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Results of the randomized phase IIB ARCTIC trial of low dose Rituximab in previously untreated CLL

Dena R Howard[1*], Talha Munir[2*], Lucy McParland[1], Andy C Rawstron[3], Donald Milligan[4], Anna Schuh[5], Anna Hockaday[1], David J Allsup[6], Scott Marshall[7], Andrew S Duncombe[8], John L O'Dwyer[9], Alison F Smith[9], Roberta Longo[9], Abraham Varghese[2] and Peter Hillmen[10].

* These authors contributed equally to this work.

Affiliations:

[1]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom

[2]Department of Haematology, St. James's University Hospital, Leeds, United Kingdom

[3]Haematological Malignancy Diagnostic Service, St. James's University Hospital, Leeds, United Kingdom

[4]Centre for Haematology and Stem Cell Transplantation, Heartlands Hospital, Birmingham, United Kingdom

[5]Department of Oncology, University of Oxford and Department of Haematology, Oxford University Hospital Trust, Oxford, United Kingdom

[6]Department of Haematology, Hull & East Yorkshire NHS Trust, Hull, United Kingdom and Hull York Medical School, University of Hull, Hull, United Kingdom

[7]City Hospitals Sunderland, Sunderland, United Kingdom

[8]Department of Haematology, University Hospital Southampton, Southampton, United Kingdom

[9]Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, United Kingdom

[10]Section of Experimental Haematology, Leeds Institute of Cancer and Pathology (LICAP), University of Leeds, Leeds, United Kingdom.

Contact details of corresponding author:

Peter Hillmen

Section of Experimental Haematology

Leeds Institute of Cancer and Pathology (LICAP)

University of Leeds, Leeds

United Kingdom

Tel: 0113-343-8604

Fax: 0113-206-8177

peter.hillmen@nhs.net

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ABSTRACT

ARCTIC was a multi-center, randomized-controlled, open, phase IIB non-inferiority trial in previously untreated Chronic Lymphocytic Leukemia (CLL). Conventional frontline therapy in fit patients is fludarabine, cyclophosphamide and rituximab (FCR). The trial hypothesized that including mitoxantrone with low-dose rituximab (FCM-miniR) would be non-inferior to FCR. 200 patients were recruited to assess the primary endpoint of complete remission (CR) rates according to IWCLL criteria. Secondary endpoints were progression-free survival (PFS), overall survival (OS), overall response rate, minimal residual disease (MRD) negativity, safety and cost-effectiveness. The trial closed at the pre-planned interim analysis. At final analysis, CR rates were 76% FCR vs. 55% FCM-miniR [adjusted odds-ratio: 0.37; 95% CI: 0.19-0.73]. MRD-negativity rates were 54% FCR vs. 44% FCM-miniR. More participants experienced Serious Adverse Reactions with FCM-miniR (49%) compared to FCR (41%). There are no significant differences between the treatment groups for PFS and OS. FCM-miniR is not expected to be cost-effective over a lifetime horizon. In summary, FCM-miniR is less well tolerated than FCR with an inferior response and MRD-negativity rate and increased toxicity, and will not be taken forward into a confirmatory trial. The trial demonstrated that oral FCR yields high response rates compared to historical series with intravenous chemotherapy.

INTRODUCTION

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

CLL is still an incurable disease, and most patients will eventually become resistant to treatment. For physically fit patients, the addition of rituximab (MabThera) to fludarabine and cyclophosphamide (FCR) has become the standard of care based on evidence from large randomized controlled trials(1, 2). However, the dose of rituximab has not been established systematically in CLL or in combination with chemotherapy. Rituximab monotherapy at a dose of 375mg/m^2 induced an overall response rate (ORR) of 13% in previously-treated CLL/small lymphocytic lymphoma (SLL)(3, 4). Thrice weekly rituximab (375mg/m^2) and higher weekly doses of rituximab (0.5-2.5g/m^2) in previously untreated patients induced a modest ORR of 43% and 40%, respectively(5-7). The poor response was thought to be due to low CD20 expression on CLL cells and rituximab binding to CD20 positive cellular debris. The loss of CD20 antigen from CLL cells when exposed to rituximab (termed “antigen shaving”) is well described in CLL. Most of the CLL cells were cleared after 30mg of rituximab followed by recrudescence of CLL cells which have lost >90% of CD20 expression. Low-dose rituximab thrice weekly at 20-60mg/m^2 may promote enhanced clearance of CLL cells by preserving CD20 expression(8). Subcutaneous rituximab thrice weekly at a dose of 20mg resulted in reduction of CD20 expression on CLL cells but sufficient expression was maintained during the course of 6-12 weeks in another study(9). Thrice weekly rituximab at 20mg/m^2 in combination with Alemtuzumab and Pentostatin showed

that this dose is able to opsonize and clear the majority of circulating cells, but the loss of CD20 is less pronounced(10). Hence, rituximab at doses of 20mg/m^2 can be effective in CLL.

The combination of mitoxantrone with fludarabine and cyclophosphamide (FCM) is reported in 60 relapsed or resistant patients with CLL(11) to yield a 78% ORR, with 50% of patients achieving a complete remission (CR) and 10 patients Minimal Residual Disease (MRD) negativity. A non-randomized Phase II trial of FCM plus rituximab (FCM-R)(12) reported 82% CRs and 93% ORR in previously untreated CLL, with 46% achieving MRD-negativity. The NCRI randomized Phase II study including FCM and FCM-R in 52 previously-treated CLL patients reported CRs of 65% (FCM-R) versus 58% (FCM), with MRD-negativity in 5 patients (FCM-R) and 3 patients (FCM)(13).

The aim of the ARCTIC (Attenuated dose Rituximab with ChemoTherapy In CLL) trial was to test the hypothesis that a low-dose of rituximab (100mg per cycle) in combination with FCM (FCM-miniR) would be as effective as standard of care (FCR). It is hypothesized that FCM-miniR may result in effective tumor clearance and preservation of CD20 expression on CLL cells.

The cost-effectiveness of delivering FCM-miniR as an alternative to the standard therapy FCR is also critical. Six cycles of rituximab at a dose of 500mg/m^2 are time consuming to give and expensive compared to low doses (100mg per cycle). The non-inferiority design of the trial helps to establish whether lowering the dose of rituximab and hence reducing the cost of treatment impacts on the efficacy in terms of CR rates, as well as the longer-term progression-free survival (PFS) and overall survival (OS) outcomes.

PATIENTS AND METHODS

Trial Design

ARCTIC was a multi-center, randomized, controlled, open-label, phase IIB non-inferiority trial including patients with previously-untreated CLL who required treatment by IWCLL criteria(14). Patients were randomized via a central computer-generated minimization programme incorporating a random element 1:1 to FCR or FCM-miniR. Randomization was stratified to ensure balance for center, Binet Stage (Progressive A or B, C), age group (≤65, 65) and sex.

The primary objective was to assess whether FCM-miniR was non-inferior to FCR in terms of CR rates, including CR with incomplete marrow recovery (CRi), in patients with previously untreated CLL. The results would be used to determine whether FCM-miniR should be taken forward into a larger definitive Phase III trial.

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

The trial was approved by relevant institutional ethical committees and regulatory review bodies. The trial was registered as an International Standard Randomized Controlled Trial (ISRCTN16544962) and on the European Clinical Trials Database (EudraCT: 2009-010998-20).

Patients

The intention was to recruit 206 patients from hospitals around the United Kingdom (UK). Eligible participants had progressive CLL requiring treatment by IWCLL criteria(14); no prior treatment

for CLL; WHO performance status 0-2; Binet Stage progressive A, B or C; and had provided written consent. Patients were not eligible if they had Hepatitis B or C; an active secondary malignancy (excluding basal cell carcinoma of the skin); an active infection or a past history of anaphylaxis following exposure to rat or mouse-derived complementarity determining region (CDR)-grafted humanized monoclonal antibody. Patients with creatinine clearance greater than 30ml/min were allowed to enter the trial with guidance on dose reduction for fludarabine. Patients with a 17p-deletion were eligible for enrollment due to lack of treatment options at the time of designing the trial. Participants were able to withdraw from the trial at any time.

Treatment and Assessments

Treatment with FCR or FCM-miniR was repeated every 28 days for a total of six cycles. Fludarabine and cyclophosphamide were administered orally at doses of 24mg/m^2/day and 150mg/m^2/day respectively for the first five days of each cycle. These doses are pharmacologically equivalent to the doses used when FCR is given intravenously for CLL(15). Full dose rituximab was administered intravenously at 375mg/m^2 on day 1 of cycle 1 and 500mg/m^2 in cycles 2-6. In participants with lymphocyte counts greater than $25x10^9$/L, the dose of rituximab was split to 100mg on day 1 with remaining rituximab given on day 2 to reduce the risk of infusion related reactions. Participants unable to tolerate oral chemotherapy were permitted to receive equivalent intravenous doses of fludarabine (25mg/m^2/day for 3 days) and cyclophosphamide (250mg/m^2/day for 3 days). FCM-miniR included intravenous mitoxantrone (6mg/m^2/day) and 100mg rituximab on day 1 of each cycle. All participants were given allopurinol at least in cycle 1. Prophylaxis for pneumocystis carinii pneumonia (PCP) and aciclovir were given throughout the treatment. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) (lenograstim

263mcg/day; days 7-13) was recommended for scheduled delays of therapy due to neutropenia. Appropriate dose reductions were recommended in participants with therapy-related cytopenias.

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

Endpoints

The primary endpoint was CR rate (including CRi) at 3 months post-treatment. Response was centrally assessed according to the IWCLL criteria(14) by two independent, experienced CLL haematologists blinded to treatment allocation. An independent arbiter reviewed discordant reports.

Secondary endpoints at 3 months post-treatment included MRD negativity, assessed in the bone marrow by highly sensitive multi-parameter flow cytometry with a level of detection below 1 CLL cell in 10 000 leukocytes(16, 17); ORR defined as at least a partial remission (PR); and safety and toxicity as graded by CTCAE V3.0(18).

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

Sample size

Previous studies showed FCR CR rates of at least 50%(19, 20). With 80% power to show non-inferiority, where this is defined as FCM-miniR being not more than 10% worse in terms of CR rates than FCR, an assumed 10% difference in favor of FCM-miniR, a 1-sided significance level

(α) of 2.5%(21) and 80% power, 98 patients were required per group. 206 patients were planned, allowing for 5% dropout.

A formal interim analysis to allow large differences between the treatment groups to be reported early was planned on the short-term efficacy data on half the required participants (n=103). A stringent significance level was required for the interim analysis (0.005, 2-sided) using the O'Brien-Fleming(22) alpha-spending function.

Statistical Methods

All analyses were conducted on the intention-to-treat (ITT) population, in which participants were included according to their randomized treatment. A per-protocol analysis was planned for the primary endpoint, including participants who received at least one cycle of treatment as protocolled and were not major eligibility violators. Safety analyses included participants according to the treatment they actually received.

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

of response or treatment allocation. Sensitivity analyses assessed the robustness of the assumptions regarding missing primary endpoint data.

Binary logistic regression models compared CR rates, proportions with undetectable MRD and ORR between the treatment groups, adjusting for the minimization factors, excluding center. The differences in proportions are reported with 95% confidence intervals (CIs). The lower limit of the CI for the CR rates was compared with the non-inferiority margin of 10%, expressed as an odds ratio (OR).

Kaplan-Meier curves are presented for the PFS and OS endpoints. Cox regression analysis formally compared time to MRD relapse, PFS and OS. Participants without evidence of an event at the time of analysis were censored at the last date they were known to be alive and event-free.

Safety analyses summarized the number of safety events occurring after randomization including treatment-related mortalities and incidence of secondary cancers.

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

An economic evaluation was conducted from a National Health Service (NHS) and Personal Social Services (PSS) perspective, with health benefit measured in Quality-Adjusted Life-Years (QALYs), using patient-reported EQ-5D-3L questionnaires(23). A within-trial analysis compared the outcomes and costs over 24 months using individual patient data from the trial, and a modified Markov model was used to estimate lifetime cost-effectiveness. The model included three health

states: disease free, recurrence and death. Results are reported in 2013 GBP (£), and for information costs are presented in US Dollars ($) using an exchange rate of 1:1.43.

RESULTS

Recruitment and Early Closure

Two-hundred participants were recruited between December 2009 and September 2012 (FCR: 100, FCM-miniR: 100) from 34 UK institutions with local ethical and management approval. At the time of reporting, it has been approximately 6 years since the trial opened to recruitment, with a median follow-up of just over 4 years.

The CONSORT diagram (Figure 1) shows the flow of participants throughout the trial.

The trial closed early in September 2012 following recommendation from the DMC and TSC. At the pre-planned interim analysis on 103 participants, 72 (69.9%) received 6 cycles of treatment [FCR: 38/51 (74.5%), FCM-miniR: 34/52 (65.4%)], and 61 (59.2%) achieved a CR [FCR: 34/51 (66.7%), FCM-miniR: 27/52 (51.9%)]. Of the participants with an assessable response, 61/85 (71.8%) achieved a CR [FCR: 34/41 (82.9%), FCM-miniR: 27/44 (61.4%)], with a difference in response rates (FCM-miniR – FCR) of -21.6% (99.5%CI: -48.0%, 4.8%), adjusted p=0.037. Although not significant at the pre-planned interim level (α=0.005), the results approached significance in favor of FCR. There was also evidence of additional toxicity in the FCM-miniR group with 65.4% (34/52) of participants experiencing a Serious Adverse Event (SAE) compared to 51.0% (26/51) with FCR. The DMC recommended ceasing recruitment immediately; the 23 participants still receiving FCM-miniR were recommended to transfer to FCR for the remainder of their treatment cycles. Twenty-one FCM-miniR participants transferred to receive treatment

with FCR (labelled FCM-miniR/FCR) following discussion with their treating clinician, two participants elected to continue to receive FCM-miniR for their remaining treatment cycles.

Patient Characteristics

Baseline characteristics are displayed in Table 1. The median age was 63 years (range 36–80) with 75 participants (37.5%) aged >65 years. There was a male predominance [135 (67.5%)], and 34 participants (17.0%) were Binet Stage progressive A, 95 (47.5%) stage B and 71 (35.5%) stage C. A majority of participants [116 (58.0%)] were WHO performance status (PS) 0, with 77 (38.5%) PS 1 and 7 (3.5%) PS 2. Overall, 103 participants (51.5%) had B-symptoms, a higher proportion with FCM-miniR [FCR: 46 (46.0%), FCM-miniR: 57 (57.0%)] whilst 115 (57.5%) had a β2-microglobulin concentration of ≥4mg/L, and 31 (15.5%) creatinine clearance levels of 30-60mls/min. Of the evaluable participants, 7/183 (3.8%) had a 17p-deletion [FCR: 4 (4.3%), FCM-miniR: 3 (3.3%)]; 30/188 (16.0%) an 11q-deletion [FCR: 10 (10.8%), FCM-miniR: 20 (21.1%)]. 104/165 participants (63.0%) were considered to be 'poorer risk' [FCR: 52 (63.4%), FCM-miniR: 52 (62.7%)], in terms of V_H mutational status i.e. V_H unmutated or involving the V_H3-21 gene.

Treatment

Of the 200 participants, 141 (70.5%) received 6 cycles of treatment [FCR: 70 (70.0%), FCM-miniR: 51 (64.5%), FCM-miniR/FCR: 20 (95.2%)] and 31 (15.5%) received ≤3 cycles of treatment [FCR: 15 (15.0%), FCM-miniR: 16 (20.3%), FCM-miniR/FCR: 0 (0.0%)] (Table 2). Two FCR participants did not receive any trial treatment, one had received prior therapy for CLL, and the other had a 17p deletion and was withdrawn from the trial, patient and clinician decision (Figure 1). Overall, 59 participants (29.5%) discontinued treatment prematurely [FCR: 30 (30.0%), FCM-miniR: 28 (35.4%), FCM-miniR/FCR: 1 (4.8%)]. Reasons included: toxicity (n=44); progressive

disease (n=3); stable disease with no or minimal response (n=3); ineligibility (n=1), patient decision (n=3); clinician decision (n=4); other (n=1). A total of 94 participants (47.0%) received G-CSF during treatment as recommended in the protocol as secondary prophylaxis, with a higher proportion in the FCM-miniR group [FCR: 42 (42.0%), FCM-miniR: 40 (50.6%)] (Table 2). Thirteen participants unable to tolerate oral chemotherapy received equivalent intravenous doses [FCR: 7 (7.0%), FCM-miniR: 5 (6.3%), FCM-miniR/FCR: 1 (4.8%)].

Efficacy

Of the 200 participants, 124 (62.0%) achieved a CR [FCR: 68 (68.0%), FCM-miniR: 39 (49.4%), FCM-miniR/FCR: 17 (81.0%)]. In the formal analysis of the primary endpoint including imputation based on MRD outcome, 111/167 (66.5%) achieved a CR, [FCR: 70/92 (76.1%), FCM-miniR: 41/75 (54.7%)]. The difference in response rates (FCM-miniR – FCR) was -21.4% in favor of FCR (95%CI: -35.8%, -7.0%). In the logistic regression analysis, the OR for achieving a CR with FCM-miniR compared to FCR was 0.37 (95%CI: 0.19, 0.73) (Table 3). A 10% non-inferiority reduction from the FCR CR rate gives an OR limit of 0.61. Since the lower limit, and in fact the mean of the 95% CI for the treatment effect is less than 0.61, and the upper limit is below 1, there is evidence that FCM-miniR is significantly inferior to FCR. The per-protocol analysis (n=166) concurred with the outcome of the ITT analysis, OR=0.38 (95%CI: 0.19, 0.75). The sensitivity analyses did not alter the findings.

There were no large differences in proportions achieving a CR by sex [Males: 76/117 (65.0%), Females: 35/50 (70.0%)], age group [≤65: 75/106 (70.8%), >65: 36/61 (59.0%)], or Binet stage [A progressive/B: 76/111 (68.5%), C: 35/56 (62.5%)]. A significantly higher proportion of

participants who received >3cycles of treatment achieved a CR [≤3cycles: 7/25 (28.0%), >3cycles: 104/142 (73.2%)], with difference [-45.2% (95%CI: -64.3%, -26.2%)].

All assessable participants with a 17p deletion failed to achieve a CR (n=6). Lower proportions of participants with an 11q deletion and 'poorer risk' V_H mutational status achieved a CR [11qdel: 14/24 (58.3%), no 11qdel: 90/133 (67.7%)], [V_H unmutated or V_H3-21: 54/87 (62.1%), V_H mutated: 36/52 (69.2%)].

Of the 200 participants, 184 (92.0%) achieved at least a PR [FCR: 94 (94.0%), FCM-miniR: 69 (87.3%), FCM-miniR/FCR: 21 (100%)]. Of the assessable participants, the ORR was 92.6% (163/176) with a higher proportion in the FCR group than FCM-miniR [FCR: 94/98 (95.9%), FCM-miniR: 69/78 (88.5%), with a difference (FCM-miniR–FCR) of -7.5% (95%CI: -15.6%, 0.6%). A binary logistic regression analysis was unable to be performed due to the small number of participants in the non-responders group.

Of the 200 participants, 85 (42.5%) achieved MRD negativity assessed in the bone marrow three-months post-therapy [FCR: 45 (45.0%), FCM-miniR: 29 (36.7%), FCM-miniR/FCR: 11 (52.4%)]. In the formal analysis of MRD (excluding FCM-miniR/FCR participants and those with a missing MRD assessment) 74/149 (49.7%) achieved MRD negativity [FCR: 45 (54.2%), FCM-miniR: 29 (43.9%)]. There was a non-significant trend towards FCM-miniR resulting in lower MRD-negativity rates at three months with a difference (FCM-miniR – FCR) of -10.3% (95%CI: -26.3%, 5.8%), adjusted OR: 0.65 (95%CI:0.33, 1.26)] (Table 3).

At the time of analysis (3-years post-randomization of the final participant), 33 (16.5%) participants have died [FCR: 14 (14.0%), FCM-miniR: 18 (22.8%), FCM-miniR/FCR: 1 (4.8%)] and 73 (36.5%) have either progressed or died [FCR: 34 (34.0%), FCM-miniR: 35 (44.3%), FCM-

miniR/FCR: 4 (19.0%)]. Figure 2 presents the PFS and OS Kaplan-Meier curves by treatment group (excluding FCM-miniR/FCR participants). At 36 months post-randomization, the PFS rate is FCR: 75.3% vs. FCM-miniR: 71.3%; with OS rate FCR: 89.1%, FCM-miniR: 84.3%. The hazard ratios (HR) were not significant in the adjusted Cox regression model [PFS: HR=1.29, 95%CI:(0.80, 2.07), p=0.298; OS: HR=1.62, 95%CI:(0.80, 3.28), p=0.178].

Of the 85 participants who were MRD-negative in the bone marrow at three months post-treatment (Table 3), 9 (10.6%) were reported to have relapsed at the MRD level in the peripheral blood or progressed [FCR: 5/45 (11.1%), FCM-miniR: 4/29 (13.8%)] at the end of the planned two-year follow-up. The curves are not presented due to the small number of events.

For the planned subgroup analyses, Kaplan-Meier curves demonstrated an improved PFS in participants who achieved a CR or MRD negativity at 3 months post-treatment (Figure 3). There was a trend towards participants with a V_H mutated gene (and not V_H3-21) i.e. 'standard risk' patients showing an improved PFS over those with 'poor risk' (Figure3). Subgroup analyses for OS show similar trends.

Economic Evaluation

Over the planned 24-month trial period, FCM-miniR produced a mean cost saving of £6 619 [$9 649] (s.d.£1 061 [$1 518]), and QALY loss of -0.059(s.d.0.06) compared to FCR. Assuming that one QALY is valued at £20 000, as per UK standard, FCM-miniR is cost-effective over the trial period, producing a positive incremental net health benefit (+0.27 QALYs; s.d.0.08) due to the short-term cost savings associated with FCM-miniR treatment. However, FCM-miniR is not expected to be cost-effective over a lifetime horizon, with an expected lifetime cost-saving of £7

723 [$11 048] (s.d. £3 281 [$4 694]), and QALY loss of -0.73(s.d.0.42), resulting in an incremental net health loss (QALY: -0.34; s.d.0.40) (Table 4).

Safety and Toxicity

The safety population included 198 participants (Figure 1). 183 SAEs were reported from 104 (52.5%) participants, from a lower proportion receiving FCR (49.0%) compared to FCM-miniR (58.2%). 145 Serious Adverse Reactions (SARs) were reported from 89 (44.9%) participants [FCR: 62 events from 41 (41.0%); FCM-miniR: 67 events from 39 (49.4%); FCM-miniR/FCR: 16 events from 9 (47.4%)]. The most commonly reported SARs, 62.1% of events (n=90), were infections and infestations (Table 5). Ninety-six (48.5%) participants required hospitalization for an SAE with similar proportions in each treatment group (Table 5).

One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported from a participant receiving FCR. A squamous cell carcinoma, two lesions on the lower back and central chest was diagnosed approximately 4 months after the participant received 6 cycles of treatment.

Non-serious adverse events (AE) were reported from 192 (97.0%) participants with similar proportions in each treatment group. Of the 2163 AEs reported, 388 (17.9%) were graded as CTCAE grade 3 or above [FCR: 168 (15.0%); FCM-miniR: 193 (22.4%); FCM-miniR/FCR: 27 (14.8%)] (Table 5).

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

Within 4 years following treatment, 26 participants (13.1%) had been diagnosed with a second cancer [FCR: 13 (13.0%); FCM-miniR: 12 (15.2%); FCM-miniR/FCR: 1 (5.3%)]. The most

commonly reported secondary cancers were non-melanoma skin cancers in 5.1% (n=10) of participants, followed by hematological cancers (AML/MDS) in 3.0% of participants (n=6) (Table 5).

DISCUSSION

Participants randomised to FCM-miniR had a significantly lower CR rate than those randomised to FCR (54.7% vs. 76.1%), indicating that FCR is the more effective treatment. This seems, at least in part, due to the higher toxicity associated with the addition of mitoxantrone to FCR with 41.1% of participants receiving FCR reporting a SAR compared with 49.4% receiving FCM-miniR. Key secondary endpoints were consistent in demonstrating that FCR has greater efficacy, with a higher proportion of participants achieving MRD negativity (FCR: 54.2%, FCM-miniR: 43.9%). Trial follow-up is still relatively immature (median 4 years), and there are a high number of censored observations, but to date the PFS and OS are favorable compared to previous studies. There are no significant differences between the treatment groups for PFS and OS.

The cost-effectiveness analysis indicates that whilst 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, although there is significant uncertainty around the long-term results.

The design of this trial and its companion trial, ADMIRE comparing FCR with FCM-R (reported in the companion paper), were based on several non-randomised Phase II trials suggesting that the addition of mitoxantrone to FCR improved outcomes in CLL. The lower dose of rituximab was based on pre-clinical and biological responses seen in small studies examining the impact of lower doses of rituximab as a single agent in CLL. Both trials failed to demonstrate the expected

improvement in outcome for the proposed interventions. The use of randomised Phase II trials allows a more critical assessment of the value of any proposed changes to treatment giving a more robust assessment prior to launching prolonged and expensive Phase III trials. Given the rapidly changing therapy in diseases such as CLL, the use of randomised Phase II trials either as stand-alone trials or as part of seamless Phase II/III designs is an efficient way to prioritise appropriate Phase III trial design and is highly recommended compared to large non-comparative Phase II trials that are commonly performed.

In addition the outcomes for both the ARCTIC and ADMIRE trials are consistent with each other and demonstrate that the delivery of fludarabine and cyclophosphamide by the oral route in FCR is at least as effective as, and possibly more effective than, FCR when the chemotherapy component is given intravenously. Oral FCR is also much more convenient for patients and results in less use of valuable medical resources as patients only require a single day case visit per cycle of treatment rather than three that is required if FCR is given intravenously.

In summary, we demonstrate that FCM-miniR is not non-inferior to FCR in terms of the primary endpoint of CR at 3-months post-treatment. In addition, FCM-miniR shows evidence of reduced efficacy in terms of MRD and survival, had increased toxicity, and is not cost-effective longer 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 and MRD negativity rates compared to historical series in which the chemotherapy was given intravenously, and remains the gold-standard therapy for CLL in participants considered fit for fludarabine-based therapy. We also demonstrate the value of randomised Phase II trials to improve the quality of future Phase III trials.

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CONFLICT OF INTEREST

Prof. Hillmen received research funding and speakers' fees from Roche Pharmaceuticals. Dr. Rawstron reports personal fees from Roche Pharmaceuticals. Dr. Munir reports personal fees from Roche Pharmaceuticals.

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

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FIGURE LEGENDS

Figure 1: CONSORT Diagram

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

a. Progression-Free Survival by treatment group

b. Overall Survival by treatment group

Figure 3: Progression-Free Survival Subgroup Analyses

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

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

c. PFS by V_H mutational risk status

Table 1 Baseline Characteristics

Table 2 Treatment Summaries

Table 3 Efficacy Summaries

Table 4 Cost-Effectiveness Results (NHS and PSS perspective)

Table 5 Safety and Toxicity Summaries

501 **FIGURES AND TABLES**

502 **Figure 1 CONSORT Diagram**

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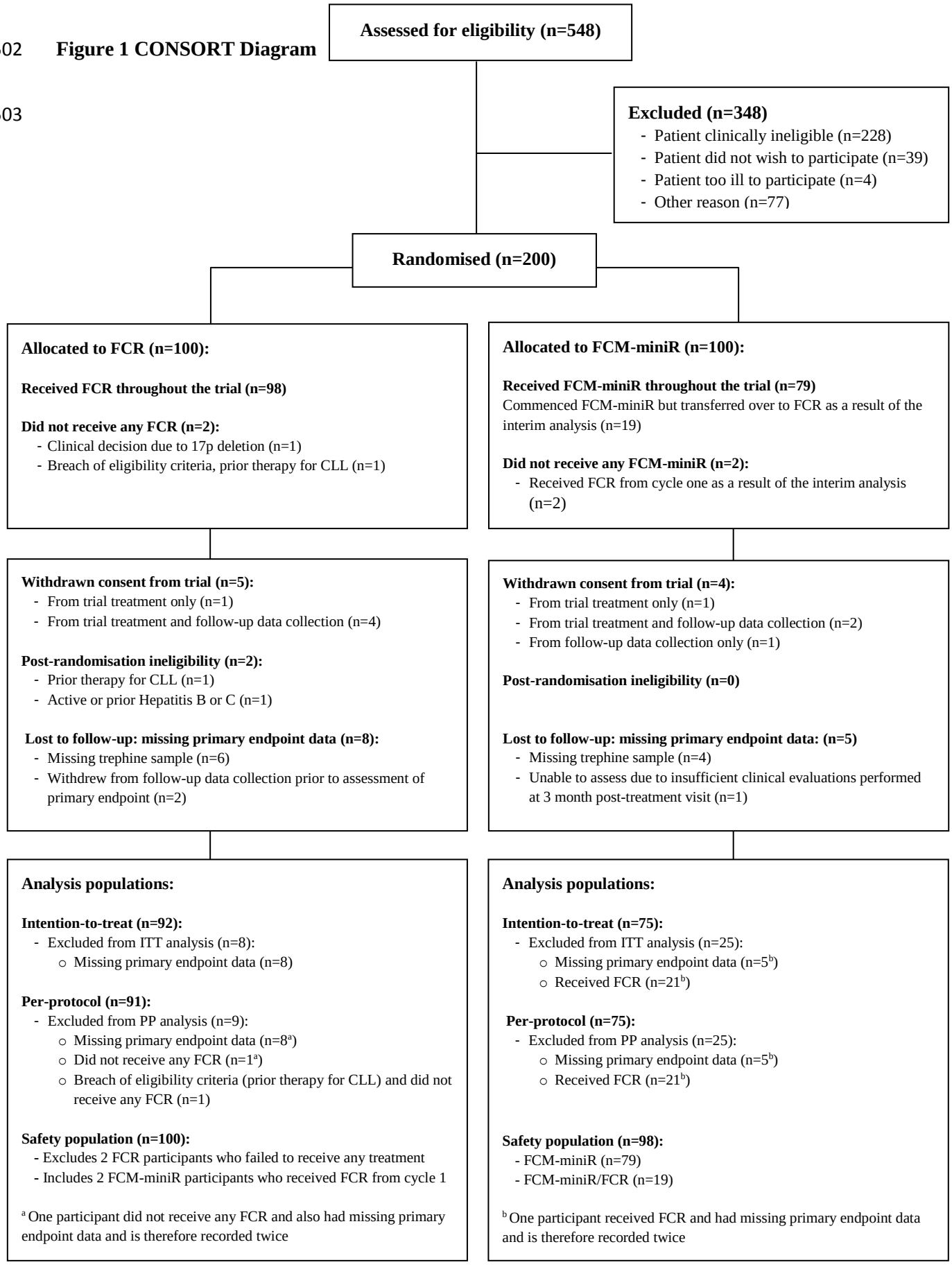

504 **Table 1 Baseline Characteristics**

	FCR (n=100)	FCM-miniR (n=100)	Total (n=200)
Age (at randomization)			
≤65	63 (63.0%)	62 (62.0%)	125 (62.5%)
>65	37 (37.0%)	38 (38.0%)	75 (37.5%)
Mean (s.d.)	61.8 (8.3)	62.6 (8.3)	62.2 (8.3)
Median (range)	63 (41, 77)	63 (36, 80)	63 (36, 80)
Sex			
Male	68 (68.0%)	67 (67.0%)	135 (67.5%)
Female	32 (32.0%)	33 (33.0%)	65 (32.5%)
Binet Stage			
Progressive A	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			
Yes	46 (46.0%)	57 (57.0%)	103 (51.5%)
No	54 (54.0%)	43 (43.0%)	97 (48.5%)
WHO performance status			
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%)
Beta-2 microglobulin concentration (mg/L)			
<4 mg/L	37 (37.0%)	35 (35.0%)	72 (36.0%)
≥4 mg/L	53 (53.0%)	62 (62.0%)	115 (57.5%)
Missing	10 (10.0%)	3 (3.0%)	13 (6.5%)
Creatinine clearance (mls/min)			
30-60mls/min	17 (17.0%)	14 (14.0%)	31 (15.5%)
>60mls/min	83 (83.0%)	86 (86.0%)	169 (84.5%)
17p deletion			
Yes (poorer risk)	4 (4.0%)	3 (3.0%)	7 (3.5%)

	FCR (n=100)	FCM-miniR (n=100)	Total (n=200)
No (standard risk)	88 (88.0%)	88 (88.0%)	176 (88.0%)
Missing	8 (8.0%)	9 (9.0%)	17 (8.5%)
11q deletion			
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%)
V_H mutational risk status			
V_H unmutated or V_H3-21 (poorer risk)	52 (52.0%)	52 (52.0%)	104 (52.0%)
V_H mutated and not V_H3-21 (standard risk)	30 (30.0%)	31 (31.0%)	61 (30.5%)
Missing	18 (18.0%)	17 (17.0%)	35 (17.5%)

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Table 2 Treatment Summaries

	FCR (n=100)	FCM-miniR (n=79)	FCM-miniR/FCR (n=21)	Total (n=200)
Discontinued treatment prematurely (received <6 cycles)?				
Yes	30 (30.0%)	28 (35.4%)	1 (4.8%)	59 (29.5%)
No	70 (70.0%)	51 (64.5%)	20 (95.2%)	141 (70.5%)
Treatment cycles received				
≤ 3 cycles	15 (15.0%)	16 (20.3%)	0 (0.0%)	31 (15.5%)
> 3 cycles	85 (85.0%)	63 (79.7%)	21 (100.0%)	169 (84.5%)
Received G-CSF during treatment (cycles 2 - 6)?				
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%)

G-CSF: Granulocyte-colony stimulating factor was given if there was significant neutropenia on a previous cycle of treatment

533 **Table 3 Efficacy Summaries**

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MRD NEGATIVITY				
MRD status	**FCR (n=100)**	**FCM-miniR (n=79)**	**FCM-miniR/FCR (n=21)**	**Total (n=200)**
MRD negative	45 (45.0%)	29 (36.7%)	11 (52.4%)	85 (42.5%)
MRD positive	38 (38.0%)	37 (46.8%)	9 (42.9%)	84 (42.0%)
Missing	17 (17.0%)	13 (16.5%)	1 (4.8%)	31 (15.5%)
MRD status	**FCR (n=83)**	**FCM-miniR (n=66)**	**Total (n=149)**	**Difference in MRD-negative rates & 95% CIs (FCM-miniR - FCR)**
MRD negative	45 (54.2%)	29 (43.9%)	74 (49.7%)	-10.3% (-26.3%, 5.8%)
MRD positive	38 (45.8%)	37 (56.1%)	75 (50.3%)	
Logistic regression analysis for the % of participants achieving MRD-negativity				
Parameter*	**Parameter estimate**	**SE**	**OR**	**95% CIs for OR**
FCM-miniR vs. FCR	-0.44	0.34	0.65	(0.33, 1.26)
COMPLETE RESPONSE				
CR status (prior to imputation using MRD)	**FCR (n=100)**	**FCM-miniR (n=79)**	**FCM-miniR/FCR (n=21)**	**Total (n=200)**
Achieved a CR	68 (68.0%)	39 (49.4%)	17 (81.0%)	124 (62.0%)
Did not achieve a CR	18 (18.0%)	28 (35.4%)	3 (14.3%)	49 (24.5%)
Missing	14 (14.0%)	12 (15.2%)	1 (4.8%)	27 (13.5%)
CR status (post imputation using MRD)	**FCR (n=100)**	**FCM-miniR (n=79)**	**FCM-miniR/FCR (n=21)**	**Total (n=200)**
Achieved a CR	70 (70.0%)	41 (51.9%)	17 (81.0%)	128 (64.0%)
Did not achieve a CR	22 (22.0%)	34 (43.0%)	3 (14.3%)	59 (29.5%)
Missing	8 (8.0%)	4 (5.1%)	1 (4.8%)	13 (6.5%)
CR status (post imputation using MRD)	**FCR (n=92)**	**FCM-miniR (n=75)**	**Total (n=167)**	**Difference in CR rates & 95% CIs (FCM-miniR - FCR)**
Achieved a CR	70 (76.1%)	41 (54.7%)	111 (66.5%)	-21.4% (-35.8%, -7.0%)

Did not achieve a CR	22 (23.9%)	34 (45.3%)	56 (33.5%)	
PRIMARY ENDPOINT ANALYSIS Logistic regression analysis for the % of participants achieving a CR				
Parameter*	**Parameter estimate**	**SE**	**OR**	**95% CIs for OR**
FCM-miniR vs. FCR	-0.98	0.34	0.37	(0.19, 0.73)

CR: Complete remission (CR/CRi)

MRD: Minimal Residual Disease

SE: Standard error

OR: Odds ratio

*Adjusted estimate of the treatment effect from the multivariable logistic regression model, adjusted for the minimization factors

Table 4 Cost-Effectiveness Results (NHS and PSS perspective)

Strategy	Total Cost (sd)	Total QALY (sd)	Inc. Cost (sd)	Inc. QALY (sd)	ICER	INB (QALYs) (sd)
Within-trial analysis (24-month horizon)*						
FCR	£17 241 (745)	1.610 (0.04)				
FCM- miniR	£10 622 (758)	1.551 (0.05)	**-£6 619** (1,061)	**-0.059** (0.06)	**£112 193****	**0.27** (0.08)
Decision model analysis (Lifetime horizon)*						
FCR	£31 314 (7 237)	7.76 (0.26)				
FCM- miniR	£23 590 (6 997)	7.04 (0.36)	**-£7 723** (3 281)	**-0.73** (0.42)	**£10 651****	**-0.34** (0.40)

*For the cost in dollars ($), use an exchange rate of 1:1.43

**Pounds saved per QALY lost

NHS: National Health Service

PSS: Personal and Social Services

QALY: Quality-Adjusted Life-Years

ICER: Incremental Cost-Effectiveness Ratio

INB: Incremental Net Benefit

566 **Table 5 Safety and Toxicity Summaries**

	FCR (n=100)	FCM-miniR (n=79)	FCM-miniR/FCR (n=19)	Total (n=198)
Serious Adverse Events (SAEs)				
Number of participants experiencing an SAE	49 (49.0%)	46 (58.2%)	9 (47.4%)	104 (52.5%)
Total number of SAEs reported	80	81	22	183
Number of participants requiring hospitalization for an SAE	46 (46.0%)	41 (51.9%)	9 (47.4%)	96 (48.5%)
Serious Adverse Reactions (SARs)				
Number of participants experiencing a SAR	41 (41.0%)	39 (49.4%)	9 (47.4%)	89 (44.9%)
Total number of SARs reported	62	67	16	145
SARs by MedDRA System Organ Class*				
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%)

	FCR (n=100)	FCM-miniR (n=79)	FCM-miniR/FCR (n=19)	Total (n=198)
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%)
Adverse Events (AEs)				
Number of participants experiencing an AE	96 (96.0%)	77 (97.5%)	19 (100%)	192 (97.0%)
Total number of AEs reported	1117	863	183	2163
CTCAE grade				
<3	943 (84.4%)	667 (77.3%)	156 (85.2%)	1766 (81.6%)
≥3	168 (15.0%)	193 (22.4%)	27 (14.8%)	388 (17.9%)
Missing	6 (0.5%)	3 (0.3%)	0 (0.0%)	9 (0.4%)
Secondary Cancers				
Number of participants reporting each secondary cancer				
Hematological (Lymphoma)	2 (2.0%)	2 (2.5%)	0 (0.0%)	4 (2.0%)

	FCR (n=100)	FCM-miniR (n=79)	FCM-miniR/FCR (n=19)	Total (n=198)
Hematological (AML/MDS)	3 (3.0%)	3 (3.8%)	0 (0.0%)	6 (3.0%)
Skin (Non-melanoma)	4 (4.0%)	5 (6.3%)	1 (5.3%)	10 (5.1%)
Skin (Melanoma)	2 (2.0%)	1 (1.3%)	0 (0.0%)	3 (1.5%)
Non-hematological (Solid tumors)	4 (4.0%)	1 (1.3%)	0 (0.0%)	5 (2.5%)

*Percentages are out of total number of SARs reported

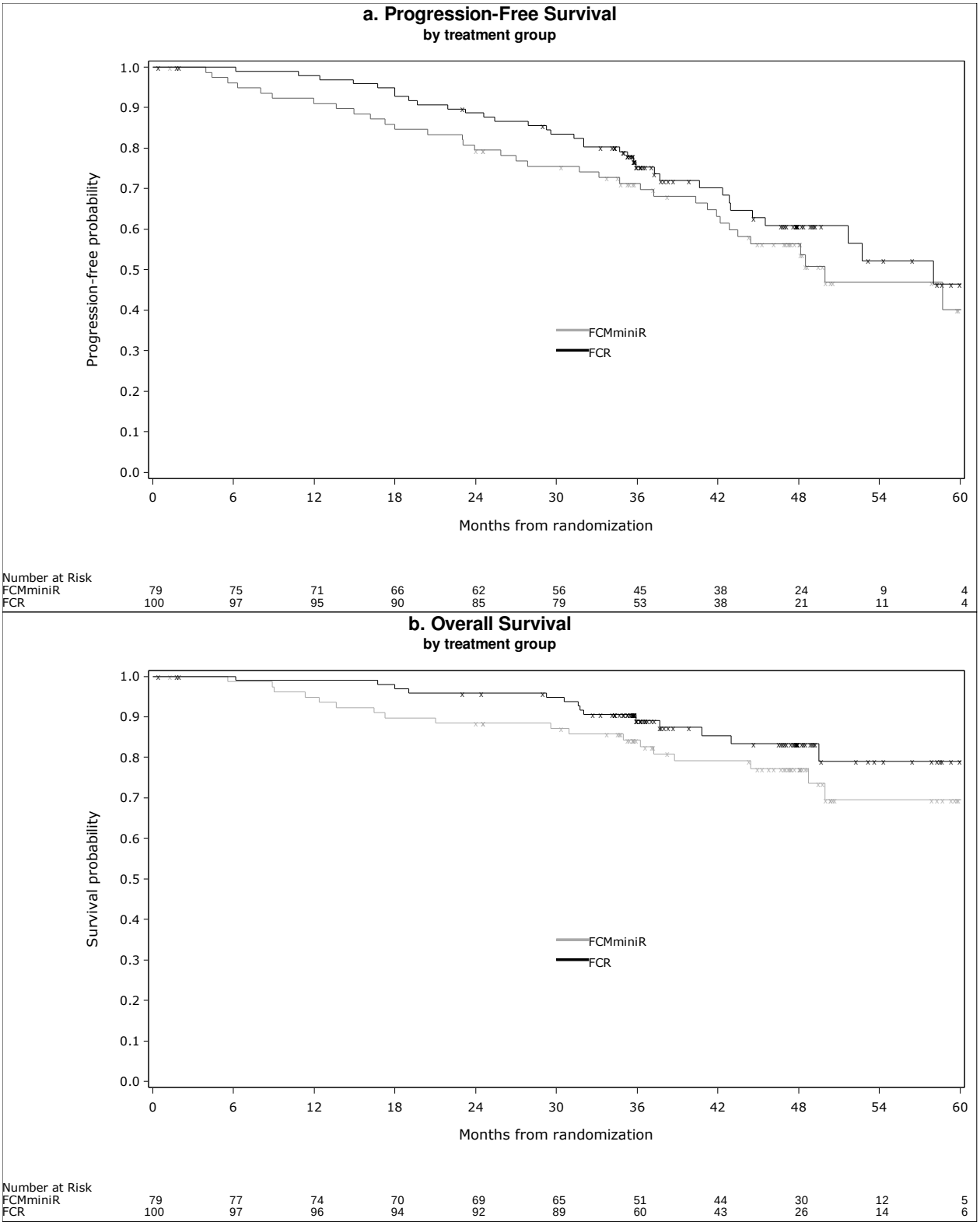
MedDRA: Medical Dictionary for Regulatory Activities

CTCAE: Common Terminology Criteria for Adverse Events

AML: Acute myeloid leukemia

MDS: Myelodysplastic syndrome

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



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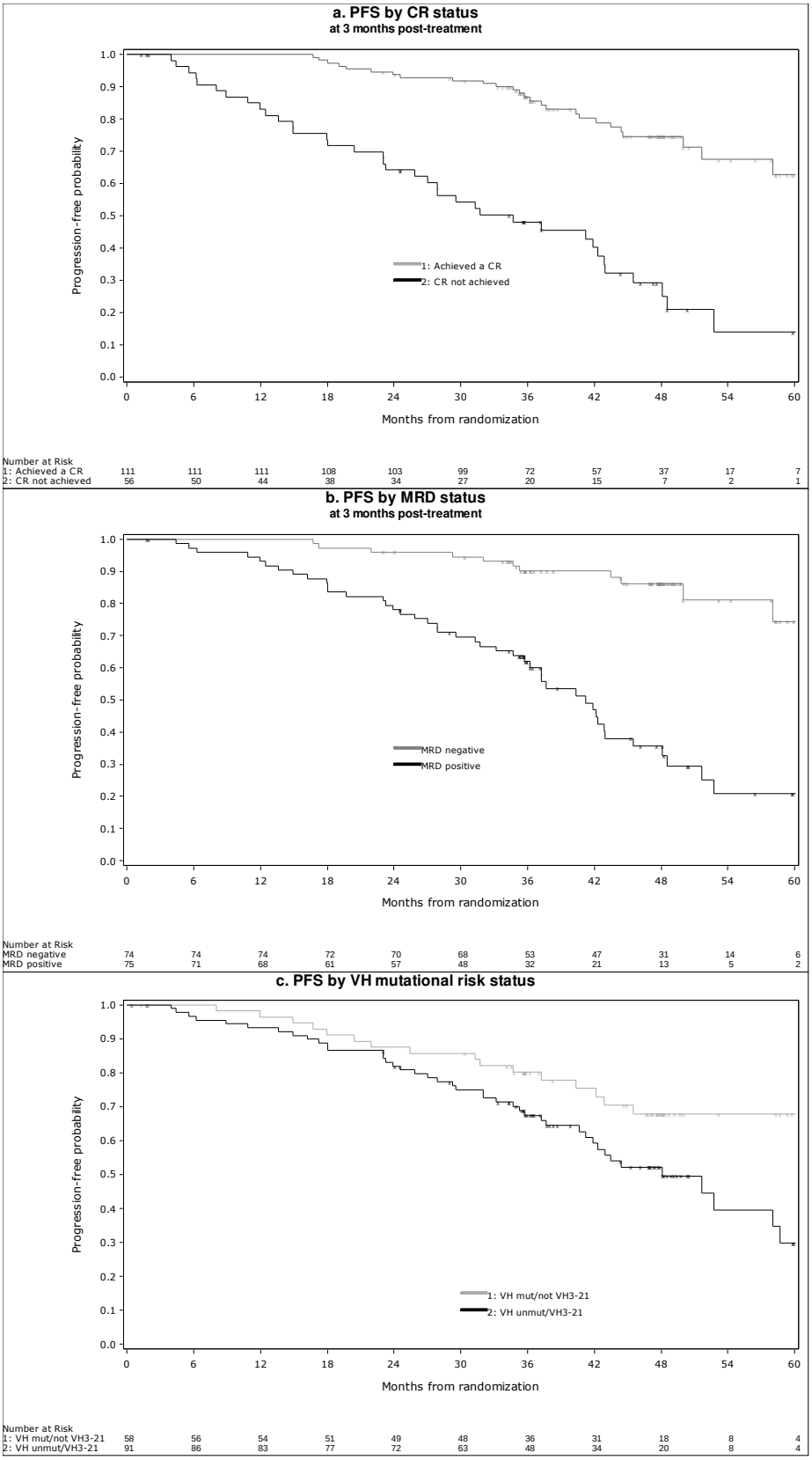
587 **Figure 3 Kaplan Meier Curves for Subgroup Analyses for Progression-Free Survival**



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