Molecular monitoring versus standard clinical care in younger adults with acute myeloid leukaemia: results from the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials

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Summary

Background In patients with acute myeloid leukaemia treated with curative intent, the detection of measurable residual disease (MRD) generally confers a poor prognosis. This study aimed to identify whether altering treatment based on MRD results can improve survival.

Methods In the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials, performed in the UK, Denmark, and New Zealand, we screened patients aged 16–60 years with newly diagnosed acute myeloid leukaemia for molecular markers suitable for disease monitoring, including *NPM1* mutations and fusion genes. Patients with a marker were randomly assigned (2:1) to either sequential molecular MRD monitoring during treatment and for 3 years after, or standard clinical care only with no molecular monitoring. In the monitoring group, treating physicians decided whether and how to incorporate the MRD results into the patient's therapy, including in cases of MRD relapse. The primary endpoint was overall survival. Prespecified subgroup analysis of the primary outcome included analysis by molecular group (*NPM1*^{mut} with *FLT3*-ITD, *NPM1*^{mut} without *FLT3*-ITD, and fusion gene transcripts). Both trials were registered with ISRCTN, ISRCTN55675535 and ISRCTN78449203, and are completed.

Findings In the AML17 trial, 1836 patients were enrolled between June 1, 2012 and Dec 31, 2014. In the AML19 trial, 965 patients were enrolled between Nov 9, 2015, and Jan 23, 2018. 637 patients were randomly assigned across both trials (289 to MRD monitoring and 144 to no monitoring in AML17 and 136 to MRD monitoring and 68 to no monitoring in AML19). With a median follow-up time of 4·9 years (IQR 3·6–5·9), overall survival at 3 years was 70% (95% CI 66–75) in patients in the monitoring group and 73% (68–80) in patients in the no-monitoring group. Meta analysis of the two studies showed no difference in overall survival (hazard ratio [HR] 1·11, 95% CI 0·83–1·49; p=0·25). In the pre-specified subgroup analysis of the primary endpoint, overall survival at 3 years in patients with both *NPM1* and *FLT3* internal tandem duplication (ITD) mutations was 69% (95% CI 60–79) in the monitoring group and 58% (45–74) in the no-monitoring group (HR 0·53, 95% CI 0·31–0·91; p=0·021). However there was no difference in survival by randomisation in patients with *NPM1* mutations without *FLT3*-ITD (overall survial 69% [95% CI 62–77] in the monitoring group and 78% [70–87] in the no monitoring group; HR 1·56, 95% CI 0·96–2·52) or those with fusion gene transcripts (overall survial 72% [95% CI 65–79] in the monitoring group and 77% [68–87] in the no monitoring group; HR 1·28, 95% CI 0·80–2·18).

Interpretation Sequential molecular MRD monitoring, coupled with MRD-guided treatment, did not improve overall survival in the entire study population; however, in the subgroup of patients with baseline *NPM1* and *FLT3* ITD mutations, we observed a survival benefit for MRD monitoring.

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Introduction

Acute myeloid leukaemia (AML) has a poor prognosis due to a high incidence of relapse and treatment-related mortality. Treatment with curative intent generally involves intensive induction and consolidation chemotherapy with or without allogeneic haematopoietic stem-cell transplantation (HSCT).[1] These treatments are associated with significant short-term and long-term toxicity, therefore improved risk stratification might improve outcomes by allowing the most toxic treatments to be reserved for those at highest risk of relapse. In this regard, highly sensitive techniques to detect measurable residual disease (MRD) after treatment have been repeatedly shown to add prognostic information to that

Research in context

Evidence before this study

We performed a PubMed search on April 3, 2024, for articles in English using the terms "measurable residual disease" OR "minimal residual disease" OR "MRD" AND "AML". We retrieved 2161 articles published between 1990 and 2024, including 177 clinical trials, most of which either reported an association between measurable residual disease (MRD) and survival, or reported MRD as a secondary endpoint of a clinical trial, or both. We found a meta-analysis of 81 clinical studies including 11 151 patients with acute myeloid leukaemia, in which overall survival and MRD were measured. When comparing patients testing negative for MRD with those testing positive for MRD, the pooled hazard ratio for overall survival was 0·37. We found no studies where patients had been randomly assigned to receive MRD monitoring or MRD-guided interventions versus standard clinical care. We found two studies where a randomised intervention was retrospectively shown to be more beneficial in patients positive for MRD. The first was a randomised trial of reduced intensity versus myeloablative conditioning before allogeneic stem-cell transplantation (HSCT), where only patients testing positive for MRD showed a benefit from myeloablative conditioning. The second was a randomised, placebo-controlled trial of the FLT3 inhibitor gilteritinib as maintenance after allogeneic HSCT, where only patients testing positive for MRD showed a benefit from gilteritinib.

Added value of this study

To our knowledge, this is the first randomised study comparing molecular MRD monitoring and MRD-guided treatment against standard clinical care with no monitoring. Our results showed that MRD monitoring did not improve overall survival compared with standard clinical care across the whole enrolled population. In a prespecified analysis of molecular subgroups, we observed a reduction in the risk of death in patients randomly assigned to monitoring who had baseline *NPM1* and *FLT3*-ITD mutations. Conversely, there was no survival benefit for monitoring in patients with baseline *NPM1* mutation without *FLT3*-ITD, or in patients with fusion gene transcripts. The most common MRD-guided intervention was pre-emptive salvage treatment at MRD relapse.

Implications of all the available evidence

MRD is well established as a prognostic biomarker in acute myeloid leukaemia. However, our data, together with other recent studies, now provide strong evidence that it can also serve as a predictive biomarker, in that in specific molecular subgroups, therapeutic intervention based on MRD results can improve patient outcomes.

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See **Online** for appendix

available at diagnosis.[2] Moreover, all patients with serially rising levels of MRD (called MRD relapse) subsequently progress to overt clinical relapse over a period of weeks to months,[1] potentially providing a window for pre-emptive intervention to prevent this.

A major unresolved question is whether MRD simply identifies patients with a poor prognosis, or whether interventions guided by MRD status can improve outcome: that is, whether it is a predictive as well as prognostic biomarker. This question has important implications for the incorporation of MRD status into treatment algorithms, as well as for the design of future clinical trials. To date, this issue has not been addressed in a randomised study.

MRD can be detected by flow cytometric or molecular assays.[3] Although both methods provide powerful prognostic information when used during the treatment period,[2,3] molecular assays generally provide a higher level of sensitivity and specificity, allowing their use in longitudinal assessment after the completion of treatment for the early detection of relapse.[3] Although AML is molecularly heterogeneous, a third of younger adults have insertions in the gene encoding nucleophosmin[4] (*NPM1*) and a further third have genomic rearrangements that generate an expressed in-frame fusion gene.[5] Both types of lesion are suitable for detection using reverse transcription quantitative PCR (RT-qPCR).[6]

Several large studies in patients with the *NPM1* mutation (*NPM1*^{mut})[7–9] and the most common fusion genes (ie, *CBFB::MYH11* and *RUNX1::RUNX1T1*)[10–12] have shown that the inadequate clearance of disease-related transcripts after treatment is associated with a greatly elevated risk of relapse and death and that serially rising levels of these and other rarer fusion transcripts[13,14] reliably predict clinical relapse. In acute promyelocytic leukaemia (APL), a unique disease subtype characterised by the *PML::RARA* fusion, treatment with arsenic trioxide at the time of MRD relapse prevents haematological relapse,[15] results in improved survival, and is recommended by international treatment guidelines.[16] Conversely there is currently no standard treatment for MRD relapse in non-APL AML.

Non-randomised data suggest that patients with a poor MRD response benefit from HSCT,[8,17,18] and post-hoc analysis of two randomised studies has shown a benefit for intensified conditioning[19] and post-transplantation maintenance therapy[20] in patients with detectable MRD undergoing HSCT. However, it is unclear whether treatment modification based on MRD results more generally can improve outcomes. Specifically, it is unclear whether treatment at the time of MRD relapse has a better outcome than treatment at clinical relapse, and lead time and other inherent biases in retrospective studies make this question impossible to definitively answer without randomisation.

To address these issues, we conducted a randomised study within two prospective clinical trials to compare overall survival between patients undergoing sequential molecular MRD monitoring, with results provided to clinicians to inform treatment, against standard clinical care without molecular monitoring.

Methods

Study design and participants

This study was performed within two large, randomised, controlled phase 3 trials for younger adults (generally aged 16–60 years; patients aged older than 60 years could enter after discussion with a trial co-ordinator) with newly diagnosed AML and a WHO performance status of 0–2, suitable for intensive chemotherapy. Full details of the inclusion and exclusion criteria have previously been reported.[21] NCRI AML17 (ISRCTN55675535) recruited patients from 136 hospitals in the UK, Denmark, and New Zealand between Sept 15, 2008, and Dec 31, 2014. During a validation period from Sept 15, 2008, to Dec 18, 2011, patients were screened for molecular MRD markers and serial samples were tested, but results were not returned to clinicians: these results have previously been reported.[9] From June 1, 2012, to Dec 31, 2014, patients with non-APL AML were enrolled and screened for molecular MRD markers: patients with an identified marker could be randomly assigned (2:1) between the monitoring and no monitoring groups. NCRI AML19 recruited patients from 123 hospitals in the UK, Denmark, and New Zealand between Nov 9, 2015, and Oct 26, 2021. Between Nov 9, 2015, and Jan 23, 2018, patients with non-APL AML enrolled and were screened for molecular markers. Eligibility for random assignment for the monitoring group differed in AML19 because of newly available data[9] regarding the high risk of relapse in patients with *NPM1*^{mut} with detectable MRD in the peripheral blood after the second course of chemotherapy. The study group therefore decided that all patients with *NPM1*^{mut} should have MRD monitoring after the first two courses of treatment, and those who tested positive for MRD in the peripheral blood after the second course of treatment (PC2) were excluded from random assignment. Patients with a molecular marker other than *NPM1*^{mut} could be randomly assigned as soon as this random assignment was identified and did not have to wait for MRD PC2 results. After entering AML17 and AML19, separate written informed consent was required to enter random assignment between the monitoring and no monitoring groups. Patients declining to participate in this part of the study could still continue in the main study. The trials were approved by Wales Research Ethics Committee 3 (reference numbers 08/MRE09/29 and 14/WA/1056).

Both trials were registered with ISRCTN, ISRCTN55675535 and ISRCTN78449203, and are completed.

Randomisation and masking

Random assignment in both studies was performed by an interactive web-based system and had to take place within 60 days of trial entry, or in the case of patients with *NPM1*^{mut} in NCRI AML19, within 60 days of peripheral blood MRD PC2 negative status being reported. No masking or blinding was used. Patients were randomly assigned (2:1) to the monitoring group or the no monitoring group, and randomisation was balanced using a minimisation algorithm that incorporated age, white blood cell count, disease type, and molecular marker. We did not collect the reasons for which eligible patients were not randomly assigned.

Procedures

G-banded karyotype and fluorescence in-situ hybridisation were performed according to local protocols using peripheral blood or bone marrow samples taken before treatment had started and the results were entered into a web-based case report form by local accredited diagnostic laboratories. Results were reviewed centrally and when these results suggested the presence of a fusion gene, this was confirmed centrally by RT-qPCR using previously published assays.[6] RNA sequencing using a targeted panel was used where cytogenetics suggested a fusion gene but standard assays were negative or not available, and these results were used to design a patient-specific RT-qPCR assay (appendix p 7). All patients with a confirmed fusion gene were eligible for random assignment. All patients underwent central screening for mutations in *NPM1* and *FLT3* using PCR-based methods. Patients with *FLT3* internal tandem duplication (ITD) without *NPM1*^{mut} were screened for *NUP98::NSD1* and *DEK::NUP214* fusions by RT-qPCR; where identified, these patients were also eligible for random assignment.

Patients were randomly assigned to different anthracycline-based and cytarabine-based induction and consolidation regimens (appendix p 8). The results of these randomisations, which were the primary outcome of these trials, are reported elsewhere.[21] Apart from patients who were randomly assigned to either lestaurtinib and placebo, (until Oct 8, 2012), no *FLT3* inhibitors were used during induction or consolidation therapy. Patients were considered high risk if they had an adverse karyotype by Medical Research Council criteria,[22] if they had a *FLT3* ITD without *NPM1*^{mut}, or if they had a validated risk score (comprising clinical risk factors and early response) of more than 2·667 (appendix p 7). Because the peripheral blood PC2 MRD status was shown to outweigh the risk score for patients with *NPM1*^{mut} in AML17, it was not applied to patients with *NPM1*^{mut} in AML19: only patients testing positive for MRD PC2 were considered high risk, and were excluded from random assignment in this study. All patients designated high risk were recommended to receive allogeneic HSCT in first complete remission; and in AML19, they could also enter a separate random assignment between liposomal cytarabine and

daunorubicin (CPX351), and a combination including fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin (FLAG-Ida).[23]

Patients with clinical relapse could enter a different substudy of either trial (relapse group) if it was open at the time they relapsed. In AML17, these patients were randomly assigned between daunorubicin and clofarabine, and FLAG-Ida. In AML19, they were randomly assigned between CPX351 and FLAG-Ida.[23] Patients not entering the relapse groups could receive salvage therapy off protocol at the discretion of the treating team.

Paired peripheral blood (20 mL) and bone marrow aspirate (5 mL) samples collected in EDTA (edetic acid) were requested after each cycle of chemotherapy, at days 30, 60, and 100 after allogenic HSCT for patients undergoing transplantation, and then every 3 months for 3 years from the end of last treatment for all patients. Early repeat samples were requested when samples were inadequate (defined as *ABL* cycle threshold >26, when a repeat within 1 or 2 months was requested, depending on the sample quality) or if there were concerns about molecular relapse or progression (when an immediate repeat was recommended). Samples underwent RNA extraction, complementary DNA synthesis, and RT-qPCR (appendix p 7) in accordance with previously published protocols for the detection of fusion gene[6] and *NPM1*^{mut} transcripts.[9] The *ABL1* gene was amplified in parallel to control for RNA quantity and quality. Commercial plasmid standards (Qiagen, Hilden, Germany) were used to quantify common leukaemia-related transcripts, with the difference-in-cycle-thresholds method used for rare transcripts. All samples were analysed in triplicate, and MRD positivity was defined as amplification with a cycle threshold of less than 40 in two or three replicates in accordance with European LeukaemiaNet guidelines.[3]

We did not use next-generation sequencing MRD either for *FLT3*-ITD or other mutations during this study because it was not clinically validated. Consequently, patients with *FLT3*-ITD mutations were monitored using co-existing *NPM1* mutated or fusion gene transcripts.

Results were reported to participating centres within 2 weeks of sampling using standardised automated email templates, which also contained recommendations for repeat sampling. Molecular relapse was diagnosed when there was a conversion from MRD negativity to positivity, which was confirmed in a second consecutive sample. Molecular progression was diagnosed when there was an increase in MRD by more than 1 $\log_{10}$, and this was confirmed on a second consecutive sample. Both of these situations would now be diagnosed as MRD relapse using the current European LeukaemiaNet criteria.[3] The decision whether or not to change treatment was made by the treating physician, with management advice on request from the chief investigator. There were no protocol-specified MRD-guided interventions, but patients with MRD relapse in AML19 were eligible to enter the relapse group.[23]

Details of adverse events were not collected in the monitoring group because individual clinicians were free to choose any appropriate therapy or none. Data regarding toxicity were collected for the different therapeutic groups and have previously been reported.[21,23]

After the trials finished recruitment, questionnaires were sent to treating physicians for patients randomly assigned to the monitoring group to establish if MRD results influenced the treatment of each patient at any stage. Specific questions were asked to identify if MRD results influenced first-line treatment, influenced the decision to perform allogenic HSCT, influenced pre-allogenic HSCT and post-allogenic HSCT therapy, and whether pre-emptive treatment was used for patients diagnosed with MRD relapse.

Outcomes

The primary endpoint was overall survival, measured from the time of random assignment into the monitor or no monitor group to the time of death or last recorded follow-up. Prespecified subgroup analysis of the primary outcome included analysis by molecular group (*NPM1*^{mut} with *FLT3*-ITD, *NPM1*^{mut} without *FLT3*-ITD, and fusion gene transcripts). Secondary endpoints included relapse-free survival time, cumulative incidence of relapse, and cumulative incidence of death in complete remission. These were measured from the date of randomisation to the date of haematological relapse or death (relapse-free survival time), the date of haematological relapse (cumulative incidence of relapse), or the date of death not preceded by haematological relapse (cumulative incidence of death in complete remission).

For cumulative incidence of relapse, death not preceded by haematological relapse was considered a competing risk, and for cumulative incidence of death in complete remission, haematological relapse was considered a competing risk. Isolated extramedullary relapse (emergence or re-emergence of disease at an extramedullary site with <5% blasts in the blood and bone marrow) was considered as a haematological relapse event. For the monitoring group, we additionally calculated relapse-free survival time for all relapse events (including MRD relapse), cumulative incidence of relapse for all relapse events, and cumulative incidence of death in complete remission, in which MRD relapse was considered as a relapse event and therefore a competing risk.

Statistical analysis

The target sample size was 600 patients, and 198 deaths were required to provide 80% power to detect a hazard ratio of 0·67 using the log-rank test. We performed a fixed-effects inverse variance model meta-analysis of the two trials using the Stata Meta package (version 18), which was also used to calculate heterogeneity statistics.

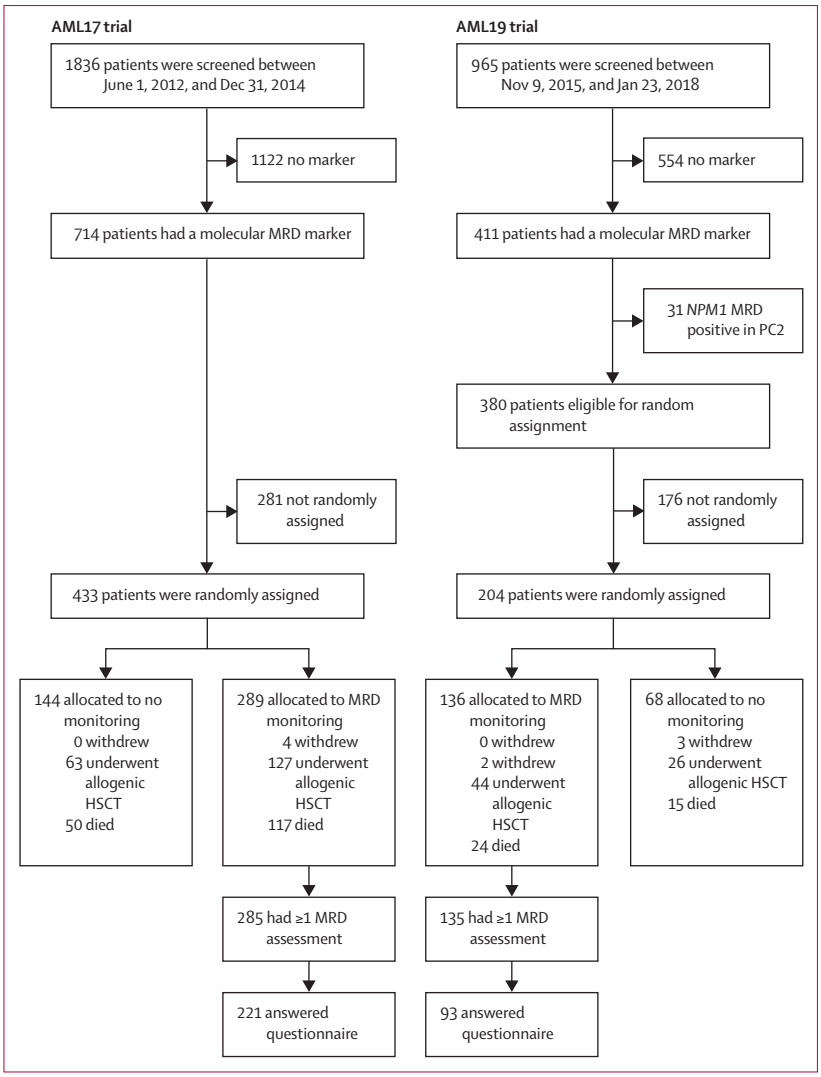

Figure 1: **Trial profile**
MRD=measurable residual disease. PC2=peripheral blood after the second course of treatment. HSCT=allogenic stem cell transplantation.

Homogeneity of study-specific effect sizes was assessed using a χ^2 test statistic. The estimate of the overall effect size was computed as the weighted average of study-specific effect sizes. Analysis was stratified by molecular marker: *NPM1*^{mut} *FLT3*-ITD^{negative}, *NPM1*^{mut} *FLT3*-ITD^{positive}, and fusion gene transcripts. The statistical analysis plan originally intended to analyse patients with core binding factor AML (ie, *CBFB::MYH11* or *RUNX1::RUNX1T1*) separately; however, there were no deaths among patients in this group in AML19, so this analysis was not possible. Therefore, in Jan 18, 2023, the statistical analysis plan was amended to group patients with core binding factor AML together with those with other fusion gene transcripts. We performed a post-hoc analysis according to the current version of the European Leukaemia Network risk group. A post-hoc sensitivity analysis was also performed excluding patients in AML17 who were peripheral blood MRD PC2 positive, because of the difference in inclusion criteria between the trials. A key aim of MRD monitoring is to identify patients who are destined to relapse and provide pre-emptive treatment when the patient is still in clinical remission; therefore, we performed a post-hoc analysis of the feasibility and outcomes of this approach.

Time-to-event endpoints were analysed using the Kaplan–Meier method and compared using the log-rank test. Unadjusted hazard ratios were reported, but additional sensitivity analyses adjusting for all minimisation factors (age, white blood cell count, disease type, and molecular group) using Cox regression models were also performed. If adjustment for all factors was not possible (eg, in molecular subgroups), sensitivity analysis adjusting for individual factors was attempted. Proportional hazards testing was performed by the scaled Schoenfeld residuals method before regression analyses, with no violation of the proportional hazards assumption found. Competing risk analyses were performed using Grey's test. All analyses were stratified by trial. Analyses were performed using STATA version 18.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the AML17 trial, 1836 patients were enrolled between June 1, 2012 and Dec 31, 2014. MRD markers were identified in 714 (39%) patients and 433 patients were randomly assigned: 289 to MRD monitoring and 144 to no monitoring. In the AML19 trial, 965 patients were enrolled between Nov 9, 2015, and Jan 23, 2018; MRD markers were identified in 411 (43%) patients, 31 patients were excluded from random assignment because of peripheral blood *NPM1* MRD PC2 positivity and 204 patients were randomly assigned: 136 to MRD monitoring and 68 to no monitoring, for a total of 637 patients randomly assigned across both trials (figure 1). The median follow-up time for all patients by reverse Kaplan–Meier analysis was 4·9 years (IQR 3·6–5·9); 5·5 years (4·9–6·4) for patients enrolled in AML17 and 3·6 years (3·0–4·1) for those in AML19.

The MRD marker identified was *NPM1*^{mut} in 399 (63%) of 637 patients (of whom 140 had a *FLT3*-ITD), *CBFB::MYH11* in 87 (14%) patients, *RUNX1::RUNX1T1* in 62 (10%) patients, *KMT2A::R* in 55 (9%) patients, and a rare fusion gene in 34 (5%) patients (appendix p 14). Baseline clinical and molecular characteristics were similar between trials and randomised groups and are shown in the table. We did not identify any major differences in baseline clinical or molecular features between patients who entered the monitoring group and

	AML17		AML19		Overall	
	No monitoring (n=144)	Monitoring (n=289)	No monitoring (n=68)	Monitoring (n=136)	No monitoring (n=212)	Monitoring (n=425)
Age, years	51 (16–70)	51 (16–69)	50 (20–64)	50 (18–67)	50 (16–70)	50 (16–69)
16–29	15 (10%)	29 (10%)	8 (12%)	16 (12%)	23 (11%)	45 (11%)
30–39	17 (12%)	38 (13%)	12 (18%)	24 (18%)	29 (14%)	62 (15%)
40–49	35 (24%)	63 (22%)	14 (21%)	28 (21%)	49 (23%)	91 (21%)
50–59	42 (29%)	88 (30%)	29 (43%)	57 (42%)	71 (33%)	145 (34%)
≥60	35 (24%)	71 (25%)	5 (7%)	11 (8%)	40 (19%)	82 (19%)
Sex						
Male	69 (48%)	143 (49%)	31 (46%)	65 (48%)	100 (47%)	208 (49%)
Female	75 (52%)	146 (51%)	37 (54%)	71 (52%)	112 (53%)	217 (51%)
White cell count, ×10⁹/L	14·1 (0·8–275·2)	19·5 (0·5–456·0)	18·5 (0·8–252·0)	16·5 (0·6–202·1)	14·7 (0·8–275·2)	18·6 (0·5–456·0)
<10	62 (43%)	108 (37%)	27 (40%)	54 (40%)	89 (42%)	162 (38%)
10–49·9	48 (33%)	113 (39%)	24 (35%)	49 (36%)	72 (34%)	162 (38%)
50–99·9	23 (16%)	41 (14%)	12 (18%)	27 (20%)	35 (17%)	68 (16%)
≥100	11 (8%)	27 (9%)	5 (7%)	6 (4%)	16 (8%)	33 (8%)
Disease history						
De-novo AML	135 (94%)	270 (93%)	64 (94%)	130 (96%)	199 (94%)	400 (94%)
Secondary AML	6 (4%)	14 (5%)	2 (3%)	2 (1%)	8 (4%)	16 (4%)
High risk MDS	3 (2%)	5 (2%)	2 (3%)	4 (3%)	5 (2%)	9 (2%)
European LeukaemiaNet 2022 risk group						
Favourable	95 (66%)	175 (61%)	40 (59%)	97 (71%)	135 (64%)	272 (64%)
Intermediate	39 (27%)	89 (31%)	19 (28%)	29 (21%)	58 (27%)	118 (28%)
Adverse	10 (7%)	25 (9%)	9 (13%)	10 (7%)	19 (9%)	35 (8%)
FLT3-ITD mutation	36 (25%)	80 (28%)	16 (24%)	27 (20%)	52 (25%)	107 (25%)
FLT3-TKD mutation	16 (11%)	28 (10%)	5 (7%)	14 (10%)	21 (10%)	42 (10%)
MRD marker						
NPM1 mutation	95 (66%)	187 (65%)	40 (59%)	77 (57%)	135 (64%)	264 (62%)
NPM1 with *FLT3*-ITD	33 (23%)	74 (26%)	13 (19%)	20 (15%)	46 (22%)	94 (22%)
NPM1 without *FLT3*-ITD	62 (43%)	113 (39%)	27 (40%)	57 (42%)	89 (42%)	170 (40%)
CBFB::MYH11	18 (13%)	33 (11%)	10 (15%)	26 (19%)	28 (13%)	59 (14%)
RUNX1::RUNX1T1	15 (10%)	30 (10%)	3 (4%)	14 (10%)	18 (8%)	44 (10%)
KMT2A::R	9 (6%)	25 (9%)	9 (13%)	12 (9%)	18 (8%)	37 (9%)
Rare fusions	7 (5%)	14 (5%)	6 (9%)	7 (5%)	13 (6%)	21 (5%)
DEK::NUP214	2	7	1	2	3	9
NUP98::R	0	1	2	3	2	4
KAT6A::CREBBP	2	1	0	1	2	2
BCR::FGFR1	0	0	0	1	0	1
ETV6::PDGFRA	0	0	1	0	1	0
RUNX1::MECOM	1	0	1	0	2	0
BCR::ABL1	0	2	1	0	1	2
PICALM:MLLT10	1	1	0	0	1	1
RUNX1::CBFA2T3	0	1	0	0	0	1
RUNX1::PRDM16	0	1	0	0	0	1
NPM1::MLF1	1	0	0	0	1	0

Data are median (range), n (%), or n. AML=acute myeloid leukaemia. ITD=internal tandem duplication. MDS=myelodysplastic syndrome. MRD=measurable residual disease. TKD=tyrosine kinase domain.

Table: **Baseline clinical and molecular characteristics for all patients entering the randomisation**

patients who were eligible but not randomly assigned (appendix pp 9–10).

Allogeneic HSCT was performed in 260 (41%) of 637 patients. Fewer allogenic HSCTs were performed in AML19 compared with AML17 (70 [34%] of 204 *vs* 190 [44%] of 433; p=0·020). There were no differences in the number of allogenic HSCTs performed according to randomly assigned group (AML17 monitoring,

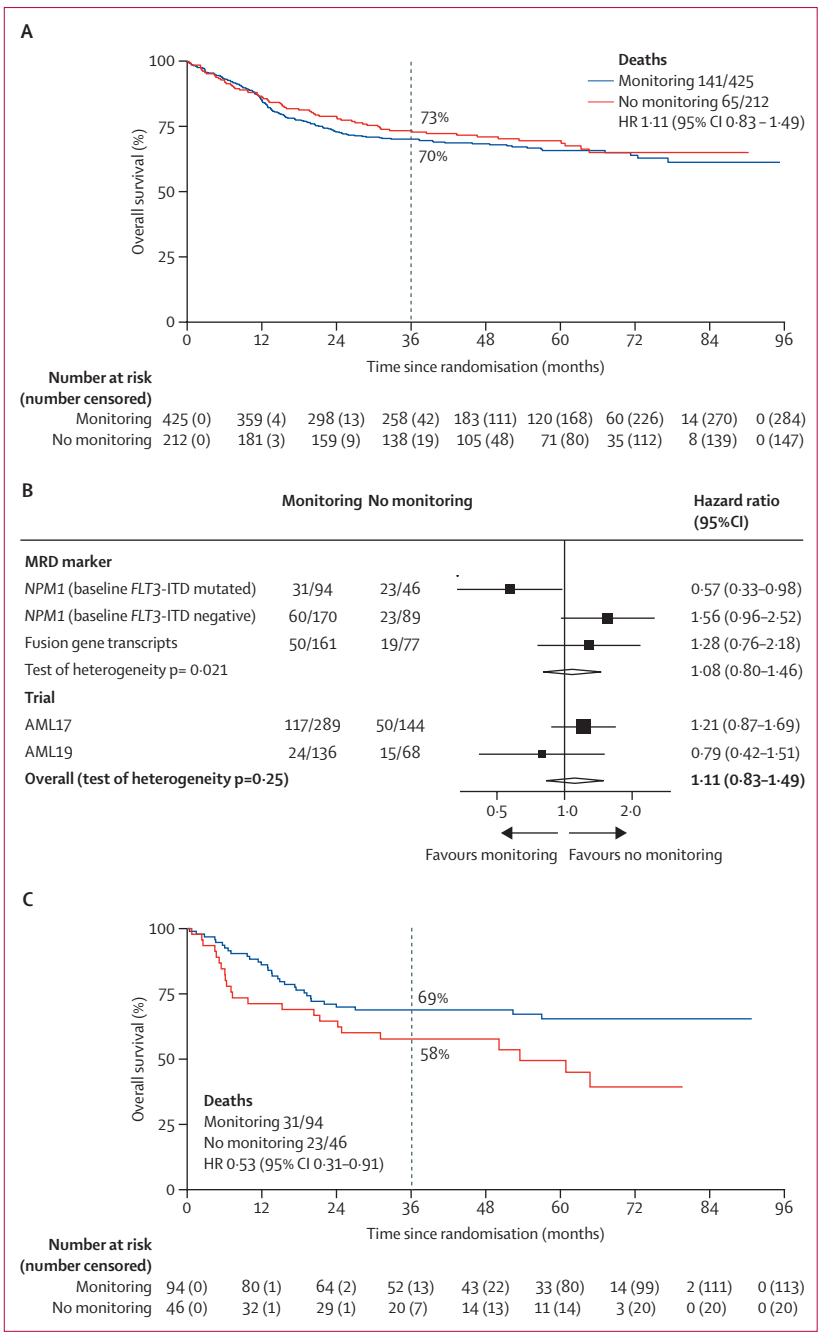

***Figure 2*: Overall survival for patients in the monitoring *vs* no-monitoring randomisation**
(A) Overall survival according to randomly assigned group, considering all patients randomly assigned across both trials. (B) Prespecified analysis of overall survival in each molecular subgroup and by trial. (C) Overall survival according to random assignment for patients with *NPM1* and *FLT3*-ITD mutations. HR=hazard ratio. ITD=internal tandem duplication.

127 [44%] of 289 *vs* no monitoring, 63 [44%] of 144; p=1·00; and AML19 monitoring, 44 [32%] of 136 *vs* no monitoring 26 [38%] of 68; p=0·47); figure 1.

A total of 8177 samples were assessed for MRD at 4826 timepoints. Of these timepoints, 3351 were assessed with paired peripheral blood and bone marrow aspirate, 1059 with bone marrow aspirate only, and 416 with peripheral blood only. 420 (99%) of 425 patients randomly assigned to MRD monitoring had at least one MRD assessment performed at any time, and the median number of bone marrow aspirate samples assessed for MRD was 11 per patient (range 1–37) and the median number of peripheral blood samples was eight per patient (range 0–29).

A total of 206 (32%) of 637 patients died during the study, exceeding the prespecified number of deaths (198) required to provide 80% power to detect a hazard ratio (HR) for overall survival of 0·67. The estimated overall survival at 3 years across both studies was 70% (95% CI 66–75) in patients in the monitoring group and 73% (68–80) in patients in the no monitoring group. Meta-analysis of the two studies showed no difference in overall survival (HR 1·11, 95% CI 0·83–1·49; p=0·25; figure 2A and B). These HRs were essentially unchanged when adjusting for age, white blood cell count, disease type, or molecular group (data not shown). Estimated overall survival at 3 years was 64% (95% CI 58–70) in patients in the monitoring group and 71% (64–79) in patients in the no monitoring group in AML17 (HR 1·21, 95% CI 0·87–1·69; appendix p 15) and 84% (78–90) and 78% (69–89) in AML19 (HR 0·79, 95% CI 0·42–1·51; appendix p 15).

In a prespecified subgroup analysis, we detected an overall survival benefit for monitoring in patients with both *NPM1*^{mut} and *FLT3*-ITD (3-year overall survival 69% [95% CI 60–79] in the monitoring group and 58% [45–74] in the no monitoring group; HR 0·53, 95% CI 0·31–0·91; p=0·021; figure 2B and 2C) with significant heterogeneity between this subgroup and all other patients. The overall survival benefit for monitoring was consistent between the two trials (AML17, HR 0·54, 95% CI 0·31–0·96; and AML19, HR 0·40, 95% CI 0·07–2·38; appendix p 16). Because of the difference in inclusion criteria, specifically the exclusion of patients with *NPM1* mutation who were MRD PC2 positive from the monitoring group in AML19, we performed a post-hoc sensitivity analysis. When patients in AML17 known to be peripheral blood MRD PC2 positive were excluded from the analysis, the survival benefit was maintained (HR 0·41, 95% CI 0·23–0·74; p=0·0032; appendix p 16). There was no difference in survival by randomisation in patients with *NPM1*^{mut} without *FLT3*-ITD (HR 1·56, 95% CI 0·96–2·52) or those with fusion gene transcripts (HR 1·28, 95% CI 0·80–2·18). (appendix p 17). In a post-hoc analysis there was no difference in survival by randomisation according to European LeukaemiaNet risk group (appendix p 18).

Using the standard definitions, there was a significant reduction in the cumulative incidence of relapse in patients in the monitoring group (HR 0·66, 95% CI 0·49–0·88; figure 3A) and a significant improvement in relapse-free survival time (HR 0·78, 95% CI 0·61–0·99; figure 3B). No significant heterogeneity in relapse-free survival time benefit from monitoring was observed when

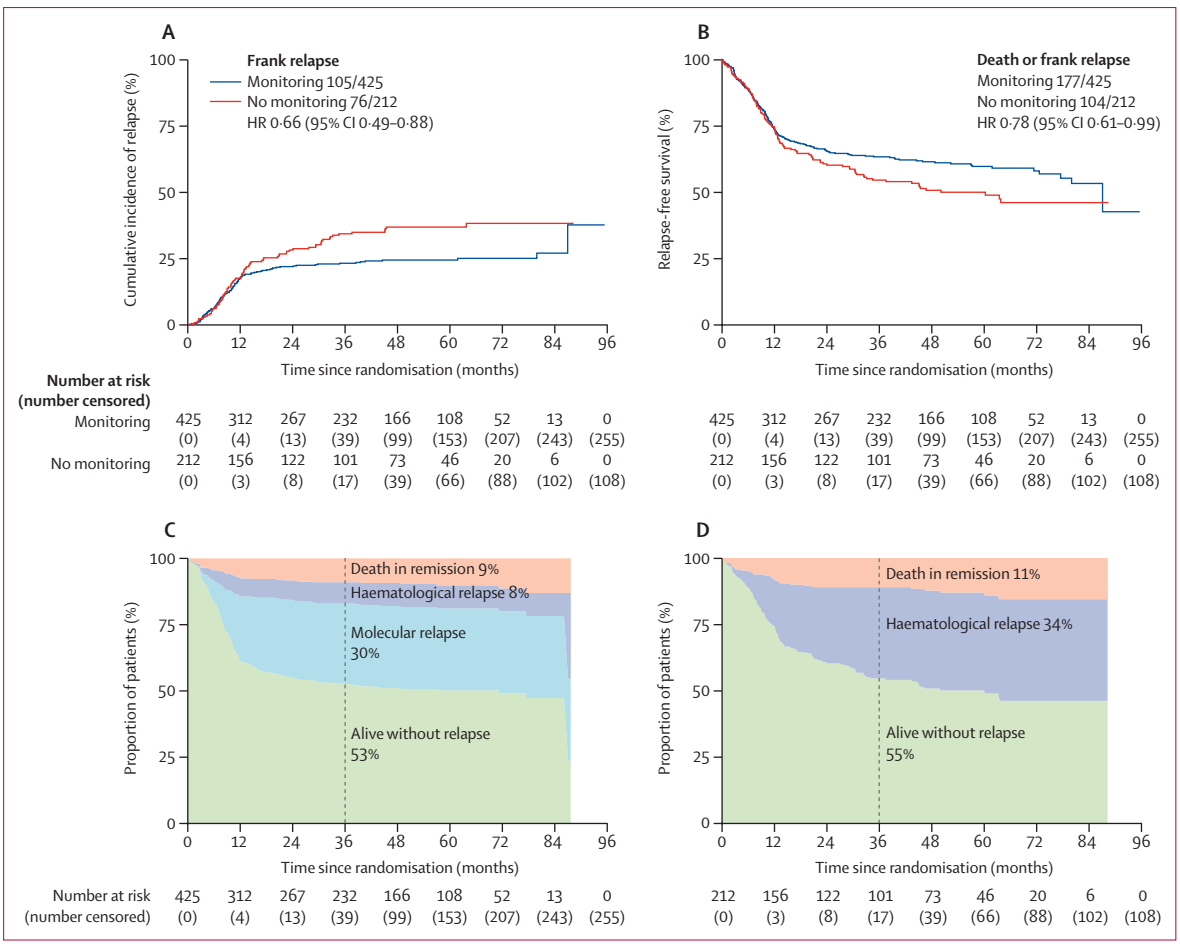

Figure 3: **Cumulative incidence of relapse and relapse-free survival for patients in the monitor *vs* no-monitor randomisation**
(A) Cumulative incidence of relapse according to randomly assigned group. (B) Relapse-free survival according to randomly assigned group. In both (A) and (B), MRD relapse was not considered a relapse event. An alternative analysis including these as events is shown in the appendix (p 22). (C) Stacked cumulative incidence plot showing the cumulative incidence of death, molecular relapse, or morphological relapse for patients in the monitoring group. (D) Stacked cumulative incidence plot showing the cumulative incidence of death and morphological relapse in the no-monitoring group. In both (C) and (D), where more than one of these events occurred, only the first is shown, and each is treated as a competing risk for the other events. Frank relapse=haematological or extramedullary relapse. MRD=measurable residual disease.

analysed by trial, molecular subgroup, or European LeukaemiaNet2022 risk group, the latter being a post-hoc analysis (appendix pp 18–21). When we performed a post-hoc analysis including confirmed MRD relapse as a relapse event in the monitoring group (here called relapse-free survival time for all), these differences were no longer apparent (cumulative incidence of relapse for all, HR 1·20, 95% CI 0·92–1·56; and relapse-free survival time, HR 1·09, 95% CI 0·86–1·38; appendix p 22). The time from relapse to allogenic HSCT did not differ between groups (appendix p 12).

There was no difference in the cumulative incidence of death in complete remission between groups, either when considering haematological relapse, or both haematological and MRD relapse as competing risks (appendix pp 24–25). The causes of death did not differ significantly by group (appendix p 12). Stacked cumulative incidence plots showing the rates of death in complete remission, molecular relapse, and haematological relapse are shown in figure 3C and D.

As part of a post-hoc analysis, confirmed MRD or haematological relapse was reported in 166 (39%) of 425 patients in the MRD monitoring group and was more frequent in AML17 than AML19 (AML17, 127 [44%] of 289 *vs* AML19, 39 [29%] of 136). 75 (45%) of 166 patients received treatment at MRD relapse when in haematological remission. This proportion was higher in AML19 (24 [62%] of 39) compared with AML17 (51 [40%] of 127).

Pre-emptive treatment was not given to the other 91 (55%) of 166 patients who relapsed. The reasons for this are shown in the appendix (p 25). Monitoring did not detect clinical relapse in 14 (8%) patients: in nine patients, clinical relapse was associated with low or negative MRD results, and in five patients (including three with isolated extramedullary relapse), clinical relapse occurred

between scheduled bone marrow assessments. In a further 11 (7%) patients, clinical relapse occurred within the monitoring period but after discontinuation of monitoring for patient or physician choice. Therefore, overall, 25 relapses (15%) were not detected by monitoring. Monitoring detected MRD relapse but did not provide a window period for pre-emptive treatment in a further 55 (33%) patients: routine samples taken for monitoring showed morphological relapse in 25 patients and morphological relapse was detected on the second sample taken to confirm MRD relapse in a further 30 patients. Monitoring provided a window period but pre-emptive therapy was not delivered before overt relapse in 11 (7%) patients, in whom the median time between confirmation of MRD relapse and starting treatment was 36 days (range 14–660 days). We did not identify a relationship between the patients' molecular markers and the likelihood of receiving pre-emptive treatment treatment in a post-hoc analysis (data not shown).

The most common treatment for MRD relapse was intensive salvage chemotherapy in 61 (81%) of 75 patients, and most patients received the FLAG-Ida regimen (49 patients), followed by CPX351 (11 patients), or fludarabine with CPX351 (one patient). For these 61 patients receiving intensive salvage therapy for MRD relapse in clinical remission, 31 (51%) became MRD negative and 17 (28%) were MRD positive but had a more than 1-log reduction in MRD, for an overall molecular response rate of 79%. Eight (13%) patients were MRD positive with no change in level, two (3%) patients had a more than 1-log increase in MRD, two (3%) patients progressed to clinical relapse, and one (2%) patient died during aplasia. Two patients did not receive salvage chemotherapy and proceeded straight to transplantation, and the other 14 (19%) of 75 patients received various non-intensive treatments, including four patients who had changes to immunosuppression or donor lymphocyte infusion, or both; four patients who received *FLT3* inhibitors (two patients who received sorafenib, one patient who received pacritinib, and one patient who received gilteritinib), and one patient each who received azacitidine monotherapy and entered a phase 1 clinical trial.

In the no-monitoring group, relapse occurred in 65 patients who had not previously undergone allogenic HSCT, and 40 (62%) received a transplantation after relapse. In the monitoring group, MRD or haematological relapse occurred in 146 patients who had not previously undergone allogenic HSCT, and 97 (66%) received a transplantation after relapse. Considering only patients with MRD relapse, 93 (74%) of 125 patients received a transplantation after relapse.

To understand how MRD results were used to guide treatment, treating physicians were asked to complete a questionnaire for each patient randomly assigned to the MRD monitoring group, and these were returned for 314 (74%) of 425 patients (figure 1). Treatment change based on MRD was reported in 133 (42%) of 314 patients overall and was higher in AML19 than AML17 (AML17, 81 [37%] of 221 *vs* AML19, 52 [56%] of 93). Treatment changes are detailed in the appendix (p 13). The most common treatment change was pre-emptive salvage therapy at MRD relapse, reported in 65 (20%) of 314 patients, followed by a change in peri-transplant management including conditioning regimen, immunosuppression, and use of donor lymphocyte infusion (41 [13%] of 314), change in the number of induction and consolidation chemotherapy cycles (17 [5%] of 314), and a decision whether or not to perform transplantation for the patient in first complete remission (ten [3%] of 314).

Discussion

Although current guidelines recommend sequential MRD monitoring for patients with AML with a molecular marker,[3] to date, no studies have examined whether this practice improves survival. In this large randomised study, we did not identify a survival benefit for MRD monitoring overall. However, in the subgroup of patients with both *NPM1* and *FLT3*-ITD mutations, which accounted for 22% of patients, we identified a large survival benefit that was consistent between trials. Molecular monitoring was associated with a reduction in the risk of death by approximately a half in these patients. Since additional monitoring uses specialist resources, and might affect a patients' quality of life, appropriate assessments were undertaken as part of the protocol and will be reported elsewhere.

The specific benefit of MRD monitoring and pre-emptive intervention in patients with *NPM1* and *FLT3*-ITD mutations might relate to the poor outcomes of this genotype at clinical relapse,[24] thought to be related to acquired resistance to chemotherapy.[25] We suggest that early intervention in a low disease burden state might partly overcome this issue. This result was observed with salvage chemotherapy as the predominant treatment for relapse, and we speculate that with the more targeted and less toxic treatments that are now available or in development for patients with this genotype, even greater benefits might emerge.

Other subgroups did not appear to benefit from monitoring. In contrast to patients with *FLT3*-ITD, patients with an isolated *NPM1*^{mut} and those with favourable risk fusion genes (together accounting for 64% of patients in this study) are usually sensitive to chemotherapy at relapse, and rates of 5-year overall survival from clinical relapse of 43–45% have previously been reported.[24] This finding might explain the absence of benefit for early intervention in this group when salvage chemotherapy was the predominant treatment method.

A notable limitation of this study is the exclusion of patients with *NPM1*^{mut} with an early unfavourable MRD response in AML19. These patients were all

directed to receive intensified chemotherapy, SCT, and sequential monitoring. Consequently, this study can provide no information regarding whether the use of MRD to choose patients for allogenic HSCT in first remission improves outcomes.

A second important limitation is the absence of protocol-specified interventions based on MRD results; since clinicians were free to act on these results as they considered appropriate, and treatment changes were not prospectively recorded, we could not identify which specific interventions might have been effective. Additionally, this study was performed mainly in younger adults receiving intensive chemotherapy, and the results cannot necessarily be extrapolated to older adults and those receiving less intensive treatments. Furthermore, *FLT3*-ITD MRD assays were not available during the course of this study, and they might have allowed further personalisation of therapy.

Perhaps the greatest limitation, however, is that this study was performed between 2012 and 2018, and few targeted therapies were available for the treatment of MRD relapse during this period. Therefore, most patients treated for MRD relapse received salvage chemotherapy. The use of such treatment has recently been called into question by a randomised study showing no benefit compared with direct transplantation in patients with clinical relapse.[26] Moreover, several targeted therapies have more recently shown encouraging efficacy for treatment of MRD relapse,[27–29] and given their much greater tolerability, it would be premature to abandon MRD monitoring for subgroups other than *NPM1*^{mut} and *FLT3*-ITD based on this study, particularly for groups where effective targeted therapies are available. Of particular interest, given the survival benefit observed in patients with *NPM1* and *FLT3*-ITD mutations, are preliminary data indicating encouraging response rates when *FLT3* inhibitors are used at MRD relapse.[30] These and other targeted approaches coupled with sequential MRD monitoring might improve survival and further randomised studies are now required to evaluate these approaches.

Contributors

RH, AB, NR, ES, and SDF conceived and designed the study. NP, JJ, and AI oversaw the analysis of patient samples. AG, MR, AK, and WV analysed samples. SK, AK, MFM, JC, UMO, REC, and SDF provided clinical oversight into the running of the study. JC and IT oversaw clinical trial management. AT, SJ, and JO verified and had full access to the raw data and performed statistical analyses. RD and NR had overall responsibility for the study and drafted the manuscript. All the authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

RD declares research support from Abbvie, Amgen, Jazz, and Pfizer; travel support from Servier and Jazz; consultancy with Abbvie, Astellas, Jazz, Pfizer, and Servier; and membership of a Data Safety and Monitoring Board with AvenCell. SK declares research support from Novartis; travel support from Servier; and consultancy with Abbvie, Astellas, Jazz, Novartis, Pfizer, and Servier. NR declares consultancy with Pfizer and Daiichi-Sankyo. All other authors declare no competing interests.

Data sharing

Any part of the dataset can be made available to other researchers by application to the trial sponsor (thomasif@cardiff.ac.uk).

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