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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Interaction between Presenting Features, Co-Occurring Mutations, MRD and Induction Treatment Influences Outcome in Adults with *NPM1* Mutated AML - an Analysis of 1357 Patients in the UK NCRI AML17 and AML19 Studies

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Background

NPM1 mutated (mut) AML is considered favourable risk unless associated with *FLT3* internal tandem duplication (ITD) or adverse karyotype. However many other genetic and clinical risk factors have been identified, including high white cell count (WCC), secondary disease, co-mutations and presence of a "triple hit" genotype (*NPM1* ^{mut}, *FLT3* ITD and *DNMT3A* ^{mut}). Although alternative classification systems have been proposed, few studies have been large enough to robustly evaluate clinical and molecular subgroups within *NPM1* ^{mut}, and none have incorporated the effects of measurable residual disease (MRD) status or treatment intensity. Therefore, clinical decision making remains challenging and inconsistent. Here, we performed comprehensive genotyping and molecular MRD assessment in two consecutive prospective randomised studies to clarify these issues.

Methods

NCRI AML17 (2009-2014) and AML19 (2015-2020) were large randomised trials for younger adults with newly diagnosed AML. Induction regimens included DA +/- etoposide (ADE) and FLAG-IDA, with or without Gemtuzumab. Patients underwent sequential MRD assessment by RT-qPCR, and diagnostic DNA samples were analysed by targeted NGS. Overall survival (OS) was calculated with the Kaplan-Meier method, while cumulative incidence of relapse (CIR) considered death as a competing risk. Relapse events included MRD relapse. All reported hazard/odds ratios are from multivariable analyses including age,

prior haematological malignancy, prior chemo/radiotherapy, WCC (log transformed), cytogenetic risk and mutation profile (*FLT3* ITD, *DNMT3A, PTPN11, N/KRAS, TET2, IDH1, IDH2, WT1, TP53* MDS-related genes).

Results

1357 patients with *NPM1* ^{mut}AML were identified, 888 in AML17 and 469 in AML19. 1100 patients had DNA available for panel sequencing, and 981 underwent MRD monitoring of whom 737 had an evaluable post course 2 (PC2) peripheral blood (PB) sample. Morphological remission (CR+CRi) was achieved in 1264/1357 patients (93%) and PC2 PB MRD negativity in 594/737 (81%). We confirmed the adverse impact of PB PC2 MRD positivity: 3y CIR was 65% vs 29% in those MRD- (p<0.001), and 3yr OS was 40% vs 79% (p<0.001). For PB PC2 MRD+ patients, CIR was >50% in all subgroups.

There was a lower rate of PC2 PB MRD negativity in patients with high presenting WCC (OR 1.14, p=0.05), *FLT3* ITD (OR 2.58, p<0.001), *DNMT3A* ^{mut} (OR 2.2, p<0.001) and *WT1* ^{mut} (HR 2.04, p=0.02). There was no effect of *FLT3* allelic ratio, while patients with both *FLT3* ITD and *DNMT3A* mutations had the lowest rate of MRD- (64%, Figure A).

Of the 594 PC2 MRD- patients, we observed higher 3y CIR in patients with high WCC (HR 1.14, p=0.01), *DNMT3A* ^{mut} (HR 1.83, p=0.001), *WT1* ^{mut}(HR 1.96, p=0.01) and *IDH1* ^{mut} (HR 1.9, p=0.002), and lower CIR in patients with *N/KRAS* ^{mut}(HR 0.53, p=0.01). Although presence of *FLT3* ITD alone was not associated with CIR (HR 0.88, p=0.7), patients with both *FLT3* ITD and *DNMT3A* mutations had 3y CIR from MRD- of 40% (HR 1.74, p=0.03). MDS-related gene mutations had no impact on achieving MRD-, nor relapse from MRD-.

Considering all patients, OS was poorer with increasing age (HR 1.03, p<0.001), WCC (HR 1.07, p<0.001), adverse karyotype (HR 2.48, p=0.01), *FLT3* ITD (HR 1.34, p=0.01), *DNMT3A* ^{mut} (HR 1.56, p<0.001) and *WT1* ^{mut}(HR 1.71, p<0.001). 3y OS was 52% in patients with both *FLT3* ITD and *DNMT3A* ^{mut}, 63% with *FLT3* ITD only, 67% with *DNMT3A* only and 75% with neither. Considering MRD- patients, only age (HR 1.02, p=0.04), *DNMT3A* ^{mut}(HR 1.75, p=0.007) and *WT1* ^{mut} (HR 1.8, p=0.048) remained associated with OS. There was no benefit to CR1 allogeneic transplant in MRD- patients (HR 0.83, 95%CI 0.51-1.34, p=0.4), including in any subgroups (heterogeneity p=0.9).

Compared with other treatments, FLAG-Ida increased MRD- (87% vs 79%, p=0.009), reduced relapse from MRD- (16% vs 34%, p<0.001) and improved 3y OS (79% vs 63%, HR 0.52, p<0.001). The OS benefit of FLAG-Ida was greatest in patients with at least one of the features associated with failure to achieve MRD- and relapse from MRD- (high WCC, triple hit or *WT1* ^{mut}, HR 0.39 95%CI 0.26-0.58, heterogeneity p<0.01).

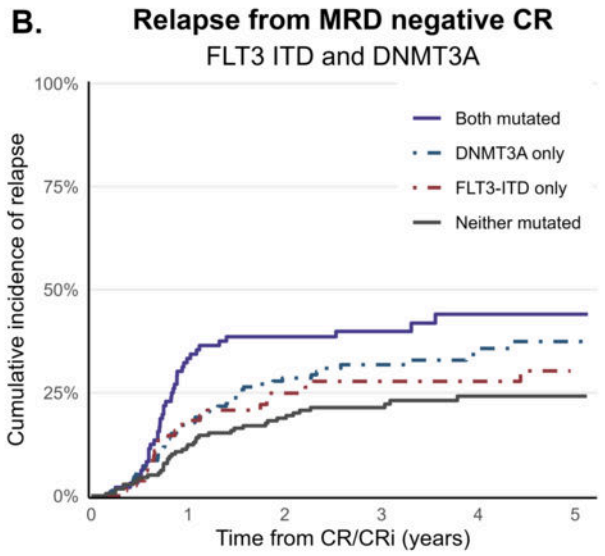
Conclusion

The "triple hit" (*NPM1*, *DNMT3A* and *FLT3* ITD) genotype, *WT1* ^{mut} and high WCC were associated with poor outcomes, due to a lower probability of achieving MRD-, and a higher relapse risk from MRD- remission. Survival was improved for patients receiving intensified induction with FLAG-Ida including patients in these high-risk groups.

Disclosures Papaemmanuil: *Isabl Inc.:* Current equity holder in private company, Current holder of *stock options* in a privately-held company, Other: CEO, Patents & Royalties: Whole genome cancer analysis; *TenSixteen Bio:* Current equity holder in private company. **Freeman:** *JAZZ:* Research Funding, Speakers Bureau; *BMS:* Research Funding; *MPAACT:* Membership on an entity's Board of Directors or advisory committees; *NOVARTIS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Dillon:** *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Consultancy, Honoraria, Speakers Bureau; *Jazz:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *AvenCell:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Astellas:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Research Funding; *Shattuck labs:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Russell:** *Pfizer:* Honoraria, Research Funding, Speakers Bureau; *Jazz Pharma:* Research Funding; *Servier:* Honoraria; *Astellas:* Honoraria.

A.	Post course 2 PB MRD negative	3-year CIR from MRD negative
All patients	81%	29%
White cell count		
Below median (<21)	85%	25%
Above median (>21)	77%	33%
FLT3 ITD		
Present	72%	32%
Low allelic ratio	72%	30%
High allelic ratio	72%	38%
Absent	86%	26%
DNMT3A		
Mutated	73%	35%
Wild type	88%	23%
FLT3 ITD and *DNMT3A*		
Both mutated	64%	40%
FLT3 ITD only	79%	28%
DNMT3A only	81%	32%
Neither mutated	92%	21%
NRAS and/or *KRAS*		
Mutated	80%	18%
Wild type	80%	32%
WT1		
Mutated	70%	36%
Wild type	82%	28%
MDS-related genes*		
Mutated	87%	30%
No mutations	79%	29%

*ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2



A. Proportion achieving MRD negativity in peripheral blood after 2 courses, and relapse from MRD negative state, by baseline disease characteristics
B. Cumulative incidence of relapse from MRD negative state, by FLT3 ITD and DNMT3A mutation status

Figure 1

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