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

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ABSTRACT

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

INTRODUCTION

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

CLL is still an incurable disease, and most patients will eventually become resistant to treatment. For physically fit patients, combination chemo-immunotherapy in the form of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care based on evidence from large randomised controlled trials(1-3). Updated analysis suggested an improvement in progression free survival (PFS) and overall survival (OS) in patients treated with FCR over FC(1, 4). Hence, this combination is considered to be the gold-standard first-line treatment in patients deemed to be suitable for fludarabine-based treatment.

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

9 (32%) patients, achieving a CR(9, 10). We previously reported a randomised phase II trial of 52 patients with relapsed CLL, with ORR with FCM and FCM-R of 58% and 65%, respectively(11) and an acceptable toxicity profile. Eight (15.4%) patients in this trial achieved MRD negativity.

The ADMIRE (Does the ADdition of Mitoxantrone Improve REsponse to FCR chemotherapy in patients with CLL) trial was designed to assess whether the addition of mitoxantone to FCR increases the depth of response in previously untreated patients with CLL requiring therapy in comparison to the standard FCR treatment. The current literature suggests that patients who respond to therapy and do not have detectable CLL by extremely sensitive techniques have a significantly prolonged survival(12-14). Therefore, one of the key secondary objectives was to compare MRD negativity within each treatment group.

PATIENTS AND METHODS

Trial Design

ADMIRE was a multi-center, randomized, controlled, open-label, parallel-group, phase IIB superiority trial assessing FCR (control) versus FCM-R (experimental) for previously untreated patients with CLL requiring treatment by IWCLL criteria(15). Patients were randomly allocated via a central computer-generated minimization programme that incorporated a random element 1:1 to receive oral fludarabine, cyclophosphamide and intravenous rituximab with or without intravenous mitoxantrone. Randomization was stratified to ensure balance for center, Binet Stage (Progressive A or B, C), age group (≤65, >65) and sex.

The primary objective of the trial was to assess whether the addition of mitoxantrone to FCR improved CR rates in patients with previously untreated CLL. The results would be used to

determine whether a larger randomized Phase III trial to formally assess survival was appropriate.

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

The trial was approved by relevant institutional ethical committees and regulatory review bodies, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial was registered as an International Standard Randomized Controlled Trial (ISRCTN42165735); and on the European Clinical Trials Database (EudraCT: 2008-006342-25).

Patients

The trial was planned to include 218 patients from hospitals around the United Kingdom (UK). Eligible patients had: progressive CLL requiring treatment by IWCLL criteria(15); no prior treatment for CLL; WHO performance status 0-2; Binet Stage progressive A, B or C; and provided written consent. Patients were not eligible if they had Hepatitis B or C; an active secondary malignancy (excluding basal cell carcinoma of the skin); an active infection; or past history of anaphylaxis following exposure to rat- or mouse-derived complementarity determining region (CDR)-grafted humanized monoclonal antibody. Patients with creatinine clearance greater than 30 ml/min were allowed to enter the trial with guidance on dose reduction for fludarabine. Patients with a 17p-deletion were eligible for enrollment due to lack of treatment options at the time of designing the trial. Patients were able to withdraw from the trial at any time.

Treatment and Assessments

Treatment with FCR or FCM-R was repeated every 28 days for a total of six cycles. Fludarabine and cyclophosphamide were administered orally at doses of 24 mg/m^2/day and 150 mg/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(16). Mitoxantrone was administered intravenously on day 1 at a dose of 6 mg/m^2 in the FCM-R group. Rituximab was administered intravenously at 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 in cycles 2-6. In participants with lymphocyte counts greater than 25x10^9/L, the dose of rituximab was split to 100 mg on day 1 with the remaining dose given on day 2 to reduce the risk of infusion related reactions. Participants unable to tolerate oral chemotherapy were permitted to receive equivalent intravenous doses of fludarabine (25 mg/m^2/day for 3 days) and cyclophosphamide (250mg/m^2/day for 3 days). All participants were given allopurinol at least in cycle 1. PCP prophylaxis and acyclovir were given throughout the treatment. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) was recommended for patients experiencing scheduled delays due to neutropenia. Appropriate dose reductions were recommended in patients with therapy-related cytopenias.

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

Endpoints

The primary endpoint was CR rate (including CRi) at 3 months post treatment. Response was centrally assessed according to IWCLL criteria(15) 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(14); ORR defined as at least partial remission (PR); and safety and toxicity as graded by CTCAE V3.0(17).

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

Sample Size

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

Statistical Methods

All analyses were conducted on the intention-to-treat (ITT) population, in which participants were included according to their randomized treatment. Safety analyses included participants according to treatment received.

Methods for handling missing endpoint data were pre-specified and approved by the Chief Investigator. Participants with a missing assessment who died from CLL or treatment-related toxicity prior to their primary endpoint assessment, or discontinued treatment early due to non-response or toxicity, were treated as non-responders/MRD-positive. In the formal statistical analysis of the primary endpoint, for participants with at least a PR but missing trephine data to confirm a CR, imputation methods treated MRD-negative participants as having a CR and

MRD-positive as not, although summaries report the un-imputed data. Participants without an available endpoint assessment were not included in the formal statistical analysis of the primary endpoint. This was appropriate as it can be assumed that data are missing completely at random (MCAR), since assessments were most likely unavailable due to samples being un-assessable or missed in error, rather than participant refusal due to level of response or treatment allocation. Sensitivity analyses assessed the robustness of the assumptions regarding missing primary endpoint data.

Binary logistic regression models compared CR rates, proportions with undetectable MRD and ORR between the treatment groups, adjusted for the minimization factors, excluding center. The differences in proportions are reported with 95% confidence intervals (CIs).

Kaplan-Meier curves are presented for the PFS and OS endpoints. Restricted mean survival time (RMST), used in the event of non-proportional hazards (18), estimated the area under the PFS curves, and treatment groups were compared using generalized linear regression, adjusted for the minimization factors, excluding center. Cox regression analysis formally compared OS between treatment groups. Participants without evidence of an event at the time of analysis were censored at the last date they were known to be alive and event-free.

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

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

RESULTS:

Patient Characteristics

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

The CONSORT diagram(19) (Figure 1) shows the flow of participants through the trial. The baseline characteristics are displayed in Table 1. The median age was 62 years (range 33–77) with 74 participants (34.4%) aged >65 years. There was a male predominance [163 (75.8%)] and 27 participants (12.6%) were Binet stage progressive A, 111 (51.6%) stage B and 77 (35.8%) stage C. A majority of participants [124 (57.7%)] were WHO performance status (PS) 0, with 83 (38.6%) PS 1 and 8 (3.7%) PS 2. Overall, 98 participants (45.6%) had B-symptoms [FCR: 51 (47.7%); FCM-R: 47 (43.5%)], whilst 123 (57.2%) had a β2-microglobulin concentration of ≥4mg/L and 30 (14.0%) had creatinine clearance levels of 30-60 mls/min. Of the evaluable participants, 14/203 (6.9%) had a 17p deletion (FCR: 9/100 (9.0%); FCM-R: 5/103 (4.9%)) and 38/203 (18.7%) an 11q deletion (FCR: 18/100 (18.0%); FCM-R: 20/103 (19.4%)). 127/201 participants (63.2%) were considered to be 'poorer risk' in terms of V_H mutational status i.e. V_H unmutated or involving the V_H3-21 gene [FCR: 68/101 (67.3%); FCM-R: 59/100 (59.0%)].

Treatment

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

Efficacy

Of the 215 participants, 125 (58.1%) achieved a CR [FCR: 60 (56.1%); FCM-R: 65 (60.2%)] (Table 3). In the formal analysis of the primary endpoint including imputation based on MRD outcome, 137/197 (69.5%) achieved a CR, with a similar proportion in each treatment group [FCR: 67/96 (69.8%); FCM-R: 70/101 (69.3%)] (Table 3). The difference in response rates (FCM-R – FCR) was -0.5% (95% CI: -13.3%, 12.4%). In the logistic regression analysis, the odds ratio (OR) for achieving a CR with FCM-R compared to FCR was 0.97 (95% CI: 0.53, 1.79), p-value=0.932, concluding that the difference between the groups is not significant at the 5% level. The sensitivity analyses did not alter the findings.

There were no large differences in proportion of participants achieving a CR by gender [Male: 100/148 (67.6%), Female: 37/49 (75.5%)], age group [≤65: 91/130 (70.0%), >65: 46/67 (68.7%)] or Binet stage [Progressive A/B: 93/130 (71.5%), C: 44/67 (65.7%)]. A significantly

higher proportion of participants who received >3 cycles of treatment achieved a CR [>3cycles: 135/183 (73.8%); ≤3 cycles: 2/14 (14.3%); difference (95%CI): -59.5% (-78.9%, -40.1%)].

Lower proportions of participants with a 17p-deletion, 11q-deletion and 'poorer risk' V_H mutational status achieved a CR [17pdel: 5/11 (45.5%); no 17pdel: 124/176 (70.5%)], [11qdel: 23/37 (62.2%); no 11qdel: 106/150 (70.7%)], [V_H unmutated or V_H3-21: 76/117 (65.0%); V_H mutated: 52/69 (75.4%)].

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

Of the 215 participants, 101 (47.0%) achieved MRD negativity assessed in the bone marrow three-months post-therapy [FCR: 54 (50.5%); FCM-R: 47 (43.5%) (Table 3). In the formal analysis of MRD (excluding participants with a missing MRD assessment), 101/184 (54.9%) achieved MRD negativity [FCR: 54/91 (59.3%), FCM-R: 47/93 (50.5%)]. There was a non-significant trend towards FCM-R resulting in lower MRD negativity rates at 3 months post-treatment with a difference (FCM-R – FCR) of -8.8% (95% CI: -23.1%, 5.5%), adjusted OR: 0.70 [95% CI: (0.39, 1.26), p=0.231] (Table 3).

At the time of analysis (4-years post-randomization of the final participant), 42 (19.5%) participants have died [FCR: 24 (22.4%), FCM-R: 18 (16.7%)], and 89 (41.4%) have either progressed or died [FCR: 44 (41.1%), FCM-R: 45 (41.7%)]. Figure 2 presents the PFS and OS Kaplan-Meier curves by treatment group. The mean PFS time up to a restricted time of 72 months post randomization was 51.7 and 52.3 months in the FCR and FCM-R groups,

respectively. The difference in the restricted mean survival between the treatment groups was not significant [FCM-R vs FCR: parameter estimate: 0.48, SE: 3.23, p=0.8823]. For OS, the hazard ratio (HR) (FCM-R vs FCR) was not significant in the adjusted Cox regression model [HR&95%CI: 0.75 (0.41, 1.39), p=0.3596].

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

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

Safety and Toxicity

The safety population included 212 participants (Figure 1). 156 SAEs were reported from 97 (45.8%) participants, a lower proportion receiving FCR (41.9%) compared to FCM-R (49.5%). 116 Serious Adverse Reactions (SARs) were reported from 76 (35.8%) participants [FCR: 55 events from 36 (34.3%); FCM-R: 61 events from 40 (37.4%)]. The most commonly reported SARs, 65.5% of events (n=76) were infections and infestations. Ninety-two (43.4%) participants required hospitalization for an SAE [FCR: 43 (41.0%); FCM-R: 49 (45.8%)] (Table 4).

One Suspected Unexpected Serious Adverse Reaction (SUSAR) was reported from a participant receiving all 6 cycles of FCM-R. They experienced prolonged myelosuppression

and had a hypoplastic marrow on their 3-month post-treatment bone marrow aspirate. The event was suspected to be related to F, C and M.

Non-serious adverse events (AEs) were reported from 210 (99.1%) participants, with similar proportions in each treatment group. Of the 2914 AEs reported, 468 (16.1%) were graded as CTCAE grade 3 or above [FCR: 222 (15.9%); FCM-R: 246 (16.2%)] (Table 4).

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

Within 5 years of participants ending treatment, 39 participants (18.4%) had been diagnosed with a secondary cancer [FCR: 19 (18.1%); FCM-R: 20 (18.7%)]. The most commonly reported secondary cancers were non-melanoma skin cancers in 6.1% (n=13) of participants, followed by non-hematological solid tumors in 5.7% of participants (n=12) (Table 4).

DISCUSSION

This multi-center collaborative trial demonstrates that oral FCR results in extremely high response and MRD negative rates (ORR: 97%, CR: 70%, MRD negativity: 59%). Trial follow-up is still relatively immature (median 5 years) and there are a high number of censored observations but to date the PFS and OS are favorable compared to previous studies. The mean PFS for both trial arms is similar with no significant difference. PFS was improved in participants achieving CR and MRD negativity. Participants with mutated V_H genes (excluding V_H3-21) had improved PFS compared to those with unmutated V_H genes or using V_H3-21. The FCM-R group results appear equivalent, but the depth of responses was no higher with the addition of mitoxantrone to FCR (OR rate: 97%; CR rate: 69%; MRD negativity rate: 51%). The MRD negativity rate in bone marrow at 3 months post treatment is lower in the FCM-R

group, although the difference is not statistically significant (p=0.231). The median age of participants was 62 years, which is comparable to other front-line CLL trials of fludarabine-based therapies. 89% of the participants received greater than three cycles of treatment, and 72% of the participants received all six cycles of treatment. PCP and acyclovir prophylaxis was recommended for all participants. Secondary prophylaxis with G-CSF was administered to 60% of participants, enabling the delivery of a maximum number of treatment cycles. This may explain the high response and MRD-negative rates in our trial. The dose of fludarabine was reduced by 50% in participants with creatinine clearance between 30-60 mls/min. The 30 (14%) participants with creatinine clearance of 30-60 mls/min had a similar CR/CRi rate of 73.4%. This might suggests that selected participants considered unfit for FCR due to renal dysfunction can tolerate dose-modified FCR with high response rates.

A slightly higher proportion of participants experienced a SAR with FCM-R (FCR: 34.3% vs FCM-R: 37.4%) and the number of SARs reported overall was higher for FCM-R (FCR: 55 vs FCM-R: 61). A similar proportion of grade 3 or 4 AEs were experienced in each treatment group (FCR: 15.9% vs FCM-R: 16.2%).

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

secondary prophylaxis with G-CSF. It was also possible to use dose adjusted FCR for participants with impaired renal function.

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

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CONFLICT OF INTEREST

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

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

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FIGURE LEGENDS

Figure 1: CONSORT Diagram

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

a. Progression-Free Survival by treatment group

b. Overall Survival by treatment group

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

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

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

c. PFS by V_H mutational risk status

Table 1: Baseline Characteristics

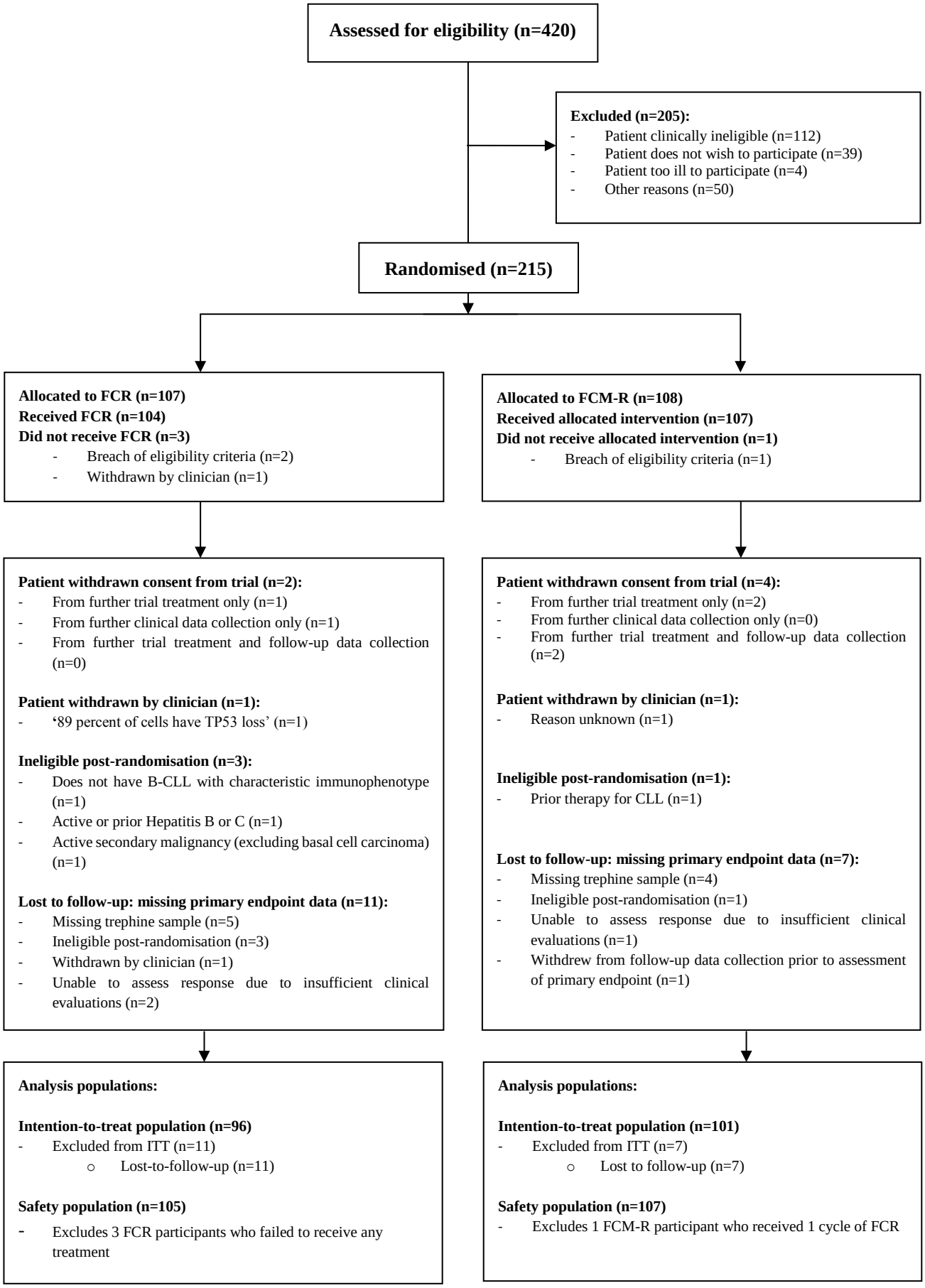
Table 2: Treatment Summaries

Table 3: Efficacy Summaries

Table 4: Safety and Toxicity Summaries

FIGURES AND TABLES

Figure 1. CONSORT Diagram



472 **Table 1. Baseline Characteristics**

	FCR (n=107)	FCM-R (n=108)	Total (n=215)
Age (at randomization)			
≤65	70 (65.4%)	71 (65.7%)	141 (65.6%)
>65	37 (34.6%)	37 (34.3%)	74 (34.4%)
Mean (s.d.)	61.5 (8.0)	61.7 (8.1)	61.6 (8.0)
Median (range)	61 (38, 76)	63 (33, 77)	62 (33, 77)
Sex			
Male	82 (76.6%)	81 (75.0%)	163 (75.8%)
Female	25 (23.4%)	27 (25.0%)	52 (24.2%)
Binet Stage			
Progressive A	13 (12.1%)	14 (13.0%)	27 (12.6%)
B	59 (55.1%)	52 (48.1%)	111 (51.6%)
C	35 (32.7%)	42 (38.9%)	77 (35.8%)
B-symptoms			
Yes	51 (47.7%)	47 (43.5%)	98 (45.6%)
No	56 (52.3%)	60 (55.6%)	116 (54.0%)
Missing	0 (0.0%)	1 (0.9%)	1 (0.5%)
WHO performance status			
0	59 (55.1%)	65 (60.2%)	124 (57.7%)
1	43 (40.2%)	40 (37.0%)	83 (38.6%)
2	5 (4.7%)	3 (2.8%)	8 (3.7%)
Beta-2 microglobulin concentration (mg/L)			
<4 mg/L	39 (36.4%)	45 (41.7%)	84 (39.1%)
≥4 mg/L	64 (59.8%)	59 (54.6%)	123 (57.2%)
Missing	4 (3.7%)	4 (3.7%)	8 (3.7%)
Creatinine clearance (mls/min)			
30-60mls/min	17 (15.9%)	13 (12.0%)	30 (14.0%)
>60mls/min	85 (79.4%)	93 (86.1%)	178 (82.8%)
Missing	5 (4.7%)	2 (1.9%)	7 (3.3%)

	FCR (n=107)	FCM-R (n=108)	Total (n=215)
17p deletion			
Yes (poorer risk)	9 (8.4%)	5 (4.6%)	14 (6.5%)
No (standard risk)	91 (85.0%)	98 (90.7%)	189 (87.9%)
Missing	7 (6.5%)	5 (4.6%)	12 (5.6%)
11q deletion			
Yes (poorer risk)	18 (16.8%)	20 (18.5%)	38 (17.7%)
No (standard risk)	82 (76.6%)	83 (76.9%)	165 (76.7%)
Missing	7 (6.5%)	5 (4.6%)	12 (5.6%)
V_H mutational risk status			
V_H unmutated or V_H3-21(poorer risk)	68 (63.6%)	59 (54.6%)	127 (59.1%)
V_H mutated and not V_H3-21 (standard risk)	33 (30.8%)	41 (38.0%)	74 (34.4%)
Unknown	6 (5.6%)	8 (7.4%)	14 (6.5%)

WHO: World Health Organisation

Table 2. Treatment Summaries

	FCR (n=107)	FCM-R (n=108)	Total (n=215)
Discontinued treatment prematurely (received <6 cycles)?			
Yes	25 (23.4%)	36 (33.3%)	61 (28.4%)
No	82 (76.6%)	72 (66.7%)	154 (71.6%)
Treatment cycles received			
≤ 3 cycles	11 (10.3%)	13 (12.0%)	24 (11.2%)
> 3 cycles	96 (89.7%)	95 (88.0%)	191 (88.8%)
Received G-CSF during treatment (cycles 2 - 6)?			
Yes	60 (56.1%)	69 (63.9%)	129 (60.0%)
No	43 (40.2%)	34 (31.5%)	77 (35.8%)
Unknown	4 (3.7%)	5 (4.6%)	9 (4.2%)

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

Table 3. Efficacy Summaries

MRD NEGATIVITY			
MRD status	**FCR (n=107)**	**FCM-R (n=108)**	**Total (n=215)**
MRD negative	54 (50.5%)	47 (43.5%)	101 (47.0%)
MRD positive	37 (34.6%)	46 (42.6%)	83 (38.6%)
Missing	16 (15.0%)	15 (13.9%)	31 (14.4%)
MRD status	**FCR (n=91)**	**FCM-R (n=93)**	**Difference in MRD-negative rates & 95% CIs (FCM-R - FCR)**
MRD negative	54 (59.3%)	47 (50.5%)	-8.8% (-23.1%, 5.5%)
MRD positive	37 (40.7%)	46 (49.5%)	
Logistic regression analysis for the % of participants achieving MRD negativity			
Parameter*	**Parameter estimate**	**SE**	**OR & 95% CIs**
FCM-R vs FCR	-0.36	0.30	0.70 (0.39, 1.26)
COMPLETE RESPONSE			
CR status (prior to imputation using MRD)	**FCR (n=107)**	**FCM-R (n=108)**	**Total (n=215)**
Achieved a CR	60 (56.1%)	65 (60.2%)	125 (58.1%)
Did not achieve a CR	22 (20.6%)	27 (25.0%)	49 (22.8%)
Missing	25 (23.4%)	16 (14.8%)	41 (19.1%)
CR status (post imputation using MRD)	**FCR (n=107)**	**FCM-R (n=108)**	**Total (n=215)**
Achieved a CR	67 (62.6%)	70 (64.8%)	137 (63.7%)
Did not achieve a CR	29 (27.1%)	31 (28.7%)	60 (27.9%)
Missing	11 (10.3%)	7 (6.5%)	18 (8.4%)
CR status (post imputation using MRD)	**FCR (n=96)**	**FCM-R (n=101)**	**Difference in CR rates & 95% CIs (FCM-R - FCR)**
Achieved a CR	67 (69.8%)	70 (69.3%)	-0.5% (-13.3%, 12.4%)
Did not achieve a CR	29 (30.2%)	31 (30.7%)	
PRIMARY ENDPOINT ANALYSIS Logistic regression analysis for the % of participants achieving a CR			

Parameter*	Parameter estimate	SE	OR & 95% CIs
FCM-R vs FCR	-0.03	0.31	0.97 (0.53, 1.79)

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

533 **Table 4 Safety and Toxicity Summaries**

	FCR (n=105)	FCM-R (n=107)	Total (n=212)
Serious Adverse Events (SAEs)			
Number of participants experiencing an SAE	44 (41.9%)	53 (49.5%)	97 (45.8%)
Total number of SAEs reported	72	84	156
Number of participants requiring hospitalization for an SAE	43 (41.0%)	49 (45.8%)	92 (43.4%)
Serious Adverse Reactions (SARs)			
Number of participants experiencing a SAR	36 (34.3%)	40 (37.4%)	76 (35.8%)
Total number of SARs reported	55	61	116
SARs by MedDRA System Organ Class*			
Blood and lymphatic system disorders	4 (7.3%)	7 (11.5%)	11 (9.5%)
Cardiac disorders	1 (1.8%)	1 (1.6%)	2 (1.7%)
Gastrointestinal disorders	4 (7.3%)	2 (3.3%)	6 (5.2%)
General disorders and administration site conditions	9 (16.4%)	8 (13.1%)	17 (14.7%)
Hepatobiliary disorders	0 (0.0%)	1 (1.6%)	1 (0.9%)
Infections and infestations	36 (65.5%)	40 (65.6%)	76 (65.5%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (1.6%)	1 (0.9%)
Renal and urinary disorders	1 (1.8%)	0 (0.0%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (1.6%)	1 (0.9%)
Adverse Events (AEs)			
Number of participants experiencing an AE	103 (98.1%)	107 (100%)	210 (99.1%)

	FCR (n=105)	FCM-R (n=107)	Total (n=212)
CTCAE grade			
<3	1171 (83.9%)	1269 (83.6%)	2440 (83.7%)
≥3	222 (15.9%)	246 (16.2%)	468 (16.1%)
Missing	3 (0.2%)	3 (0.2%)	6 (0.2%)
Total	1396 (100%)	1518 (100%)	2914 (100%)
Secondary Cancers			
Number of participants reporting each secondary cancer			
Hematological (Lymphoma)	4 (3.8%)	2 (1.9%)	6 (2.8%)
Hematological (AML/MDS)	3 (2.9%)	3 (2.8%)	6 (2.8%)
Skin (Non-melanoma)	4 (3.8%)	9 (8.4%)	13 (6.1%)
Skin (Melanoma)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Non-hematological (Solid tumors)	6 (5.7%)	6 (5.6%)	12 (5.7%)
Unknown	1 (1.0%)	1 (0.9%)	2 (0.9%)

*Percentages out of the total number of SARs reported

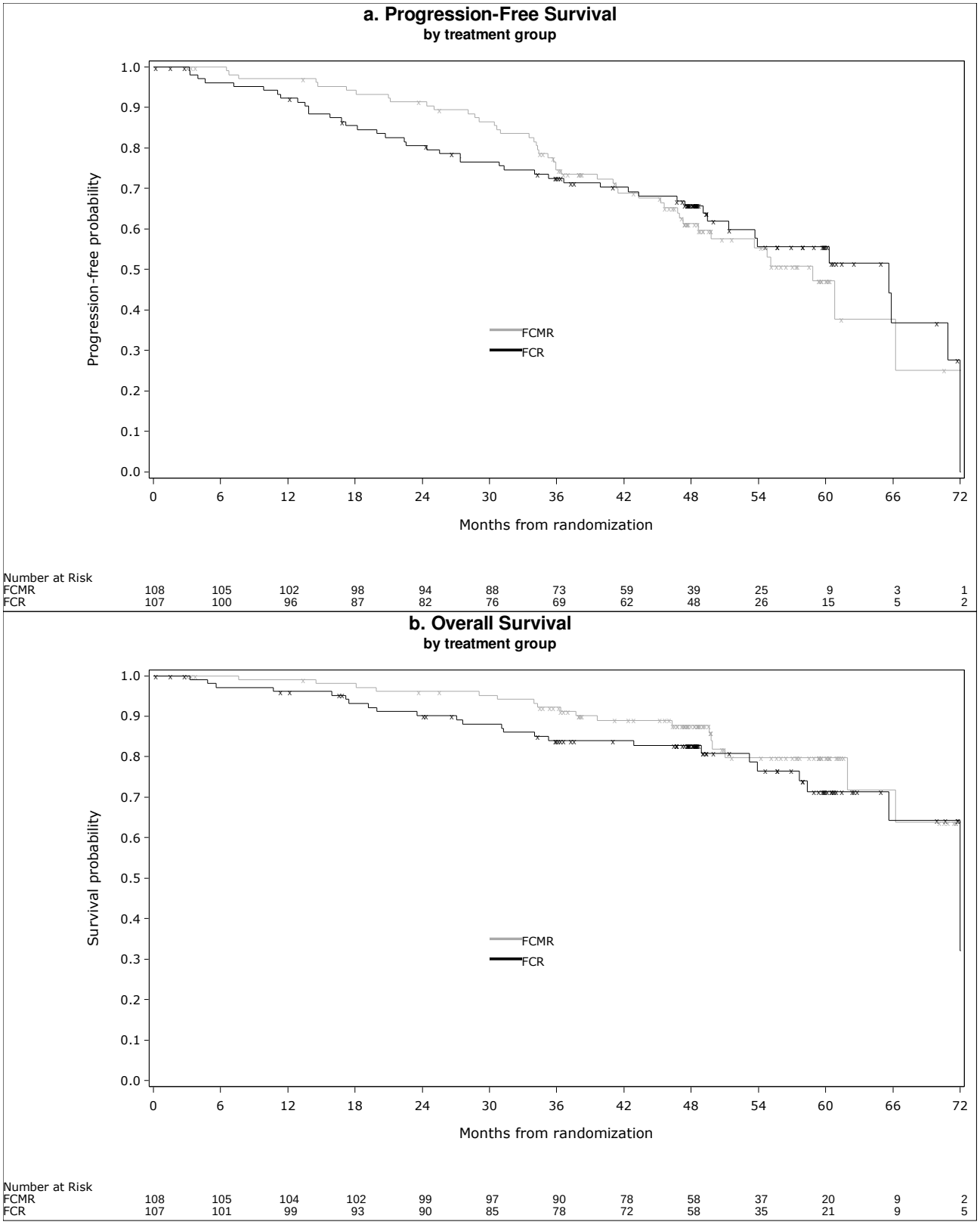
MedDRA: Medical Dictionary for Regulatory Activities

CTCAE: Common Terminology Criteria for Adverse Events

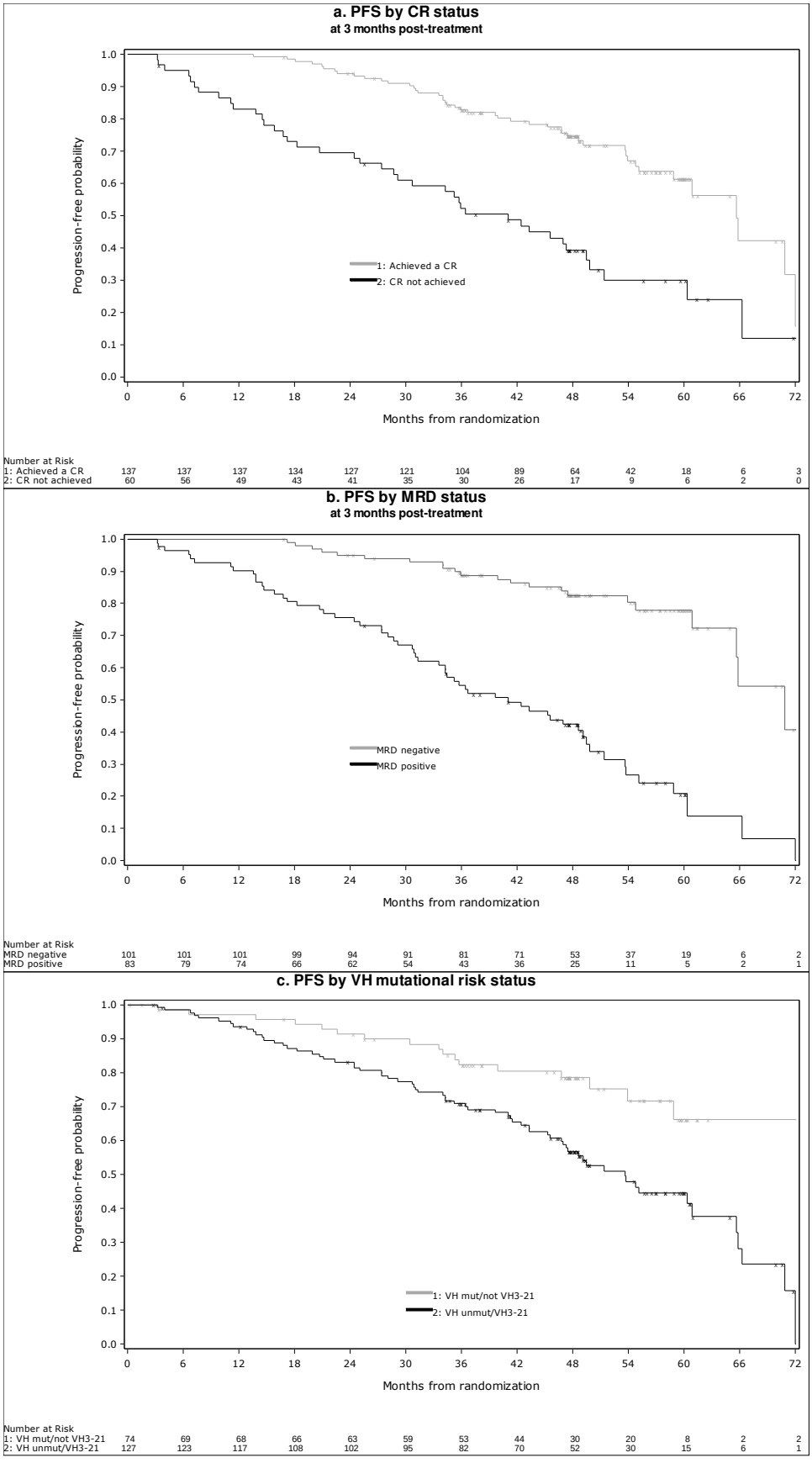
AML: Acute myeloid leukemia

MDS: Myelodysplastic syndrome

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



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



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