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# All patients with acute myeloid leukemia and *FLT3*-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? – the CON

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**Title.**

# All patients with acute myeloid leukemia and *FLT3*-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? – the CON

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**Running heads.**

All *FLT3*-ITD AML should have CR1 allo-SCT. Also TKI era.

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**Trial registration.**

Not applicable

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***"The worst form of inequality is to try to make unequal things equal."* – Aristotle**

Allogeneic stem cell transplantation (allo-SCT) is an important curative treatment option for a significant proportion of patients with acute myeloid leukemia (AML) although it is well recognized that a subset of patients achieve long-term remission without transplantation.[1] Importantly allo-SCT entails a not insignificant risk of non-relapse mortality (NRM) due to complications related to the procedure. Therefore, careful evaluation between risk of disease relapse and NRM is needed for the challenging decision of whom to transplant in first complete remission (CR1).[2] In this respect there increasing interest in using measurable residual disease (MRD) analysis post-induction to help refine decision making around post remission treatment between allogeneic transplant or chemotherapy consolidation. For this purpose highly sensitive MRD assays are required to identify patients with a lower risk of relapse who could avoid the higher NRM associated with allo-SCT and be cured with intensive chemotherapy alone. This is particularly relevant for patients with ELN intermediate risk disease where decisions are more nuanced than for patients with adverse risk disease where transplant is recommended.[1,3] Another important consideration is the effectiveness of salvage therapy and transplant for relapsed patients not transplanted in CR1. It has become generally accepted that transplant is indicated when the estimated relapse risk without transplant is >40%, although more effective salvage options using targeted therapies at molecular relapse might change this calculation.[3] Consequently, we argue that not all patients with *FLT3*-ITD-mutated AML benefit from CR1-allo-SCT in the era of high sensitivity MRD testing and with the availability of *FLT3* inhibitors in frontline treatment and at relapse.

Mutations of the FMS-like tyrosine kinase 3 (*FLT3*) gene occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most common type of *FLT3* mutation present in 25% of cases.[4,5] *FLT3*-ITD-mutated (*FLT3*-ITD$^+$) AML is associated with poorer outcomes, with higher relapse rates and reduced overall survival.[6–9] Consequently many centers have considered the presence of a baseline *FLT3*–ITD an indication for transplant in CR1, although there is considerable variation in both recipient selection and transplant strategies.[2] Importantly *FLT3*-ITD$^+$ AML is not one disease, with the mutation frequently co-occurring with other cytogenetic and molecular aberrations.[4,5] Although a *FLT3*-ITD typically confers ELN intermediate risk, a smaller proportion of patients are assigned as favorable or adverse, depending on other genomic lesions detected at diagnosis.[1,5] Thus in the UK NCRI AML19 clinical trial which was predominately for younger AML patients <60 years, the most frequently comutated gene was *NPM1* which was detected in 55% of cases. In 3% of cases CBF gene fusions were present. Adverse comutated genetic lesions included *DEK*:*NUP214* (2%), *UBTF*-TD (6%), *KMT2A*-PTD (9%), *MECOM* (1%) *and KMT2A* (2%) rearranged cases. (Figure 1. unpublished data). Overall, the *FLT3*-ITD-mutated cohort was divided into ELN 2022 favorable risk 4%, intermediate risk 90% and adverse risk 6%. These findings, highlight the disparity of clinical outcomes in *FLT3*-ITD-mutated AML and have implications for the optimal treatment choice, including the decision to allograft.

For patients with *NPM1* mutations, early retrospective studies indicated that allo-SCT improved overall survival (OS) for patients with coexisting *FLT3*-ITDs, in particular those with an allelic ratio (AR) >0.5.[10,11] These studies were performed before the development of sensitive molecular MRD techniques, which have been shown to be strong predictors of relapse and survival in *NPM1*$^{mut}$ AML with or without *FLT3*-

ITDs.[12–14] Analysing data from the UK NCRI AML17 trial, Ivey et al[14] reported that patients who were *NPM1*$^{mut}$/*FLT3*-ITD$^{+}$ and *NPM1* MRD negative (MRD$^{-}$) by RT-qPCR in the peripheral blood (PB) after 2 courses of chemotherapy had a cumulative incidence of relapse of 35% at 5 years compared to 92% in patients testing MRD positive (MRD$^{+}$). The suggestion was that MRD assessment could be used to stratify post induction treatment decisions regarding to transplant or not. Patients who were PB *NPM1* MRD$^{-}$ having a favorable survival of 76% at 5 years may not benefit from a CR1 transplant. Similar results have been reported by Cocciardie et al[15] from the AMLSG 09-09 trials, there was no benefit for CR1-allo-SCT patients who were in molecular remission following the second chemotherapy course. To address this question more comprehensively, Othman et al[16] used data from 2 prospective, randomized, multi-center UK NCRI clinical trials of intensive chemotherapy AML17( 2009-2014) and AML19 (2015-2020)) involving 737 *NPM1*$^{mut}$ patients (median age 52 yrs) of whom 286 had a *FLT3*-ITD. Both trials took place before the availability of approved *FLT3* inhibitors. In AML19 all patients underwent MRD testing after the first 2 chemotherapy courses and based on the findings from AML17[14] only patients testing MRD$^{+}$ in PB post course 2 (PC2) were recommended for CR1 transplant (unless they had adverse risk cytogenetics). Peripheral blood MRD$^{-}$ patients continued with 2 courses of HDAC consolidation. Patients from both trials could also be entered into a randomization to continue with *NPM1* MRD monitoring every 3 months for 2 years from the end of treatment. Overall we observed significant heterogeneity of overall survival (OS) benefit from an allogeneic transplant in CR1 according to PC2 PB MRD status. Whilst there was a substantial survival benefit for MRD$^{+}$ patients undergoing allo-SCT (3-year OS with CR1-allo vs without,: 61% vs 24%; hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.24-

0.64; P < .001) no benefit was seen for MRD$^-$ patients (3-year OS with CR1-allo vs without: 79% vs 82%; HR, 0.82; 95% CI, 0.50-1.33; P = .4)(Figure 2). Looking specifically at the 286 patients comutated with *FLT3*-ITD, 28% were PB PC2 MRD$^+$ for *NPM1* and again those who received CR1-allo-SCT benefited with a significantly better survival (3-year OS, 45% vs 18%; HR, 0.52; 95% CI, 0.29-0.93; P = .03). In contrast there was no survival benefit for MRD$^-$ patients, CR1-allo was performed in 20% of the MRD$^-$ patients and the 3-year OS, was 83% vs 76% with no transplant; (HR, 0.80; 95% CI, 0.37-1.71; P =0.6). CR1-allograft did reduce the cumulative incidence of relapse in MRD$^-$ patients and improved relapse free survival however no subgroup could be identified with a survival benefit for transplant including those with a high *FLT3*-ITD allelic ratio >0.5 or triple mutated patients with a *DNMT3A* mutation or those with a high white cell count. However as the majority of patients in these trials were <60 years these findings may not extend to older patients Relapse occurred in 30%-40% of MRD$^-$ patients not transplanted in CR1, of these 60% went on to an allogeneic transplant in CR2 with survival of 50% at 3 years which was superior to MRD$^+$ relapsing who had a poor outcome. Recent data showing the prognostic impact of *FLT3*-ITD detection by ultra-sensitive NGS may help provide additional prognostic information to that currently provided by *NPM1* MRD testing in assessing the risk of relapse in *NPM1*$^{mut}$/*FLT3*-ITD comutated cases.[17] Beyond the PC2 MRD assessment point, MRD$^-$ patients not transplanted in CR1 should continue with MRD monitoring following subsequent cycles of consolidation.[18] Patients MRD$^-$ in the PB PC2 are frequently still positive in the bone marrow (BM) at that time point but become MRD$^-$ with subsequent consolidation. Patients with persisting *NPM1* MRD positivity in the bone marrow at the end of treatment (EOT) are at a higher risk of relapse and need close monitoring.[14,19] Using ELN definitions of molecular

persistence at low copy number (MP-LCN) Tiong et al[20] reported that almost half of those with persisting EOT positivity become $MRD^-$ on follow up but those with a *FLT3*-ITD are at higher risk of disease progression and warrant consideration of pre-emptive treatment. An EOT BM MRD assessment is therefore an additional checkpoint to further refine the decision to perform a CR1-allo-SCT in *NPM1*$^{mut}$/*FLT3*-$ITD^+$ patients.

For patients in remission a recent study has shown that prospective monitoring and treatment of MRD relapse improves survival in patients with *NPM1*$^{mut}$/*FLT3*-$ITD^+$ AML. Potter et al[12] randomised 637 patients from the UK NCRI AML17 and AML19 trials with a variety of molecular markers to undergo sequential molecular MRD monitoring during treatment and then for 3 years, or to continue with standard clinical care only with no molecular monitoring. Although there was no overall survival benefit for molecular monitoring in the whole population, a pre-specified subgroup analysis demonstrated a significant survival benefit for monitoring in *NPM1*$^{mut}$/*FLT3*-$ITD^+$ subgroup where the risk of death was almost halved. .

For patients with *FLT3* mutations the therapeutic landscape has changed since these studies were performed with the approvals of midostaurin and quizartinib for use with upfront chemotherapy and as single agent maintenance.[21,22] The introduction of *FLT3* inhibitors into routine clinical practice has further called into question the therapeutic benefit of CR1-allo-SCT, diminishing the relapse risk without transplant to <40% in selected *FLT3*-ITD-mutated subgroups. In the landmark phase III RATIFY trial, midostaurin was evaluated in combination with standard induction and consolidation chemotherapy and as maintenance in adults <60 years with *FLT3*-

mutated AML.[21] There was a significant improvement in the primary endpoint of overall survival in all *FLT3* subgroups in the midostaurin arm. CR1-allo-SCT for consolidation was not mandated, but all trial participants were eligible at investigator discretion, regardless of *FLT3* mutation status. Accordingly, in the midostaurin arm 28% of participants underwent a CR1-allograft, versus 22% in the placebo arm. In a retrospective analysis, the impact of CR1-allo-SCT was evaluated and a strong beneficial effect for transplant was only found in the adverse risk group.[23] Although these results should be interpreted with caution, as the trial was not powered for this particular subgroup analysis, this finding does support that transplantation can potentially be delayed until relapse in the favourable and intermediate risk group. QuANTUM-First evaluated quizartinib with standard induction and consolidation chemotherapy and/or allo-SCT, followed by maintenance therapy in *FLT3*-ITD-mutated AML.[22] Schlenk et al[24] recently published a QuANTUM-First post-hoc analysis assessing the impact of CR1-allo-SCT and quizartinib. Protocol specified CR1-allo-SCT was performed in 53% of patients. Multivariable analyses showed quizartinib and allo-SCT as significant predictive factors for improved OS. Notably, excluded from this group were patients with $NPM1^{mut}$/*FLT3*-$ITD^{+}$ low allelic ratio, as at the time the trial was conducted CR1-allo-SCT was not recommended in this group.[25]

*FLT3* inhibitors are able to induce deeper molecular responses when combined with upfront chemotherapy, thereby potentially reducing the proportion of $MRD^{+}$ patients with a transplantation indication.[26] In the UK NCRI AML19v2 trial where midostaurin was combined with DA plus gemtuzumab ozogamicin (GO) induction, PC2 PB MRD negativity for *NPM1* was 80% compared to 68% in those receiving DAGO without midostaurin in the earlier AML19v1 trial.[27,28] Likewise the availability of *FLT3*

inhibitors as maintenance could also reduce the risk of relapse for $MRD^-$ patients not transplanted in first remission.

A key objective of MRD monitoring however is to identify patients who are destined to relapse and instigate pre-emptive treatment while the patient is still well and in clinical remission.[29] For this purpose *NPM1* provides an ideal marker as the majority of molecular relapses allow a window of opportunity for intervention. In the UK NCRI AML17 and AML19 trials which took place in an era (2012-2018) before the widespread availability of *FLT3* inhibitors for the treatment of relapse, the most common intervention for MRD relapse was intensive salvage chemotherapy.[12] An alternative approach is to use targeted therapy where outcomes may be better than those achieved at haematological relapse. Othman et al[30] reported on a series of 56 patients treated with *FLT3* inhibitors at molecular failure of *FLT3*-mutated AML, 60% had a molecular response with 45% achieving a molecular complete molecular remission with the highest responses being seen in those with molecular relapse rather than molecular progression. Most patients were treated in the outpatient setting with low toxicity and approximately half were bridged to allogeneic transplant with an overall survival of 80% at 2 years. In a separate study patients undergoing molecular monitoring for $NPM1^{mut}$ or core-binding factor AML (CBF-AML) who received preemptive therapy at the time of molecular relapse had improved survival compared to those who received salvage therapy after having progressed from molecular to morphologic relapse.[31] Importantly loss of *FLT3* mutations at relapse is reported to occur in almost 50% of patients receiving frontline *FLT3* inhibitors so repeat testing at relapse is essential to optimize salvage therapy.[32]

CBF-AML are defined by the presence of either inv(16)(p13q22)/t(16;16)(p13;q22)/*CBFB::MYH11* or t(8;21)(q22;q22)/*RUNX1::RUNX1T1*. These leukemias are characterized by a high rate of CR and long-term cure and transplant is normally reserved for relapsed disease.[33,34] *FLT3*-ITDs are present in approximately 2-3% patients with CBF-AML and do not alter the 2022 ELN favorable genetic risk assignment.[1,35] However, In a recent multicenter, retrospective study Kayser et al[36] suggested that patients with CBF-AML and *FLT3*-ITD comutation should not be classified as favorable-risk, although notably very few had been treated with GO or midostaurin and there was no evidence that allo-SCT in CR1 improved overall survival. Both CBF fusion genes provide an ideal target for disease monitoring by RT-qPCR; however, importantly these transcripts may show persistent low-level expression after treatment and this is not predictive of relapse.[18] Therefore, unlike other molecular subtypes, the goal of treatment is to reduce levels below specific thresholds, rather than to achieve MRD negativity. Benefit for a CR1 transplant in CBF-AML has only been demonstrated for patients who have high-level MRD positivity after 3 or 4cycles of treatment.[37] We recommend ongoing monitoring in the BM every 2 months for the first year CBF patients, particularly for those with a *FLT3*-ITD, then 3 monthly for another 2 years.[18]

To summarise the question of which patients with AML should receive an allo-SCT and when this transplantation should take place is still debated and of is a moving target as we incorporate new drugs and non-transplant outcomes improve. Although allo-SCT remains the most effective anti-leukemic treatment available other factors are relevant to any decision about the survival benefit of transplant in CR1 including the risk of relapse, the risk of the transplant itself and the prospects for successful

salvage treatment if the patient does relapse. The 2022 ELN recommendations state that not only genetic abnormalities at the time of diagnosis but also results from MRD analyses should be taken into consideration for a comprehensive genetic risk assessment.[1] For some patients with *FLT3*-ITDs including those with *NPM1* mutations or CBF-AML, molecular MRD assessment at defined time points gives additional personalised information of the risk of relapse to inform choices of post-remission therapy, reserving transplant for relapse in MRD negative patients. This approach spares a significant number of patients the risk of transplant-related mortality and short and long-term morbidity associated with allo-SCT. Ongoing molecular MRD monitoring is an essential part of this strategy allowing for early intervention if molecular relapse occurs. This strategy is being followed in the ongoing Optimise-*FLT3* trial in the UK. The results of which will provide further clarity to guide treatment decisions in *FLT3*-ITD-mutated AML in the current therapeutic and diagnostic era.

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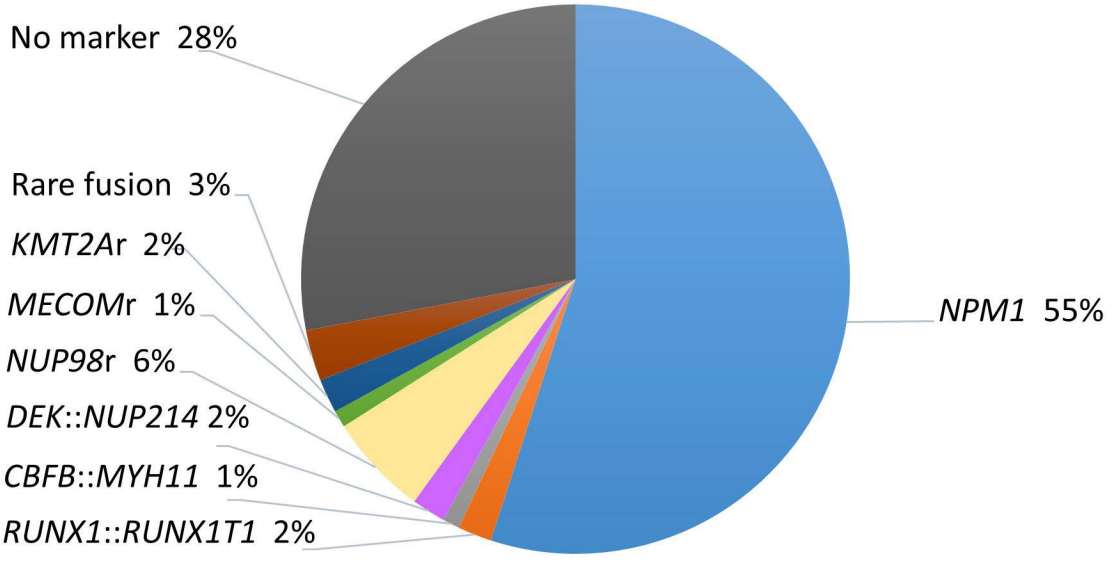
**Figure 1.** Co-occurring molecular lesions suitable for molecular MRD monitoring in *FLT3*-ITD mutated AML in the UK NRCI AML19 clinical trial cohort.

**Figure 2.**[16] **Overall survival based on receipt of CR1-allo.** HRs represent the hazard of death associated with CR1-allo, from time-dependent Cox regression. (D) *NPM1* mutant with *FLT3*-ITD AML, MRD POS, in PB after 2 induction courses. Simon-Makuch plot of OS based on CR1-allo. (E) *NPM1* mutant with *FLT3*-ITD AML, MRD NEG, in PB after 2 induction courses. Simon-Makuch plot of OS based on CR1-allo. CR1 alloSCT, allogeneic stem cell transplantation in first complete remission.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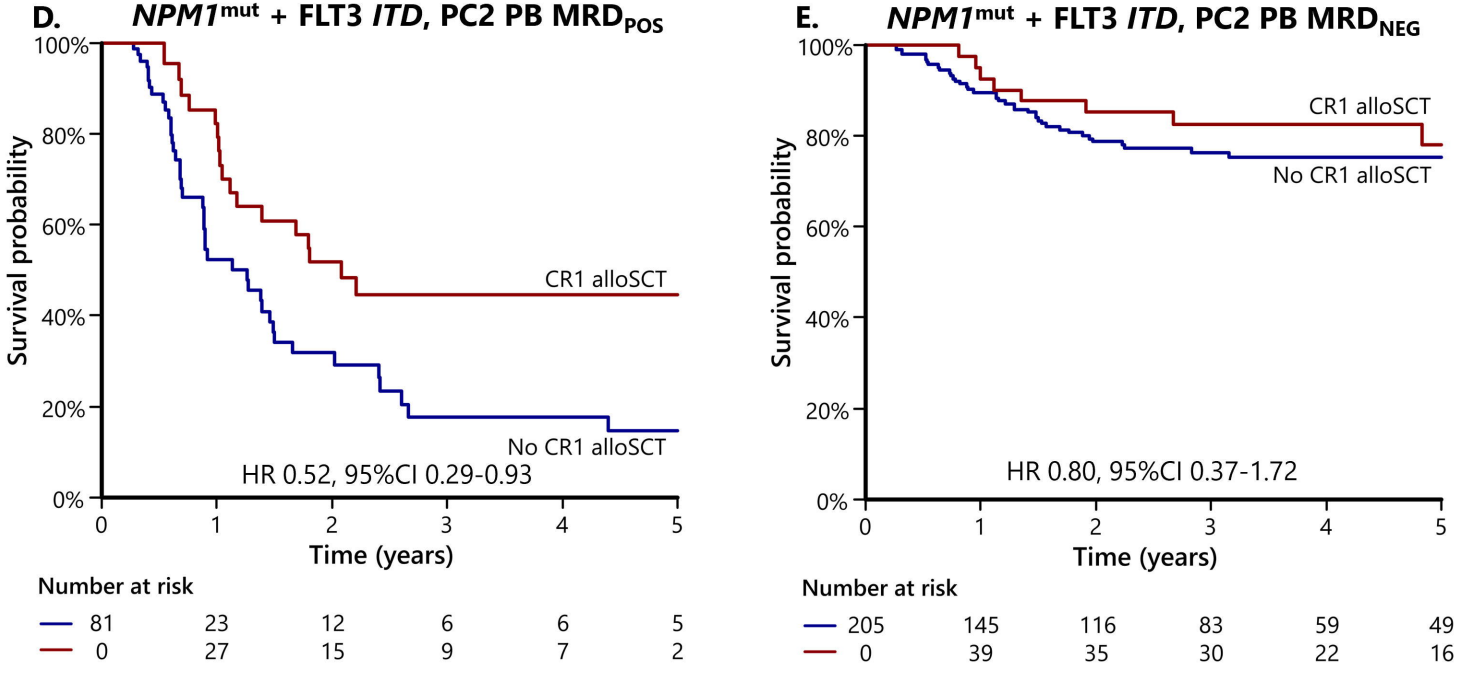
D.
NPM1mut + FLT3 ITD, PC2 PB MRDPOS
100%
80%
60%
40%
20%
0%
Survival probability
CR1 alloSCT
No CR1 alloSCT
HR 0.52, 95%CI 0.29-0.93
0
1
2
3
4
5
Time (years)
Number at risk
81 23 12 6 6 5
0 27 15 9 7 2
E.
NPM1mut + FLT3 ITD, PC2 PB MRDNEG
100%
80%
60%
40%
20%
0%
Survival probability
CR1 alloSCT
No CR1 alloSCT
HR 0.80, 95%CI 0.37-1.72
0
1
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Time (years)
Number at risk
205 145 116 83 59 49
0 39 35 30 22 16