Preleukemic clones in NPM1-mutated Acute Myeloid Leukemia may be associated with evolution to myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN)

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INTRODUCTION
Nucleophosmin 1 gene (NPM1) mutations account for 30% of AML and 50% of cytogenetically normal (CN) AML. NPM1 mutated AML without FLT3-ITD (NPM 1+FLT3-ITD−) is classified in the favorable risk group. Recent studies, including from our group, showed that most NPM1+ FLT3-ITD− AML also carry mutations in other genes such as DNMT3A, IDH1, IDH2, TET2 mutations which may constitute “preleukemic” clones, as suggested by the fact that those mutations often persist in patients with undetectable NPM1 minimal residual disease (MRD) after intensive chemotherapy (Peterlin Haematologica 2015, Corces-Zimmerman PNAS 2014). On the other hand, a recent report showed that virtually all relapses in NPM1+ AML carried NPM1 mutation, arguing against the fact that relapse can emerge from preleukemic clones independently of the presence of NPM1 mutation (Hills NEJM 2016).

OBJECTIVES
To characterize evolution to MDS/MPN in patients with de novo CN NPM1+ FLT3-ITD− AML in complete remission (CR) and to determine the underlying genetic mechanisms.

METHODS
Over a 10-year period, 33 de novo NPM1+ FLT3-ITD− AML (median age 55 years) were treated with intensive chemotherapy at our center, and 31 achieved CR. 12 (37%) remained in hematological CR with undetectable NPM1-MRD, 14 (44%) relapsed with the same NPM2 mutation, and 6 (19%) developed MDS or MPN while still in molecular CR for NPM1 (Fig. 1). 12 of the relapsing patients and all 6 patients with MDS or MPN evolution had sequential molecular analysis using NGS of PCR-amplified exons of a panel of the 26 genes most frequently mutated in myeloid malignancies.

RESULTS
The 6 patients who developed MDS or MPN with undetectable NPM1-MRD, after a median of 14 months (range: 4-30), were all aged > 55 years, and included 2 RARS, 2 RCMD, 1 CMML type 1 and 1 primary myelofibrosis (PMF). They all had normal karyotype at AML diagnosis but at MDS stage, one had trisomy 8 and one had isochromosome X. 2 had normal karyotype and 2 were not evaluable. 3 patients were treated with Azacitidine, two with erythropoietin. The patient with PMF was treated with Ruxolitinib and cyoreduction. 3/6 patients subsequently developed AML, but only one had NPM1+ MRD at that time.

Median survival after evolution to MDS/MPN was 3.8 years compared to one year in patients in the relapse group. In all 6 cases, a “preleukemic” clone with at least 1 mutation in TET2 (n=4), JAK2 (n=2), ASXL1 (n=1), IDH2 (n=3) or spliceosome genes (SRSF2, SF3B1, U2AF1, (n=3)) was found at AML diagnosis, and was still present (with stable or increasing variant allele frequency) at the time of MDS or MPN diagnosis (Fig. 2 and 4). In the 12 relapsing patients, “preleukemic” mutations were also present at AML diagnosis in 10/12 cases. However, they possibly differed between the 2 groups: At AML diagnosis, TET2 and/or spliceosome mutations were identified in 5/6 (83%) patients who developed MDS or MPN, versus 2/12 (17%) patients who relapsed, (p=0.01). Conversely, 8/12 patients who relapsed had mutations in DNMT3A or IDH1, versus 0/6 patients who developed MDS or MPN (p=0.025). At AML relapse, mutations co-occurring with NPM1 mutation were identical to those observed at AML diagnosis (Fig 3).

CONCLUSION
Evolution to MDS or MPN after AML was observed in 18% of our cohort of patients with de novo NPM1+FLT3-ITD− AML. It was associated with a higher frequency of TET2 and spliceosome mutations. The high incidence of such evolution may be related to the relatively advanced age of our patient cohort. Interestingly, in most patients with AML relapse, preleukemic clones were observed at AML diagnosis but with different mutational patterns, possibly pointing out different pathophysiological mechanisms.

NPM1-MRD follow-up is a robust tool to predict AML relapse in NPM1-mutated AML. However, MDS or MPN can occur in older patients with negative MRD.

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REFERENCES

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