PROGNOSTIC VALUE OF *FLT3*-ITD RESIDUAL DISEASE IN ACUTE MYELOID LEUKEMIA

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INTRODUCTION

- Internal tandem duplications (ITD) in *FLT3* are one of the most common aberrations in AML and considered late event mutations in leukemogenesis
- MRD detection of *FLT3*-ITD by RQ-PCR is not feasible, due to variety in patient-specific ITDs (sequence, position, and length)
- Recent advances in NGS enable accurate molecular detection of *FLT3*-ITD MRD
- However, systematic studies evaluating the applicability of *FLT3*-ITD MRD are lacking

AIM

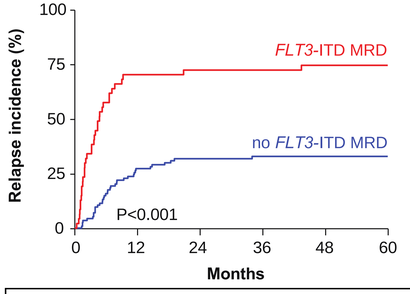
To comprehensively investigate the impact of NGS-based *FLT3*-ITD MRD detection on treatment outcome of AML patients in the context of current prognostic factors

METHODS

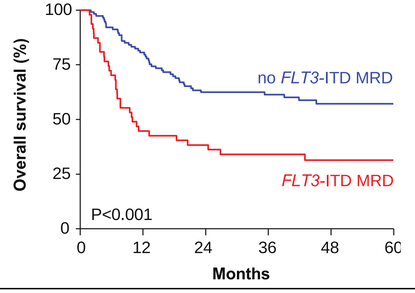
- Patients: 161 *de novo* AML patients with a *FLT3*-ITD at diagnosis, treated within HOVON-SAKK multicenter clinical trials
- NGS: performed at diagnosis and in complete remission (CR) following two cycles of standard induction chemotherapy (LOD 10^{-4}, median VAF in CR 0.008%)
- Libraries were paired-end sequenced with custom primers on the Illumina MiSeq platform
- Clinical Endpoints:
  - Cumulative incidence of relapse (CIR)
  - Overall survival (OS)

RESULTS

Relapse by *FLT3*-ITD MRD (n=161)



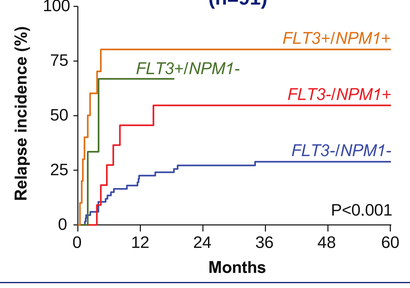
Overall survival by *FLT3*-ITD MRD (n=161)



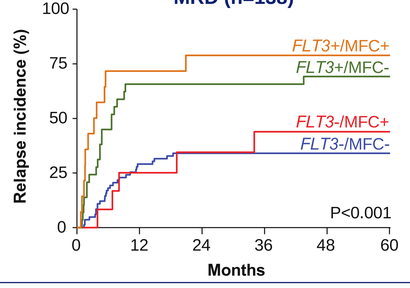
Multivariate analysis of prognostic factors

Variable	Relapse Incidence		Overall Survival	
	HR (95% CI)	P Value	HR (95% CI)	P Value
***FLT3*-ITD MRD** (detection vs. no detection)	3.55 (1.92-6.56)	<0.001	2.51 (1.42-4.43)	0,002
Age (per 10 years)	1.05 (0.86-1.29)	0,621	1.20 (0.97-1.49)	0,087
WBC at diagnosis (>100x109/L vs. ≤100x109/L)	2.96 (1.73-5.07)	<0.001	1.89 (1.05-3.43)	0,035
***NPM1* mutation at diagnosis** (mutant vs. wild type)	1.21 (0.68-2.16)	0,522	1.30 (0.75-2.23)	0,348
***FLT3*-ITD ratio at diagnosis** (high vs. low)	1.76 (1.00-3.09)	0.050	1.60 (0.96-2.67)	0.070
Number of cycles to attain complete remission (2 vs. 1 cycle)	1.84 (1.10-3.09)	0.020	1.73 (0.98-3.06)	0,058

Relapse by *FLT3*-ITD and mutant *NPM1* MRD (n=91)



Relapse by *FLT3*-ITD and flow cytometry (MFC) MRD (n=138)



CONCLUSIONS

- NGS-based *FLT3*-ITD MRD detection identifies AML patients with a profound increased risk of relapse and death that outweighs currently used prognostic factors
- *FLT3*-ITD MRD can better identify AML patients that relapse compared to mutant *NPM1* MRD detection or multiparameter flow cytometry MRD alone
- We therefore propose to incorporate *FLT3*-ITD MRD in AML treatment protocols

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