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Results of the randomised phase IIB ARCTIC (Attenuated dose Rituximab with ChemoTherapy In CLL) trial of low dose Rituximab in previously untreated CLL

Author List: 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 Duncombe[8], John L O'Dwyer[9], Alison 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]MRC Haematology Unit, University of Oxford, Oxford, United Kingdom

[6]Department of Haematology, Hull & East Yorkshire NHS Trust, Hull, United Kingdom

[7]City Hospitals Sunderland, Sunderland, United Kingdom

[8]Department of Haematology, Southampton University Hospital, 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.

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Contact details of corresponding author:

Peter Hillmen

Section of Experimental Haematology

Leeds Institute of Cancer and Pathology (LICAP)

University of Leeds, Leeds

United Kingdom

Peter.Hillmen@nhs.net

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ABSTRACT

Purpose

A multi-centre, randomised-controlled, open, phase IIB non-inferiority trial in previously untreated Chronic Lymphocytic Leukemia (CLL). Conventional frontline therapy for fit patients with CLL is fludarabine, cyclophosphamide and rituximab (FCR). The key assumption for ARCTIC was that the addition of mitoxantrone to FCR with the use of low dose rituximab (FCM-miniR) would be a non-inferior alternative to FCR.

Patients and Methods

206 patients were to be randomised to FCR or FCM-miniR. The primary endpoint was Complete Remission (CR) according to IWCLL criteria. Secondary endpoints were progression-free survival (PFS), overall survival (OS), overall response rate (ORR), minimal residual disease (MRD) eradication, safety and cost-effectiveness.

Results

200 participants were recruited from 34 UK centres. A pre-planned interim analysis led to early trial closure. 100 participants completed FCR, 79 FCM-miniR and 21 commenced FCM-miniR but crossed over to FCR following Data Monitoring Committee (DMC) recommendations. At final analysis, CR rates were 76% for FCR compared to 55% for FCM-miniR [adjusted odds-ratio:0.37; 95%CI:0.19-0.73]. MRD-negativity rates were 54% for FCR compared to 44% for FCM-miniR. More participants experienced a Serious Adverse Reaction (SAR) with FCM-miniR compared to FCR (49% vs. 41%). At a median of 50 months follow-up, PFS and OS survival were good compared to previous studies with no significant difference between the

treatment groups. The economic analysis indicates that FCM-miniR is not expected to be cost-effective over a lifetime horizon.

Conclusions

FCM-miniR is less well tolerated with poorer response and MRD-negativity rates and increased toxicity than FCR, and therefore FCM-miniR will not be taken forward into a Phase III trial. The trial demonstrated that oral FCR yields extremely high response rates compared to historical series with intravenous chemotherapy.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia above the age of 50 years. For physically fit patients, the addition of rituximab to fludarabine and cyclophosphamide (FCR) has become the standard of care based on evidence from large randomised controlled trials[1,2]. However, the dose of rituximab has not been established systematically in CLL. 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 78% ORR, 50% achieving complete remission (CR) and 10 patients achieving Minimal Residual Disease (MRD) negativity. A non-

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randomised 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 randomised 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 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). Higher doses of rituximab are required as a single agent due to the tumor burden, resulting in better overall response rates (ORRs). However, it is hypothesised 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-centre, randomised, controlled, open, phase IIB non-inferiority trial including patients with previously-untreated CLL who required treatment by IWCLL criteria[14].

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Patients were randomised via a central computer-generated minimisation program incorporating a random element 1:1 to FCR or FCM-miniR. Randomisation was stratified to ensure balance for centre, 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) who provided general oversight for the trial.

The trial was approved by the National Research Ethics Service Leeds (East) Research Ethics Committee. The trial was registered as an International Standard Randomised Controlled Trial (ISRCTN16544962) and on the European Clinical Trials Database (EudraCT:2009-010998-20).

Patients

The intention was to include 206 patients from ethically approved 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 with Hepatitis B or C; an active secondary malignancy (excluding basal cell carcinoma); an active infection or a past history of anaphylaxis

following exposure to rat or mouse-derived complementarity determining region (CDR)-grafted humanized monoclonal antibody were not eligible. Patients with creatinine clearance greater than 30ml/min were allowed with guidance on dose reduction for fludarabine. 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 for first five days of each cycle respectively. 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. Participants with neutropenia delaying therapy received G-CSF (lenograstim 263mcg/day; days 7-13) on all remaining cycles. All participants were given allopurinol at least in cycle 1. PCP prophylaxis and acyclovir were given throughout the treatment. Secondary prophylaxis with G-CSF was recommended with delays of therapy due to neutropenia and appropriate dose reductions were recommended in response to cytopenias.

Participants were followed up for response to treatment at 3 months post-treatment, 12, 18 and 24 months post-randomisation or until disease progression requiring treatment, and for survival until death.

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Endpoints

The primary endpoint was CR rate at three months post-treatment. Response was centrally assessed according to IWCLL criteria[14] by two independent, experienced CLL haematologists blinded to treatment allocation. An independent arbiter reviewed discordant reports.

Secondary endpoints at three months post-treatment included MRD eradication, assessed in the bone marrow by highly sensitive multiparameter flow cytometry with a level of detection below 1 CLL cell in 10000 leukocytes[15]; ORR defined as at least a partial remission (PR); and safety and toxicity as graded by CTCAE V3.0.

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

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) (estimated from the EQ-5D questionnaires)[16]. A within-trial analysis compared the outcomes and costs over 24 months, and a modified Markov model was used to estimate lifetime cost-effectiveness.

Sample size

Previous studies showed FCR CR rates of at least 50%[17,18]. 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 favour of FCM-miniR, a 1-sided significance level (α) of 2.5%[19] 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[20] alpha-spending function.

Statistical methods

All analyses were conducted on the intention-to-treat (ITT) population, in which participants were included according to their randomised 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 and toxicity 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 protocol treatment or discontinued treatment early due to non-response or toxicity were treated as non-responders/MRD-positive. In the formal primary analysis, 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 excluded. 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.

Binary logistic regression models compare CR rates, proportions with undetectable MRD and ORR between the treatment groups, adjusting for the minimisation factors, excluding centre. The

differences in proportions are reported with 95% confidence intervals (CIs). The lower limit of the CI for the CR rates is compared with the non-inferiority margin of 10%, expressed as an odds ratio (OR).

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

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

The economic evaluation uses a within trial analysis, in which cost-effectiveness is assessed within the 24-month trial period using individual patient 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.

Sensitivity analyses assess the robustness of the assumptions regarding missing primary endpoint data.

RESULTS

Recruitment and Early Closure

200 participants were randomised between December 2009-September 2012 (FCR:100, FCM-miniR:100) from 34 UK institutions with local ethical and management approval. 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, CR rates were 82.9% for FCR compared to 61.4% for FCM-miniR, difference -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 favour of FCR. There was also evidence of additional toxicity in the FCM-miniR group. The DMC recommended ceasing recruitment immediately; with participants receiving FCM-miniR recommended to transfer to FCR for the remainder of their treatment cycles. 21/23 FCM-miniR participants transferred to receive treatment with FCR (labelled FCM-miniR/FCR) following discussion with their treating clinician, two from cycle one.

Patient Characteristics

Baseline characteristics are displayed in *Table 1*. The median age was 63 years (range 36–80) with 75(37.5%) aged >65 years. There was a male predominance 135(67.5%), and 34(17.0%) were Binet Stage progressive A, 95(47.5%) stage B and 71(35.5%) stage C. 116(58.0%), 77(38.5%) and 7(3.5%) were WHO performance status 0, 1 and 2 respectively. 103(51.5%) had B-symptoms, a higher proportion with FCM-miniR [FCR:46(46.0%), FCM-miniR:57(57.0%)]. 115(57.5%) had β2-microglobulin ≥4mg/L, whilst 31(15.5%) had creatinine clearance of 30-60mls/min. Of the evaluable patients, 7/183(3.8%) were 17p-deleted (FCR:4, FCM-miniR:3); 30/188(16.0%) were 11q-deleted (FCR:10, FCM-miniR:20) and 104/165(63.0%) were considered to be 'poor risk' in terms of VH mutation status.

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 ≤3cycles of treatment

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[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 one was 17p deleted and withdrawn from the trial. 59(29.5%) discontinued treatment early [FCR:30(30.0%), FCM-miniR:28(35.4%), FCM-miniR/FCR:1(4.8%)]. Reasons were: toxicity(n=44); progressive disease(n=3); stable disease with no or minimal response(n=3); ineligibility(n=1), patient choice(n=3); clinician decision(n=4); other(n=1). 94(47.0%) received G-CSF during treatment as planned in the protocol as secondary prophylaxis, with a higher proportion of those receiving FCM-miniR [FCR:42(42.0%), FCM-miniR:40(50.6%)](*Table 2*).

Efficacy

Of the 200 patients, 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 [based on 167 participants: FCR:92(92.0%), FCM-miniR:75(75.0%)], 66.5%(n=111) achieved a CR, [FCR:70(76.1%), FCM-miniR:41(54.7%)], with difference -21.4% in favour of FCR (95%CI:-35.8%,-7.0%). 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 affect the findings.

There were no large differences in proportions achieving a CR by sex [Males:65.0%, Females:70.0%], age group [≤65:70.8%, >65:59.0%], or Binet stage [A progressive/B:68.5%,

C:62.5%]. A significantly higher proportion who received >3cycles of treatment achieved a CR [≤3cycles:28.0%, >3cycles:73.2%], difference[-45.2%(95%CI:-64.3%,-26.2%)].

All assessable 17p deleted participants failed to achieve a CR(n=6). Lower proportions of 11q deleted and poor risk VH mutated participants achieved a CR [11qdel:58.3%, not-11qdel:67.7%], [VHPoor:62.1%, VHStandard:69.2%].

The ORR was 92.6%(163/176) with a higher proportion achieving at least a PR with FCR than FCM-miniR [FCR:94/98(95.9%), FCM-miniR:69/78(88.5%), 95%CI for difference:(-15.6%,0.6%)].

Of the 200 patients, 85(42.5%) achieved MRD-negativity [FCR: 45(45.0%), FCM-miniR:29(36.7%), FCM-miniR/FCR:11(52.4%)]. There was a non-significant trend towards FCM-miniR resulting in lower MRD-negativity rates at three months post-treatment [FCR:45/83(54.2%), FCM-miniR:29/66(43.9%), difference:-10.3%(95%CI:-26.3%,5.8%), adjusted OR:0.65(95%CI:0.33,1.26)](*Table 3*).

The median follow-up for survivors is 50 months (range:36-70). 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%) 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). At 36 months post-randomisation, the PFS rate is FCR:75.3%, 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]. Note the relatively short follow-up leading to a high number of censored observations.

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Of the 85 participants who were MRD-negative in the bone marrow at three months post-treatment(*Table 3*), only 9(10.6%) participants have relapsed at the MRD level in the peripheral blood or progressed (FCR:5, FCM-miniR:4).

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 standard VH mutation risk showing an improved PFS over those with poor risk, but no evidence of a difference for 11q deletion status(*Figure3*). Subgroup analyses for OS show similar trends.

Cost-effectiveness

Over the planned 24-month trial period, FCM-miniR produced a mean cost saving of £6,619(s.d.£1,061), and QALY loss of -0.059(s.d.0.06) compared to FCR. Assuming that one QALY is valued at £20,000, FCM-miniR is cost-effective over the trial period, producing a positive incremental net health benefit (+0.27 QALYs; s.d.0.08). However, FCM-miniR is not expected to be cost-effective over a lifetime horizon, with an expected lifetime cost-saving of £7,723(s.d.£3,281), 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*). 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%)]. A further 38 Serious Adverse Events (SAEs) were not suspected to be related to trial treatment.

One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported in the FCR group. A squamous cell carcinoma, two lesions on the lower back and central chest was diagnosed approximately 4 months after six cycles of treatment.

Adverse Events (AE) were reported from 192(97.0%) participants. 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%)].

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

Within 3 years following treatment, 26(13.1%) participants had been diagnosed with a secondary cancer [FCR:13(13.0%); FCM-miniR:12(15.2%); FCM-miniR/FCR:1(5.3%)]. The most common type being skin (non-melanoma) 13(6.6%) followed by haematological (AML/MDS) 7(3.5%).

DISCUSSION

Participants randomised to FCM-miniR had a significantly lower CR rate than those randomised to FCR (54.7% vs. 76.1%), indicating the 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. Key secondary endpoints were consistent in demonstrating that FCR has greater efficacy, with a higher proportion of participants achieving eradication of MRD (FCR:54.2%, FCM-miniR:43.9%). The follow-up in the trial is still relatively immature (median 50 months from randomisation) but to date the PFS and OS are good compared to previous studies, and there is

no significant difference between the treatment groups, although there is a trend towards improved survival for FCR participants.

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.

In summary, we demonstrate that FCM-miniR is not non-inferior to FCR in terms of the primary end-point 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 eradication 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.

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SUPPLEMENTARY MATERIAL

Trial Protocol

The ARCTIC trial protocol can be accessed from the NIHR website:

http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0016/51721/PRO-07-01-38.pdf

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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 MRD status at 3 months post-treatment

b. PFS by CR status at 3 months post-treatment

c. PFS by VH mutation risk status

d. PFS by 11q deletion status

Table 1 Baseline Characteristics

Table 2 Treatment Summaries

Table 3 Efficacy Summaries

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

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FIGURES

Figure 1 CONSORT Diagram

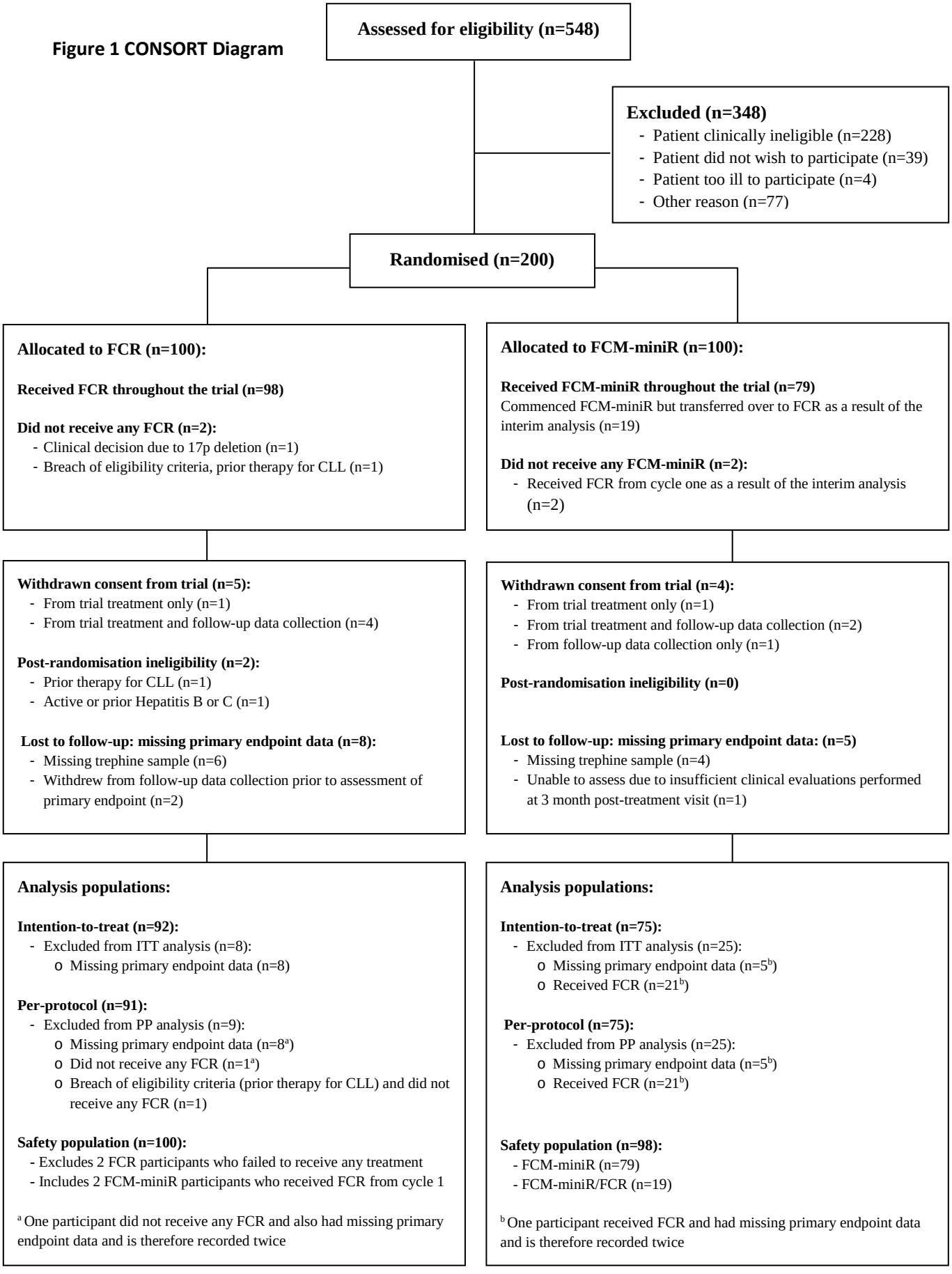

Table 1 Baseline Characteristics

	FCR (n=100)	FCM-miniR (n=100)	Total (n=200)
Age (at randomisation)			
≤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 deleted			
Yes (poorer risk)	4 (4.0%)	3 (3.0%)	7 (3.5%)
No (standard risk)	88 (88.0%)	88 (88.0%)	176 (88.0%)

	FCR (n=100)	FCM-miniR (n=100)	Total (n=200)
Missing	8 (8.0%)	9 (9.0%)	17 (8.5%)
11q deleted			
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 status*			
Poor risk	52 (52.0%)	52 (52.0%)	104 (52.0%)
Standard risk	30 (30.0%)	31 (31.0%)	61 (30.5%)
Missing	18 (18.0%)	17 (17.0%)	35 (17.5%)

*Poor risk - VH unmutated, or involving the VH3-21 gene; Standard risk - VH mutated and not involving the VH3-21 gene

WHO: World Health Organisation

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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 early (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

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Table 3 Efficacy Summaries

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%)
Achievement of the primary endpoint	**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%)	
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)
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				

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%)
Achievement of the primary endpoint	**FCR (n=92)**	**FCM-miniR (n=75)**	**Total (n=167)**	**Difference in CR rates & 95% CIs (FCM-miniR - FCR)**
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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)
MRD status	**FCR (n=100)**	**FCM-miniR (n=79)**	**FCM-miniR/FCR (n=21)**	**Total (n=200)**
Parameter*	**Parameter estimate**	**SE**	**OR**	**95% CIs for OR**
FCM-miniR vs. FCR	-0.44	0.34	0.65	(0.33, 1.26)

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 minimisation 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)

NHS: National Health Service

PSS: Personal and Social Services

QALY: Quality-Adjusted Life-Years

ICER: Incremental Cost-Effectiveness Ratio

INB: Incremental Net Benefit

*Pounds saved per QALY lost

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

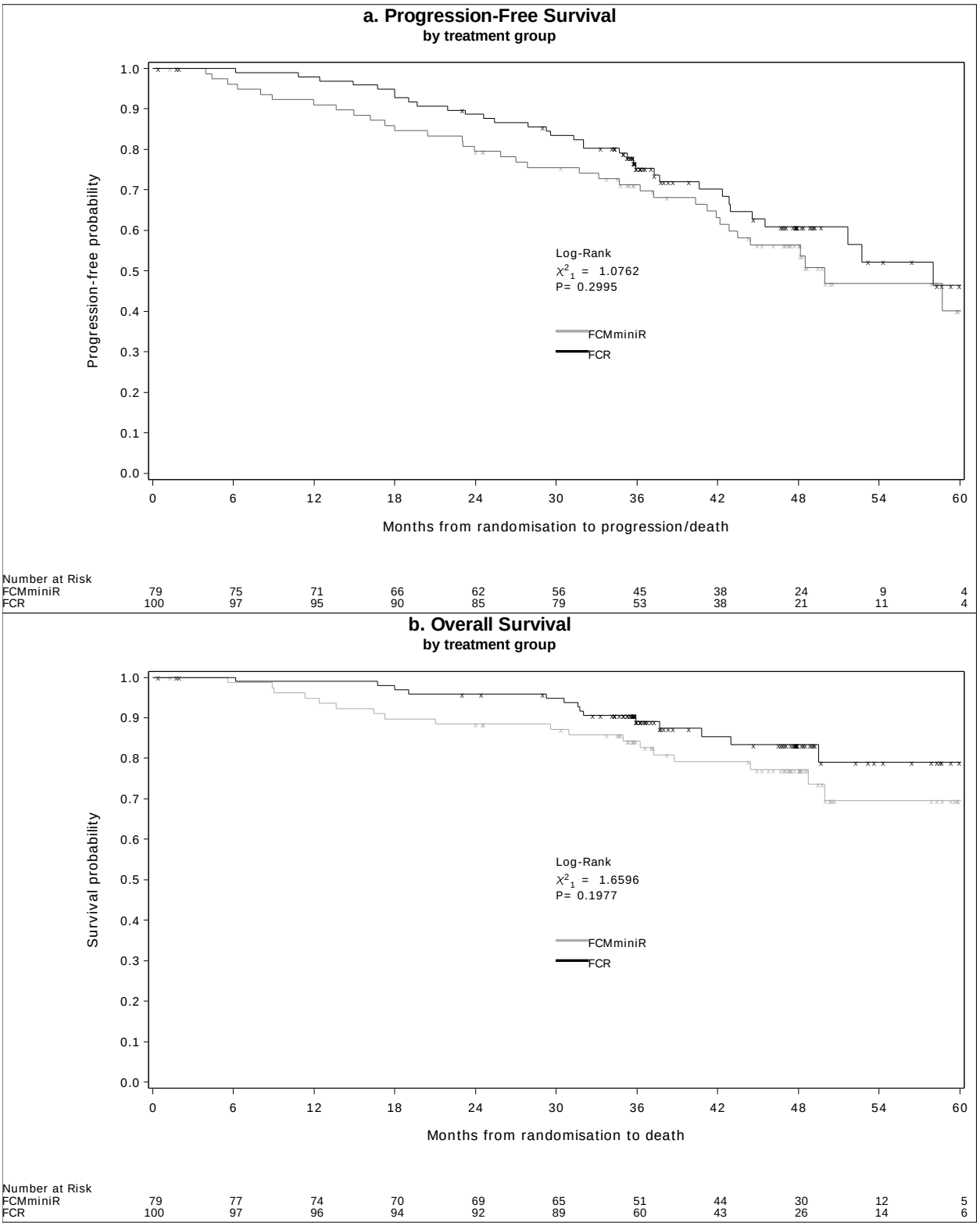

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Figure 3 Kaplan Meier Curves for Subgroup Analyses for PFS