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# P503 A RANDOMISED TRIAL OF MOLECULAR MONITORING VERSUS STANDARD CLINICAL CARE IN YOUNGER ADULTS WITH ACUTE MYELOID LEUKAEMIA: RESULTS FROM THE UK NCRI AML17 AND AML19 STUDIES

**Topic:** 3. Acute myeloid leukemia - Biology & Translational Research

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**Background:**

Several studies have demonstrated the prognostic impact of measurable residual disease (MRD) evaluated by molecular methods in patients with AML with recurrent genetic abnormalities. It remains unclear whether intervention guided by MRD results improves outcome.

**Aims:**

We performed a randomised study to evaluate the effect of providing sequential MRD results to treating clinicians, compared to clinical monitoring only. The primary endpoint was overall survival. Secondary endpoints included health care resource use and quality of life, which will be reported separately.

**Methods:**

The UK NCRI AML17 and AML19 studies included patients generally aged 18-60y with newly diagnosed AML eligible for intensive chemotherapy. Cytogenetics, PCR and RNA sequencing were used to identify targets for molecular MRD monitoring (*NPM1* mutation [mut] or any fusion gene). Patients with a molecular marker were randomised 2:1 to receive MRD monitoring after each cycle of chemotherapy and then every three months for two years, or no monitoring.

For patients randomised to monitoring, results were provided to treating clinicians who made the decision to intervene or not in conjunction with a trial co-ordinator; there were no protocol specified interventions. Early repeat samples were requested when samples were inadequate or concerning for molecular relapse or progression. Treating clinicians answered a questionnaire about how the MRD results influenced treatment.

Earlier results from AML17 indicated a high risk of relapse for $NPM1^{mut}$ patients testing MRD positive in the blood after two cycles of chemotherapy (PB PC2+). Therefore, in AML19 all $NPM1^{mut}$ patients received MRD monitoring after the first two cycles and PB PC2+ patients were excluded from the randomisation.

**Results:**

638 patients entered the monitoring randomisation: 433 in AML17 (between 2012-2014) and 205 in AML19 (between 2015-2018). The MRD marker was *NPM1*$^{mut}$ in 398 (62%, of whom 140 had a *FLT3* ITD), *CBFB::MYH11* in 87 (14%) *RUNX1::RUNX1T1* in 62 (10%) *KMT2A::R* in 52 (8%) *DEK::NUP214* in 12 (2%) and other fusion gene in 27 (4%).

In AML17, 3y overall survival (OS) was 64% in patients randomised to monitoring and 71% in patients randomised to no monitoring (HR 1.2 p=0.2). In AML19 3y OS was 84% and 78% respectively (HR 0.79, p=0.46). Meta analysis of the two studies showed no difference in overall survival (HR 1.11, 95CI 0.83-1.49, figure 1a).

In a pre-specified subgroup analysis, we detected an overall survival benefit for monitoring in patients with *NPM1*$^{mut}$ and *FLT3*$^{ITD+}$ (HR 0.53, 95CI 0.31-0.91, p=0.02) with significant heterogeneity between this subgroup and the remaining patients. When excluding PB PC2 MRD+ patients in AML17, the survival benefit was maintained (HR 0.41 95CI 0.23-0.74, p<0.01, figure 1b).

We did not detect a survival benefit in any of the other subgroups, either when defined by molecular marker or ELN group.

The most common MRD-guided treatment changes were reduction in the number of chemotherapy cycles given to MRD negative patients, pre-emptive treatment mainly with salvage chemotherapy at the time of molecular relapse while in haematological remission, allogeneic stem cell transplant, and modification of pre- and post- transplant care including immunosuppression and donor lymphocyte infusion. Few molecularly targeted interventions were deployed.

**Summary/Conclusion:**

In this large randomised study we observed a substantial survival benefit for MRD monitoring in patients with AML with *NPM1*$^{mut}$ and *FLT3*$^{ITD+}$ mutations. This suggests a benefit from early salvage therapy prior to overt relapse specific to this group. This study was performed at a time when few MRD-guided molecularly targeted interventions were available.