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ADVANTAGES AND PROGNOSTIC VALUE OF NEXT-GENERATION SEQUENCING–BASED MUTANT NPM1 MEASURABLE RESIDUAL DISEASE DETECTION IN AML

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INTRODUCTION

- Mutations in *NPM1* are among the most common genetic aberrations in AML, occurring in ~25% of all patients.
- Mutant *NPM1* Minimal Residual Disease (MRD) monitoring is currently assessed by using RT-qPCR on cDNA.
- Next Generation Sequencing (NGS) approaches on DNA are not influenced by variations in *NPM1* gene expression levels and detect all *NPM1* variants in a single assay.
- However, no comprehensive studies have been performed yet for mutant *NPM1* MRD detection using NGS on DNA.

AIM

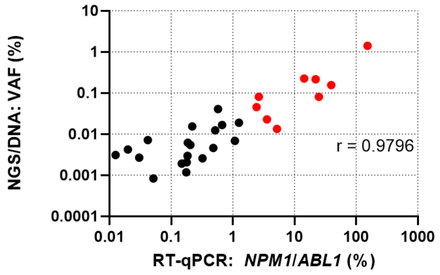
- To comprehensively investigate the use of NGS on both cDNA and DNA for the detection of mutant *NPM1* as MRD marker in AML.
- To explore the prognostic significance of NGS-based mutant *NPM1* MRD in the context of *FLT3* internal tandem duplications (ITD).

METHODS

- Patients: 119 (cDNA) or 310 (DNA) mutant *NPM1* de novo AML patients treated in HOVON-SAKK clinical trials. MRD measurements were performed on patients in complete remission (CR) following two cycles of induction chemotherapy.
- RT-qPCR: Performed on cDNA. Mutant *NPM1* copies were measured in relation to copies of the housekeeping gene *ABL1*.
- NGS: Performed on cDNA or genomic DNA. Libraries were paired-end sequenced with custom primers on the Illumina NovaSeq platform.

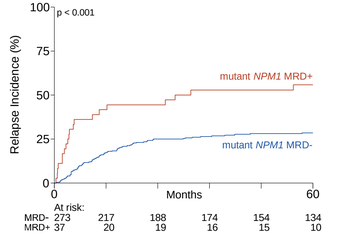
RESULTS

High correlation between RT-qPCR and NGS in detecting mutant *NPM1* MRD

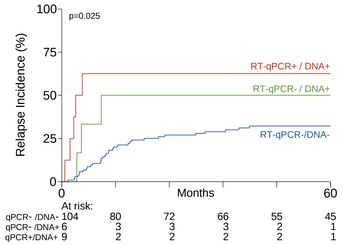


NGS/DNA with VAF threshold of >0.01% mutant *NPM1* MRD identifies patients with an increased risk of relapse

Relapse incidence by mutant *NPM1* MRD (VAF>0.01%) as detected by NGS (n=310)

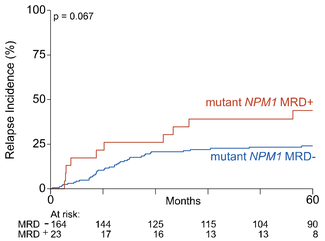


Relapse incidence by mutant *NPM1* MRD as detected by RT-qPCR (*mNPM1/ABL1* >2%) and NGS (VAF>0.01%)

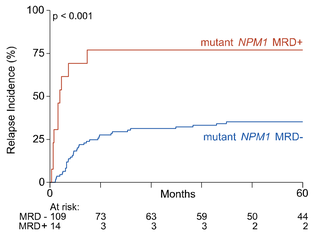


Co-occuring *FLT3*-ITD at diagnosis increases relapse incidence for mutant *NPM1* MRD

Relapse by mutant *NPM1* MRD in AML patients without *FLT3*-ITD (n=187)



Relapse by mutant *NPM1* MRD in AML patients with a *FLT3*-ITD (n=123)



CONCLUSIONS

- Detection of mutant *NPM1*, defined as >2% mutant *NPM1/ABL1* for RT-qPCR and >0.01% VAF for NGS, in complete remission in AML patients leads to a significantly higher risk of relapse.
- NGS-based detection of mutant *NPM1* MRD with DNA as input is an attractive alternative for mutant MRD detection by RT-qPCR.
- Mutant *NPM1* MRD monitoring by NGS using DNA enables the identification of an additional group of AML patients with a significantly increased risk of relapse.
- The prognostic significance of mutant *NPM1* MRD is greatest in patients with a co-occurring *FLT3*-ITD.

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