of the eyes or urine, hair loss, damage to the muscles of the heart, which may change the rhythm of the heartbeat, but it is unlikely to cause a problem in this study as the total dose of mitoxantrone is smaller than that likely to cause heart problems. Your heart will be monitored before you start the treatment to make sure that you are not at risk of these side effects.

Rituximab infusion can often cause mild and temporary side effects occurring mainly during the first infusion: fever, chills, headache, generally feeling unwell, tiredness, itching, redness of the skin, nausea and a mild drop in blood pressure. Most of these side effects disappear

upon temporary slowing or discontinuation of the infusion, or administration of paracetamol and/or anti-allergic medication. Less than 10% of patients have suffered from severe side effects with the first dose of rituximab including shortness of breath, dizziness and a fall in blood pressure. This has proved fatal in a very small number of cases. You will be monitored very carefully during and after the first dose to ensure that the rituximab may be stopped and appropriate treatment given if such side effects occur. Rituximab is given as a day case by a slow infusion to reduce the risk of reactions. If you are receiving FCR in the trial then the rituximab infusion will take 5 to 6 hours on the first dose and then slightly less on the subsequent courses of treatment. Since a lower dose of rituximab is given in the FCM-miniR patients then the initial infusion should take about 90 minutes and subsequent infusions should be completed in about an hour. Treatment with rituximab has also been associated with an increased risk of developing a viral or bacterial infection. In most cases these infections can be treated very easily but very rarely (that is less than 1% of patients) these may become serious and have occasionally proven fatal.

If you do decide to take part in the study, you must report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

Do I need to make any lifestyle changes?

Your body's ability to fight infections will be lowered while you are on the treatment and for a few months afterwards. There is a slightly increased risk of getting rare and unusual infections while your immunity is lowered. During that period it is advisable to avoid contact with people who have sore throats, colds, flu, diarrhoea and vomiting, or other kinds of infection, such as chickenpox.

If you have pets or work with animals you will need to be extra careful. It is usually safe to pet or stroke animals as long as you wash your hands thoroughly afterwards. It is best to avoid handling any animal waste, such as litter trays or manure, as this can increase your chances of getting an infection.

It is important to avoid places and activities which make you more vulnerable to get infection with fungus like aspergillus. This can grow in dead leaves, grain stores, compost piles or other decaying vegetation. Brick, mortar and cement dust may also contain this fungus. It is preferable to avoid gardening activities like mowing the lawn. Wash your hands well after gardening and other outdoor activities

It is better to avoid any vaccination while you are on the treatment as some of the vaccinations can be harmful and most of them will not mount an adequate immune response while you are on the treatment.

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It is preferable to avoid going abroad due to various reasons like accessibility to healthcare services, the drugs used and their complications may be unfamiliar in certain areas and vaccination if needed.

While you are on the treatment a 'clean' diet is recommended. This means avoiding certain food items like raw or lightly cooked eggs, shellfish, liver pâté, soft cheeses, takeaway food, uncooked salads. All food should be cooked thoroughly and stored in recommended temperature and use by date. It is still important to eat fruits and vegetables and it is recommended to eat those fruits and vegetables which are peelable.

Pregnancy during treatment, information for women and / or men

The effects of the drugs in both arms of the study on the unborn child are unknown. You cannot take part in the study if you are pregnant or breast feeding.

If, as a woman, you are able to become pregnant you **must** use a medically approved form of contraception; an intra-uterine device ('coil'), the contraceptive pill or injection and condoms are considered medically approved forms of contraception. You **must** continue to use a medically approved form of contraception whilst receiving any of the study drugs and for twelve months after you finish your last treatment cycle. Talk to your doctor if you are unsure about any other forms of contraception you may be using.

If, as a man, you are engaging in heterosexual activity with a woman who is able to become pregnant, you **must** use a medically approved form of contraception. You **must** continue using a medically approved form of contraception whilst receiving any of the study drugs and for twelve months after you finish your last treatment cycle.

If you are female and become unexpectedly pregnant you **must** inform your doctor immediately and you will be withdrawn from the study treatment. Other treatment options will be discussed with you at that time. If you are a male and your partner becomes unexpectedly pregnant you **must** also inform your doctor immediately so that your partner's pregnancy can be monitored.

How is my condition monitored?

Your progress will be monitored carefully. Your doctor will perform an examination before you start treatment and then after you have received 3 cycles of treatment. If your doctor is happy that you are tolerating the treatment he/she will then decide that you can receive the next 3 cycles of treatment. If you are not tolerating treatment your doctor may decide that you need to stop receiving further treatment. Your doctor will then assess you at the end of treatment and also 3 months after treatment and then 12 months, 18 months and 24 months after you first agreed to take part in the study. Further long term follow up will be discussed by your doctor at the time.

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As already mentioned you may experience side effects which should be reported to your doctor at each visit.

Please tell us about any problems, as we can often help.

What are the possible disadvantages and risks of taking part?

As already discussed you may experience side effects following treatment with any of the study drugs. You will be monitored regularly whilst receiving study treatment. You will be examined by the study doctors and blood tests will be taken to check for side effects. If you suffer any side effects which you think may be related to the study, please inform the study nurse or doctor as soon as possible.

The effectiveness of the treatments may be different in certain individuals and therefore may have no direct benefit to your disease.

Taking bone marrow samples may cause you some pain or discomfort. If you decide to participate in the study a bone marrow sample will be collected before you receive treatment and 3 months after your treatment has ended. However, you should be aware that a bone marrow sample would also be collected at these time points as part of your standard care if you decide not to participate in the study.

The number of blood samples taken as part of the study is also the same as that taken as part of your routine care.

The additional CT scans will give a radiation dose equivalent to that received from normal background radiation over approximately 15 years. This carries a very small increase in your risk of developing cancer in later years (with a risk of about 1 in 400 of fatal cancer), but a Clinical Radiation Expert has certified that the exposures are justified by the potential benefits of the new treatment to yourself and to future patients.

Being involved in a research study such as a clinical trial involves a degree of commitment such as regular hospital visits and additional tests, as described above. It is not expected that you will need to stay in hospital over night but occasionally this may be necessary to treat any side effects.

What are the possible benefits of taking part?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope that the treatments will help you, but the effectiveness of the treatments may be different in certain individuals and therefore this cannot be guaranteed. The addition of rituximab to chemotherapy appears to add to the effectiveness of treatment in CLL and all patients within this study will receive rituximab as part of their treatment. It is believed that low dose rituximab may be just as effective as full dose rituximab and that it may have fewer side effects than full dose rituximab, but the trial will need to show this. Research studies such as clinical trials are essential for progress in the development of treatments for diseases. Although we cannot guarantee that the treatments will be beneficial to you, the results

obtained from this study will also provide important information which may help people with CLL in the future. Without research such as this, no improvement is possible.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Your doctor will give you further information, if necessary.

What happens when the research study stops?

Should you require further treatment for your disease after you have finished treatment in this study, further treatment options will be discussed with you by your doctor. Whether further treatment is required or not, you will continue to be reviewed on a regular basis as part of the study. We will follow your progress for 2 years after you have finished trial treatment and this will involve at least 3 visits after the end of your therapy, usually on a 6 monthly basis. Once you have reached the 2 year post randomisation time point we would then like to follow you annually for the rest of your life in order to assess your long term progress after taking part in the study.

Additional research

There is also the opportunity to take part in an additional research project called the UK CLL Trials BioBank. This project involves having additional blood samples and a saliva sample taken before you start treatment. If your doctor is able to extract enough bone marrow when a sample is taken before you start treatment and 3 months after treatment has ended, part of the sample will also be sent to the UK CLL Trials BioBank. Another blood sample will also be taken if your disease re-occurs. The samples will be sent to and stored by the UK CLL Trials BioBank at the Royal Liverpool University Hospital, and they will then be will be analysed for things that might be of value in predicting how well individual patients respond to treatment and shed light on possible new treatments. If you wish to take part in the UK CLL Trials BioBank your doctor will provide you with a separate consent form and patient information sheet which are specific to this project. Participation in the additional research is entirely optional, and your decision to participate will not affect your participation in the rest of the study.

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Will my taking part be kept confidential?

If you consent to take part in this study, the records obtained while you are taking part as well as related health records will remain strictly confidential at all times. Please refer to Part 2 of this information sheet which provides further details of confidentiality.

Contact Details

If you have any further questions about your disease or clinical studies, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent cancer information charity (freephone: [redacted]; address: [redacted]; website www.cancerbackup.org.uk) or CancerHelp, an information service about cancer and cancer care for people with cancer and their families by Cancer Research UK (Tel: [redacted]; website www.cancerhelp.org.uk). If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) has published a booklet titled 'Understanding Clinical Trials'. Contact UKCRC: Tel: [redacted]; website www.ukcrc.org

Your contact telephone numbers:

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This completes Part 1 of the Information Sheet. If the Information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a clinical trial or study, new information becomes available or the drugs that are being studied. If this happens, we will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

What will happen if I don't want to carry on with the study?

If you withdraw consent from further study treatment, your data and samples will remain on file and will be included in the final study analysis. In line with Good Clinical Practice guidelines, at

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the end of the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

Who has organised, reviewed and funded the research and who will be supervising it?

The study is being organised by the University of Leeds, who will collect and analyse your data. The study was reviewed and approved by the National Cancer Research Institute CLL Sub-Group Committee, the Leeds East Research Ethics Committee and the Local Research Ethics Committee situated at your hospital.

The study is being funded by the Health Technology Assessment Programme (HTA) which is part of the National Institute for Health Research (NIHR). Part of the funds will be used by the University of Leeds who are organising the study and collecting and analysing your data. Part of the funds will also be used by the Haematological Malignancy Diagnostic Service (HMDS) at St. James's University Hospital who will study the blood and bone marrow samples which you have given.

What if there is a problem?

If a medical emergency related to your treatment for this study occurs while you are at home, you should initially try to contact the haematology unit where you received your treatment <<contact details will be added>>. If this is not possible you should go to the Accident and Emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who, with your consent, will already have been informed of your participation in the study.

Complaints:

If you wish to complain, or have concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Harm:

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

Will my taking part in this study be kept confidential?

If you decide to participate in ARCTIC, the information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, on paper and electronically, at the Clinical Trials Research Unit (CTRU) at the University of Leeds

under the provisions of the 1998 Data Protection Act. The CTRU will hold a copy of the consent form that you sign, which will have your name on it. This information will not be accessed by any other personnel. In addition some of the study information collected, for example the Health Economics Patient Questionnaire Booklets, will be securely stored on paper and electronically at the Academic Unit of Health Economics at the University of Leeds; this information will only be accessible by a member of the research team.

Every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. This information will usually be removed by a member of the study team at your hospital, but may also be removed by the CTRU upon receipt. You will be allocated a study number, which will be used as a code to identify you on all study forms. Only the CTRU and your hospital will be able to identify you from this number.

With your permission, the CTRU may register your details (which will include your full name, date of birth, NHS number and last known address) with the Office of National Statistics, so that if you move away we will be able to find out how you are doing.

With your permission, your relevant medical records may be inspected by authorised individuals from the research team or the University of Leeds (the study Sponsor). They may also be looked at by the regulatory authorities to check that the study is being carried out correctly. In addition, some of your data may be passed to other organisations (possibly in other countries where the data protection standards and laws are different from the UK) to monitor the safety of the treatment(s) that you are receiving. This data will have your name removed so that you cannot be identified from the information.

When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like to obtain a copy of the published results, please ask your doctor.

Involvement of the General Practitioner/Family Doctor (GP):

Your GP, and the other doctors involved in your clinical care, will be notified and kept informed of your participation in ARCTIC, but otherwise all information about you and your treatment will remain confidential.

What will happen to any samples I give?

Researchers at the central laboratories at the Leeds Teaching Hospitals NHS Trust will have access to your blood and bone marrow. The researchers will use the samples to look at a variety of factors in your CLL cells. These factors might have a positive or negative impact on the probability of your CLL responding to treatment. This information will help to identify which factors are important and will help our treatment of future patients with CLL. Although these samples will be analysed for this study, (i.e. research) some of the results may be useful to your doctor for your clinical management.

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The samples will therefore be labelled according to NHS standard practice and will not be made anonymous, so that the results can be fed back to your study doctor. The laboratories will handle your samples with the same duty of confidentiality as they would for any clinical sample. They will be retained at the end of the study as a record of the completed research study in order to verify the research results, if required.

If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained; your data will have your personal details removed, but will be coded so it can be linked back to your details. You will not be identified in the results of future studies. Ethical approval will be obtained for any future studies involving your data or samples.

There is also the opportunity to take part in an additional research project called the UK CLL Trials BioBank. As previously discussed, this project involves having additional blood samples taken along with a saliva sample before you start treatment. If your doctor is able to extract enough bone marrow when a sample is taken, before you start treatment and 3 months after treatment has ended, part of the sample will also be sent to the UK CLL Trials BioBank. In addition, if and when your CLL progresses after therapy then a further blood sample will be taken for the UK CLL Trials BioBank to help investigate why the CLL has returned. The samples will be sent to and stored by the UK CLL Trials BioBank at the Royal Liverpool University Hospital, and they will be analysed for things that might be of value in predicting how well individual patients respond to treatment and shed light on possible new treatments. If you wish to take part in the UK CLL Trials BioBank your doctor will provide you with a separate consent form and patient information sheet which are specific to this project.

Your samples will **not** be used for commercial purposes.

Will any genetic tests be done?

If you decide to take part in the additional UK CLL Trials BioBank project then genetic tests may be performed on your samples.

Certain genetic changes in the CLL cells are important for the development of CLL and also for the likelihood of individual patients responding to treatment. These genetic changes will be analysed in your CLL. In addition it is likely that certain genes may increase the likelihood that an individual will develop CLL and increasing numbers of genes and combinations of certain genes are being identified. These current and new genetic changes will be studied in the samples taken from this study. This work is important to understand that leukaemia develops and progresses because something goes wrong with one or more genes. In order to understand more about CLL and improve its treatment it is therefore necessary to examine leukaemia cells for genetic abnormalities.

In addition, many normal genes can exist in slightly different forms called “polymorphisms”; this is what makes each human being unique. It is important to study gene polymorphisms in CLL as doing so could shed light on why the disease affects some people but not others, why

it behaves differently in different patients, and why treatments work better in some patients than others.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in a medical journal and also on the CancerHelp website. Should you wish to see the results, or the publication, please ask your study doctor. You will not be identified in any report or publication.

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Patient ID:	Initials:
Date of Birth:	Hospital Number:
EudraCT Number:	Version:
Principal Investigator:	

ARCTIC

Attenuated dose Rituximab with ChemoTherapy In CLL:

A randomised, phase IIB trial in previously untreated patients with Chronic Lymphocytic Leukaemia (CLL) to compare fludarabine, cyclophosphamide and rituximab (FCR) with FC, mitoxantrone and low dose rituximab (FCM-miniR)

PATIENT CONSENT FORM

	Patient initial after each question
1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	.....
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.	.....
3. I understand that my medical records may be looked at by authorised individuals from the research team, regulatory bodies or Sponsor in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my medical records for the above study and any further research that may be conducted in relation to it.	.....
4. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the trial, unless I specifically withdraw consent for this. I understand that my identity will remain anonymous outside of the NHS.	.....
5. I agree to allow any information or results arising from this study to be used for healthcare and/or medical research purposes including monitoring the safety of the treatment that I will receive. I understand that my identity will remain anonymous outside of the NHS.	.....
6. I agree for my details (which will include my name, date of birth, NHS number and address) to be registered with the Office of National Statistics (ONS) or traced via the NHS Strategic Tracing Service so that information about my health status may be obtained by the CTRU if necessary.	.....
7. I understand that a copy of this Consent Form will be sent to the CTRU	.....

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8. I agree that my GP, or any other doctor treating me, will be notified of my participation in this study. .....

9. I agree to take part in the study .....

The following points are OPTIONAL.

Even if you agree to take part in this study, you do not have to agree to this section

Please initial after each question

	Yes	No
10. I give permission for surplus specimens from my leukaemia that have been stored in the hospital pathology laboratory to be retrieved and used in the future for CLL cancer research.	☐	☐

Name of patient	Date	Signature

Name of Person taking consent	Date	Signature

(1 copy for patient; 1 for the CTRU; Original stored in Investigator Site File)

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