



# Impact of Molecular Markers and Cytogenetic Abnormalities on Long-Term Overall Survival and Disease-Free Survival after Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

Hôpitaux de Lyon

Mauricette Michallet<sup>1</sup>, Mohamad Sobh<sup>1</sup>, Xavier Thomas<sup>1</sup>, Mohamed El-Hamri<sup>1</sup>, Carole Charlot<sup>1</sup>, Fiorenza Barraco<sup>1</sup>, Giovanna Cannas<sup>1</sup>, Franck E Nicolini<sup>1</sup>, Emmanuelle Nicolas-virelizier<sup>1</sup>, Claudiu Plesa<sup>1</sup>, Youcef Chelghoum<sup>1</sup>, Jacques Troncy<sup>1</sup>, Jean-Pierre Magaud<sup>2</sup>, Isabelle Tigaud<sup>3</sup>, Sandrine Hayette<sup>1</sup>

<sup>1</sup>Hematology, Hopital Edouard Herriot, 5 Place d'Arsonval, Lyon, Cedex 03 69437, France

<sup>2</sup>Hematology (Biology) and UMR5239 CNRS, Hospices civils de Lyon Centre Hospitalier Lyon Sud, 165 Chemin du Grand Revoyet, Pierre Benite, France

<sup>3</sup>Laboratoire de Cytogénétique, Centre Hospitalier Lyon Sud, Lyon, France

## Introduction

We performed a retrospective analysis from our transplant registry on first allogeneic hematopoietic stem cell transplantations (HSCT) for acute myeloid leukemia (AML) patients (pts) between 1996 and 2007. Our principal objective was to analyze the impact of molecular markers on the long-term overall and disease-free survival (OS and DFS) after first allogeneic HSCT. We found 364 pts, only 63 pts had retrospectively available conserved cells at diagnosis. The expression levels of WT1, Evi1, Flt3 and Hoxa9 were performed by quantitative RT-RQPCR. The mutational status of MLL duplication, FLT3 (internal tandem duplication or nucleotide substitutions) (ITD), NPM1 and CEBP $\alpha$  were determined by PCR, RFLP and/or sequencing analysis. All pts except 1 had a karyotype analysis at diagnosis

## Materials and methods

63 patients : 27 (43%) males and 36 (57%) females Median age = 41years (18-64)

### AML characteristics:

- FAB classification was:  
M0 : 6 M1: 10  
M2: 13 M4: 6  
M5: 21 M6: 3  
M7: 1 and 3 unclassified

- Karyotype analysis :  
25 (40%) normal karyotype,  
37 (60%) pts presented cytogenetic abnormalities :  
favourable prognosis in 5 cases (8%)  
intermediate in 13 cases (21%) and poor in 19 cases (31%)

- Molecular markers evaluated in all pts:

Flt3over-expression (ov-ex) : 4(6%) FLT3 ITD+ : 19 (30%)  
MLLdup : 3 (5%) Hoxa9 ov-ex : 10 (16%)  
Evi1 ov-ex : 7 (11%) NPM1mut+ : 15 (24%)  
WT1 ov-ex : 25 (40%) CEBP $\alpha$ mut+ : 1 (this marker was evaluated only in 12 pts)

-Associations between these markers and the karyotype prognosis groups are shown in Figure1.

### Transplantation characteristics:

- Median interval diagnosis-transplantation : 6 months (2.6-68.5)
- Before conditioning : 41 CR (26 CR1, 14 CR2 and 1 CR3), 8 PR and 14 in relapse
- Twenty five (40%) pts received a non-myelo-ablative conditioning and 38 (60%) a myelo-ablative one.
- 23 (36.5%) pts received PBSC, 37 (59%) bone marrow and 4 (6.5%) cord blood cells from 47 (75%) HLA siblings and 16 (25%) unrelated donors.

## Results

- 59 (94%) pts engrafted,
- 42 developed AGVHD (21gr1, 13 gr2 and 8 gr4),
- Among 51 evaluable pts : 13 developed cGVHD (7 limited and 6 extensive).
- At the last follow-up :  
20 pts have relapsed, 29 pts are alive (28 CR and 1PR)
- 34 died: 18 (53%) from TRM and 16 (47%) from relapse
- Median follow-up: 48 months
- OS (whole population): 40% (33-47)
- DFS (whole population): 40% (34-46) (max FU:130 months)

### Univariate analysis:

- Significant impact of FLT3 ITD and over-expression of FLT3RQ on long-term DFS, (p=0.03 and p=0.02) and Trend on long-term OS (p=0.08).

The known benefic impact of NPM1mut+, was erased because the majority of this group presented an associated FLT3 ITD+

## Conclusion

In conclusion, allogeneic HSCT in this high risk population of AML pts, allowed a good probability of long-term OS and DFS, despite the presence of high number of bad molecular markers and cytogenetic abnormalities. Finally, AML pts with FLT3 ITD+ seem not benefit from allogeneic HSCT as well as patients with NPM1mut+ when associated with FLT3ITD+

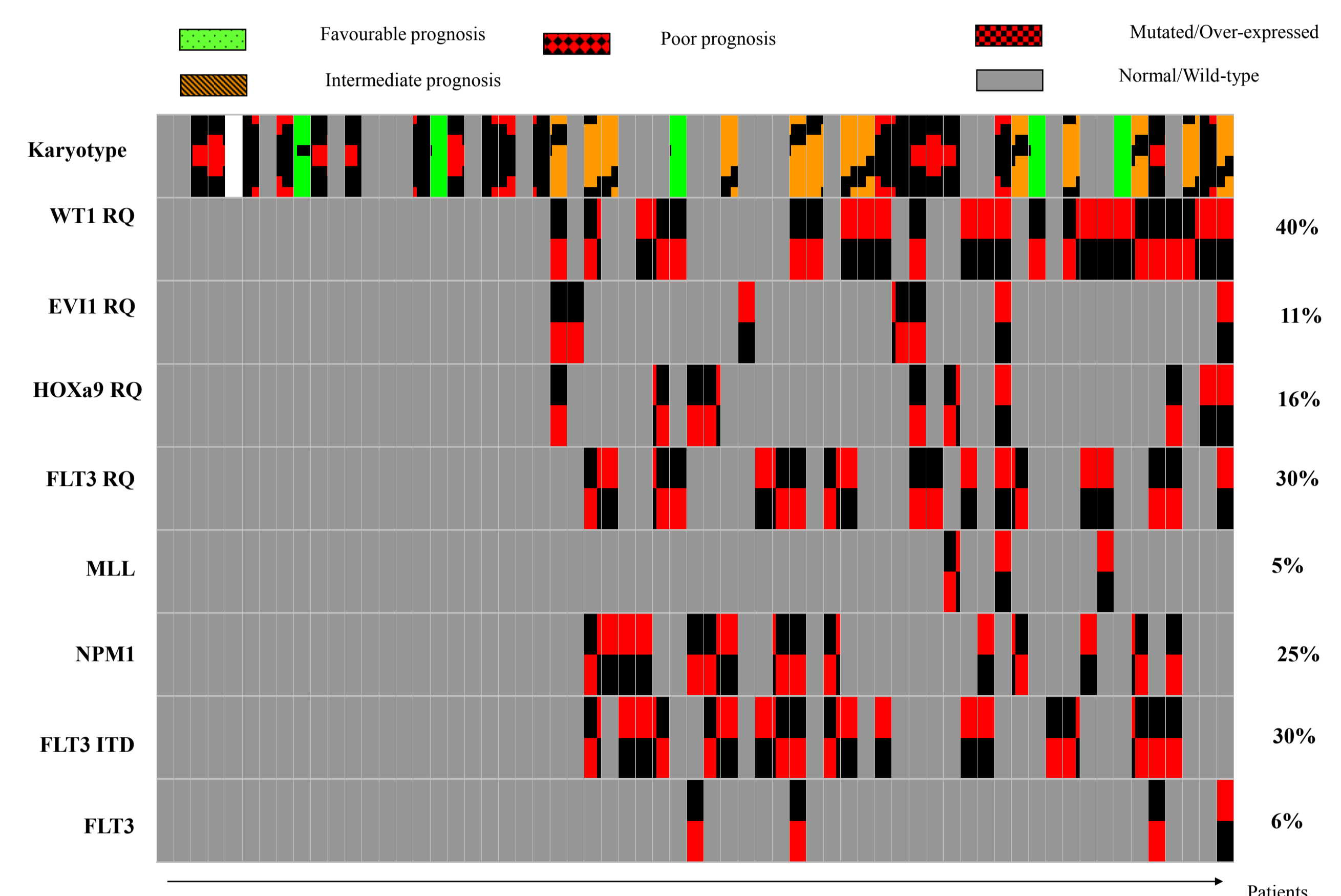


Figure 1: Frequencies and distribution of different molecular markers and karyotype subgroups

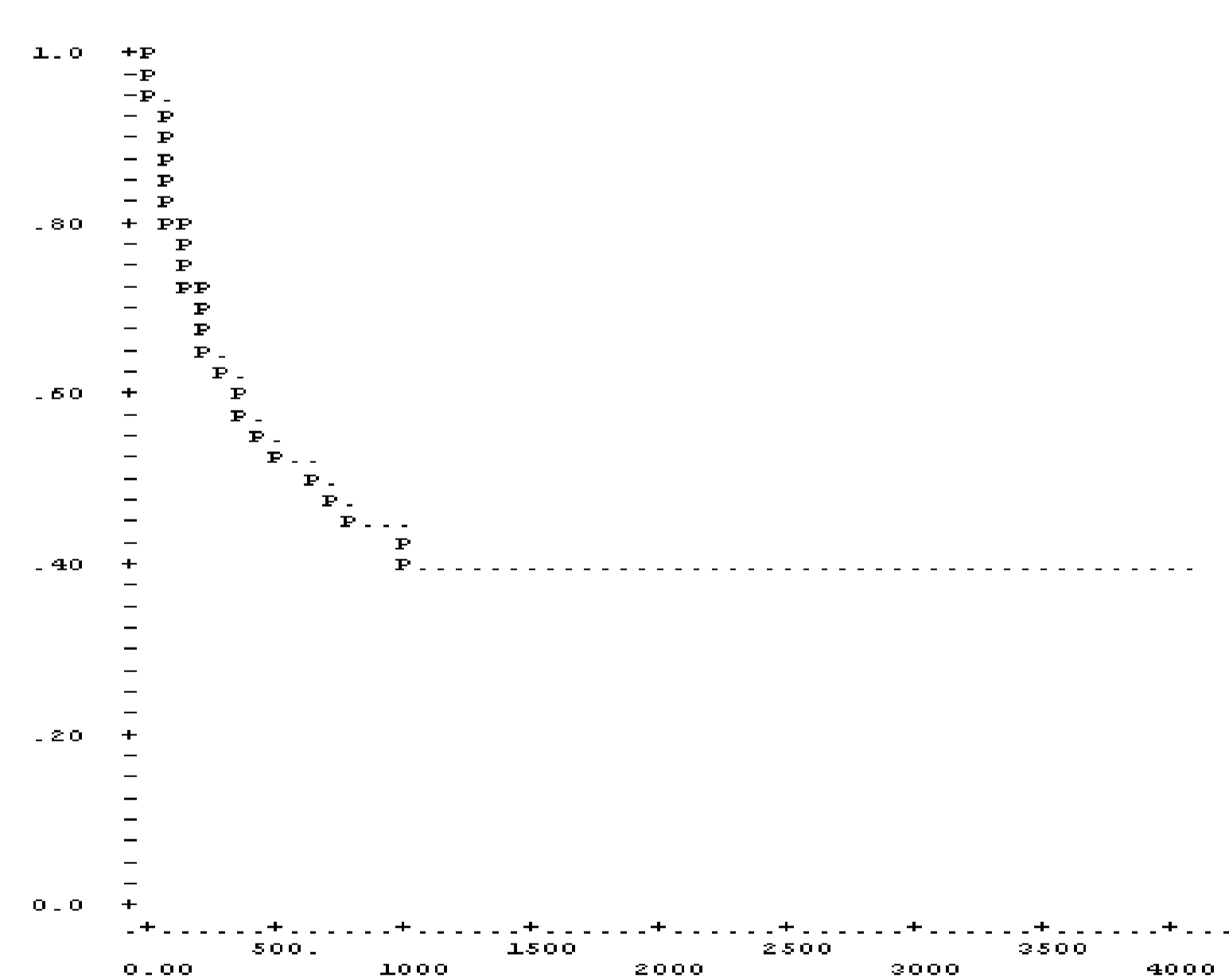


Figure 2: Probability of overall survival for the whole population

	OS	DFS
FLT3 ov-ex	50%(25-75)	50%(25-75)
FLT3 normal	40%(33-47)	34%(32-46)
FLT3 ITD+	27%(16-38)	25%(15-35)
FLT3 ITD -	46%(38-54)	47%(41-55)
Hoxa9 ov-ex	50%(35-65)	50%(35-65)
Hoxa9 normal	38%(31-45)	38%(31-45)
EVI1 ov-ex	28%(11-45)	28%(11-45)
EVI1 normal	43%(36-50)	42%(35-49)
NPM1mut+	32%(20-44)	33%(21-45)
NPM1mut-	43%(35-55)	42%(35-49)
WT1 ov-ex	37%(22-47)	34%(25-43)
WT1 normal	43%(34-52)	44%(35-53)
Fav. Prognosis	83%(67-98)	83%(67-98)
Int. Prognosis	50%(39-61)	52%(42-62)
Poor. Prognosis	24%(16-32)	24%(16-32)

Table 1: OS and DFS according to karyotype and molecular markers