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## Flow MRD Monitoring Combining LAIP/Dfn and CD34+ CD38- LSCs Is a Strong Predictor of Outcome in Adult AML Independently of the ELN-2022 risk

First Results from the Multicentric Acute Leukemia French Intergroup MRD Flow Network (BIG-1 Study)

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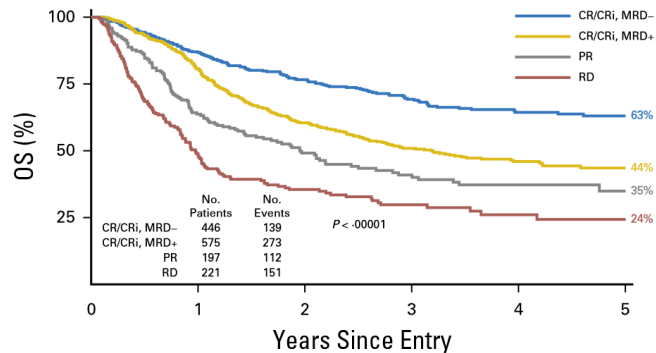


No disclosure



# Introduction

- Prognostic value of detectable flow LAIP/DfN MRD after cycle 1, close to partial remission

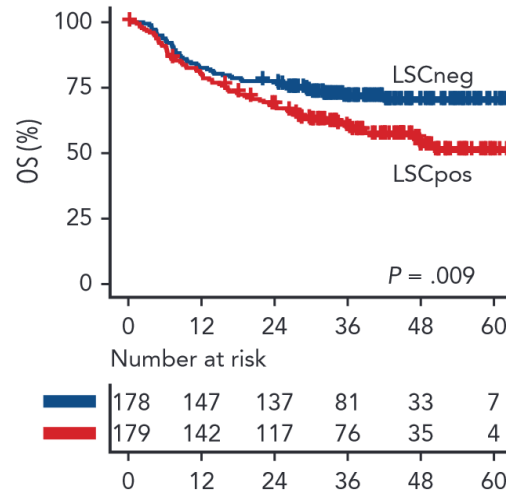


No. at risk:	0	1	2	3	4	5
CR/CRi, MRD-	446	373	272	192	122	71
CR/CRi, MRD+	575	451	272	173	97	41
PR	197	121	72	47	31	11
RD	221	104	56	29	16	10

**NCRI AML17 trial**  
N=1434; median age, 51 years

Freeman SD, et al. *J Clin Oncol.* 2018

- Prognostic value of CD34+ CD38- LSCs at diagnosis and after cycle 2 in intermediate/adverse-risk AML patients



**HOVON-SAKK132 trial**  
N=764; median age, 54 years

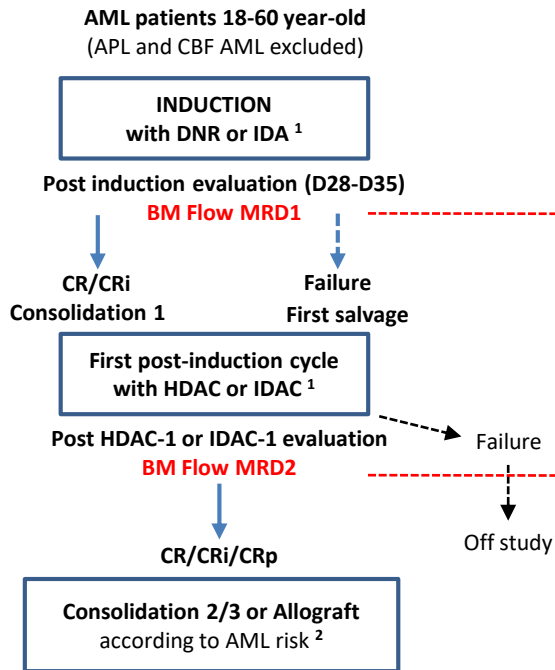
Lok Lam Ngai, et al. *Blood* 2023

# Objectives

- To validate a multicentric standardized LAIP/DfN & LSC MRD follow-up across the French Flow MRD network (30 labs.)
- To evaluate the prognostic value of baseline level of CD34+ CD38- LSC on OS (overall survival) in the prospective French BIG-1 AML trial (NCT02416388)
- To evaluate the prognostic value of LAIP/DfN MRD and LSC MRD on OS in this trial, in general and in the different ELN-2022 risk groups

# Study population

## The French intensive BIG-1 trial



**N= 315**  
out of the 1228 patients  
included in the BIG-1 trial  
between 01-2018 and 07-2021

- Median age, 49 years
- ELN-2022 risk group
  - 97 favorable (80 *NPM1m*),
  - 87 intermediate,
  - 110 adverse,
  - 21 non classif.
- N= 284 achieved CR/CRi
  - 262 after induction
  - 22 after first salvage

## Number of patients studied by flow

### Baseline

- LSC N=280  
(cutoff, 1% of BM blasts)

### After induction (MRD1)

- LAIP/DfN MRD, N= 298  
(cutoff, 0,1% of WBC)
- LSC MRD, N=222  
(cutoff, 0,01% of WBC)
- Both LAIP/DfN and LSC MRD, N=220

### After consolidation 1/salvage (MRD2)

- LAIP/DfN MRD, N= 253
- LSC MRD, N=197
- Both LAIP/DfN and LSC MRD, N=193

<sup>1</sup>: similar outcomes; see Hunault *et al.* ASH 2023 (manuscript in revision)

<sup>2</sup>: molecular *NPM1* MRD was considered for *NPM1m* AML risk classification

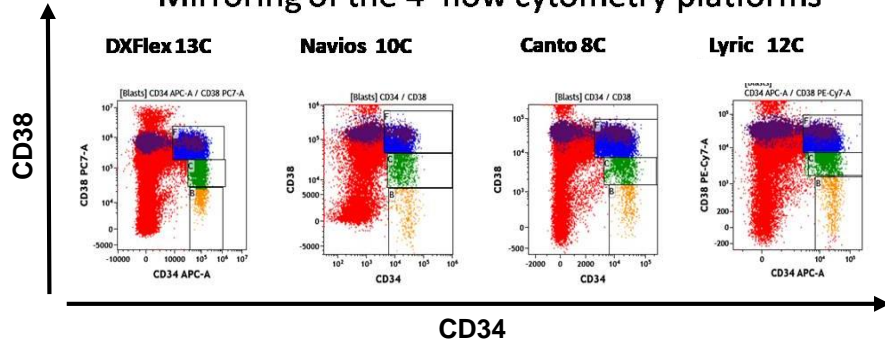
# Multicentric French Intergroup Flow Network Platforms

30 Flow Labs: 18 BD (Canto / Lyric) + 12 BC (Navios / DxFlex)



Panel Flow8c	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8
T 1 LAIP	CD7+CD56	CD13	CD33	CD34	CD38	CD117	CD19	CD45
T 2 LSC	CD90	MIX LSC: TIM3+CLL1+CD97	CD123	CD34	CD38	CD117	CD45RA	CD45

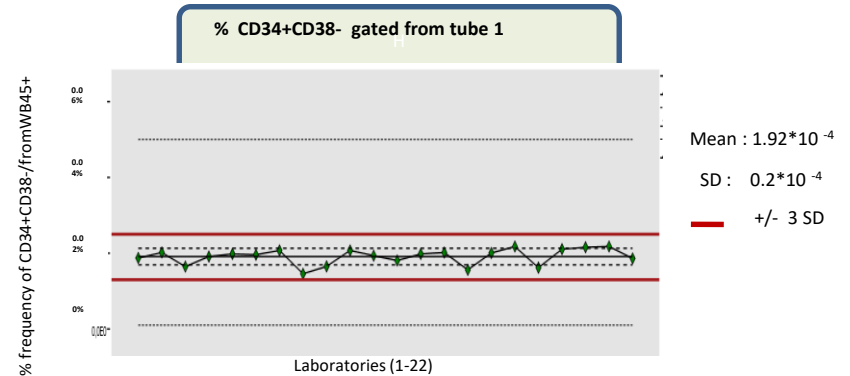
## Mirroring of the 4 flow cytometry platforms



Plesa et al, Annual ASH Meeting 2022

From 8c-10c to 12c-13c

## Inter-laboratory comparisons for Quality Assessment of Fluorescent profiles and Gating QC (Quality Control Sample)



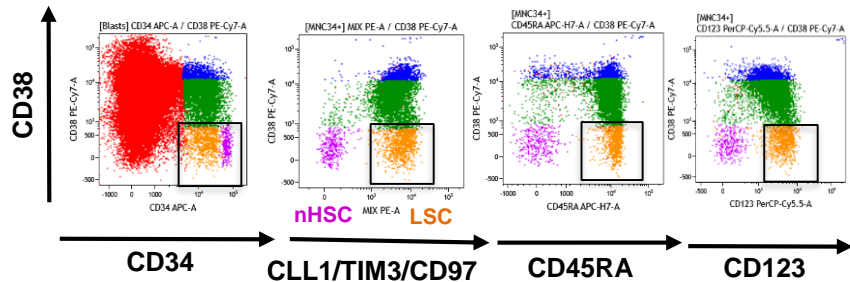
- EEQ inter-French Network Flow labs
- ELN DAVID -EQA exercise of analysis & reporting – NEQAS collaboration
- ELN DAVID-EQA Program to provide LSC MRD Testing by Flow in Interlaboratory Study– NEQAS collaboration (UK/ALFA/HOVON)

## One Flow Lab with 30 Cytometers:

High level of standardization and inter-center reliability of MRD flow quantification (regularly Web Educational Training in the Flow group, data reviewed by two coordinators experts)



# I – Prognostic value of baseline CD34+ CD38- LSC detection



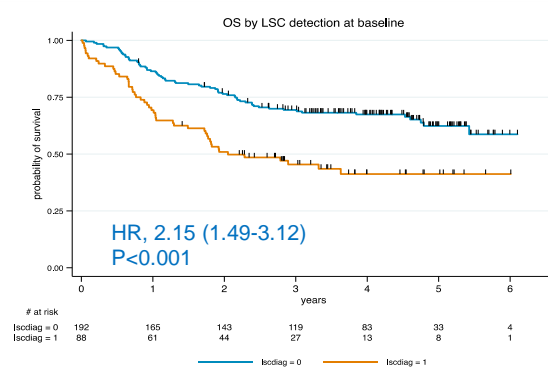
At least 1 aberrant immunophenotype (**CLL1/TIM3/CD97/CD45RA/CD123**) in immature CD34+ CD38- cells

- Sensitivity of assays  $10^{-5}$  (LOD  $10^{-4}$ )
- **Cutoff of LSC positivity at diagnosis,  $\geq 1\%$  of CD45/ssc blasts**

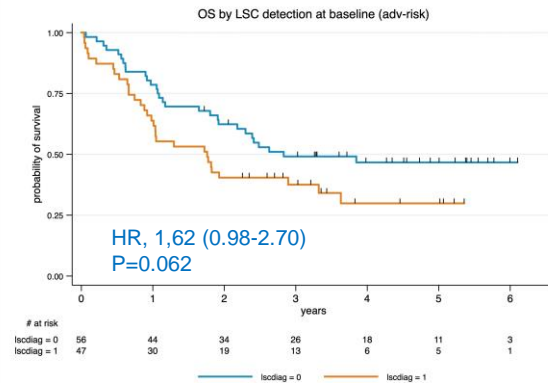
N= 280 patients

LSCs	ELN22				Total
	FAV	INT	ADV	nc	
<1%	76	47	56	13	192 (69%)
$\geq 1\%$	5 (6%)	28 (37%)	47 (46%)	8	88 (31%)
Total	81	75	103	21	280

P<0.001



## Contribution of the ELN-2022 adverse-risk group



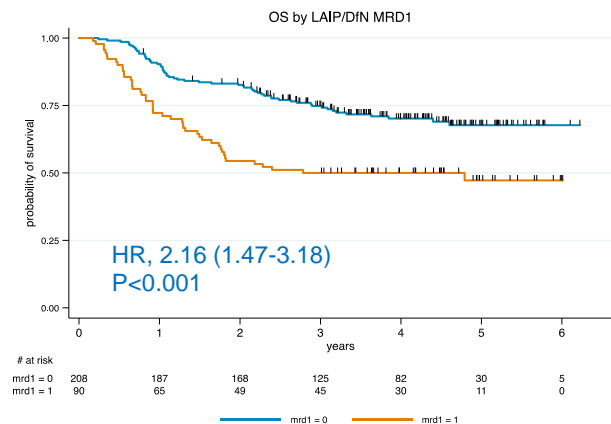
# II – Prognostic value of LAIP/DfN and LSC at MRD1

Includes some primary induction failure (PIF) patients

**LAIP/DfN MRD1, N= 298 patients**

MRD1	ELN22				Total
	FAV	INT	ADV	nc	
<0.1%	74	60	65	9	208 (70%)
≥ 0.1%	16 (18%)	30 (33%)	37 (36%)	7	90 (30%)
<b>Total</b>	<b>90</b>	<b>90</b>	<b>102</b>	<b>16</b>	<b>298</b>

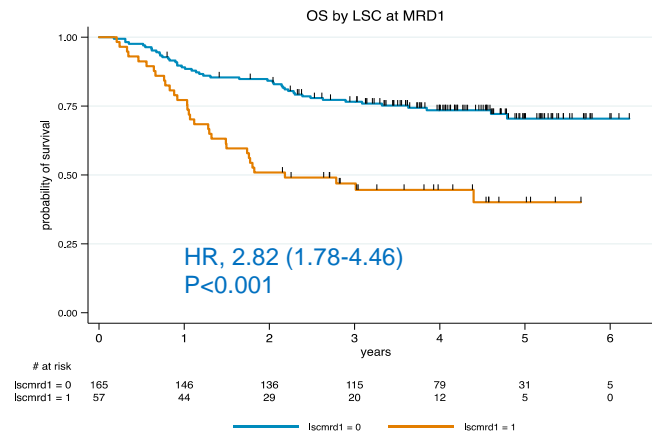
P= 0.012



**LSC MRD1, N= 222 patients**

LSC MRD1	ELN22				Total
	FAV	INT	ADV	nc	
<0.01%	61	47	48	9	165 (74%)
≥0.01%	9 (13%)	15 (24%)	28 (37%)	5	57 (26%)
<b>Total</b>	<b>70</b>	<b>62</b>	<b>76</b>	<b>14</b>	<b>222</b>

P= 0.006



**In multivariate analysis, LAIP/DfN and LSC MRD1 were still associated with a worse prognosis, independently of the ELN-2022 risk groups**



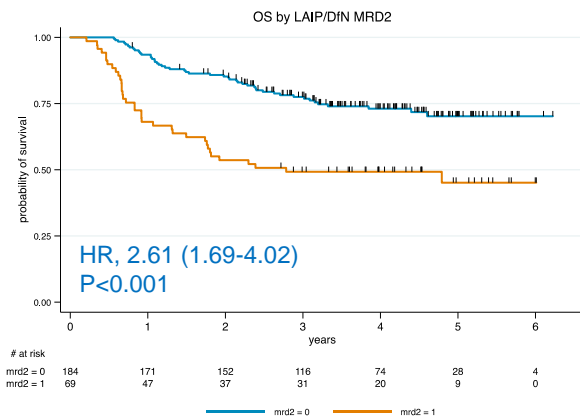
# III – Prognostic value of LAIP/DfN and LSC at MRD2

Includes some primary induction failure (PIF) patients

LAIP/DfN MRD2, N= 253 patients

MRD2	ELN22				Total
	FAV	INT	ADV	nc	
<0.1%	63	53	55	13	184 (73%)
≥ 0.1%	11 (15%)	24 (31%)	30 (35%)	4	69 (27%)
<b>Total</b>	<b>74</b>	<b>77</b>	<b>85</b>	<b>17</b>	<b>253</b>

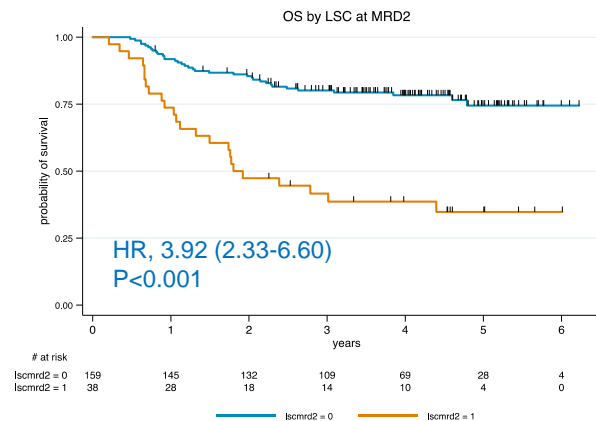
P= 0.021



LSC MRD2, N= 197 patients

LSC MRD2	ELN22				Total
	FAV	INT	ADV	nc	
<0.01%	58	47	43	11	159 (81%)
≥0.01%	7 (11%)	12 (20%)	17 (28%)	2	38 (19%)
<b>Total</b>	<b>65</b>	<b>59</b>	<b>60</b>	<b>13</b>	<b>197</b>

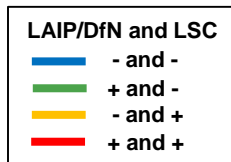
P= 0.09



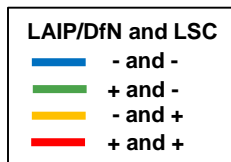
In multivariate analysis, LAIP/DfN and LSC MRD2 were still associated with a worse prognosis, independently of the ELN-2022 risk groups

# IV – Combining LAIP/DfN and LSC MRD

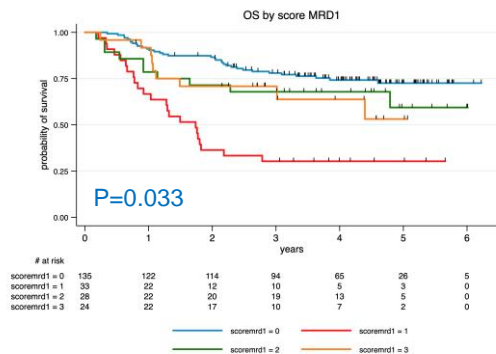
- All patients (including some primary induction failure patients)



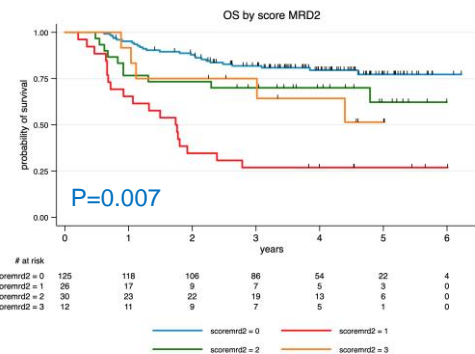
- Patients who achieved CR/CRi only



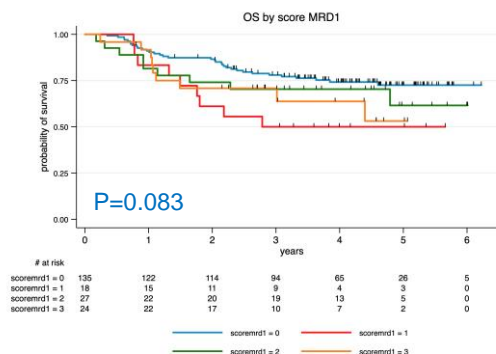
**MRD1, N= 220 pts**



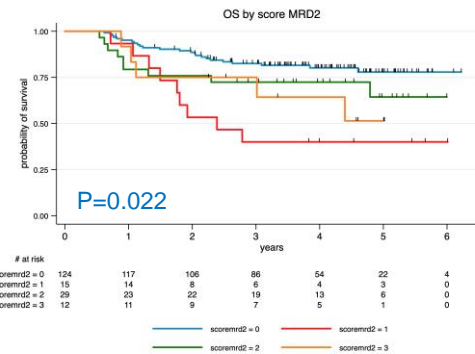
**MRD2, N= 193 pts**



**MRD1, N= 204 pts**



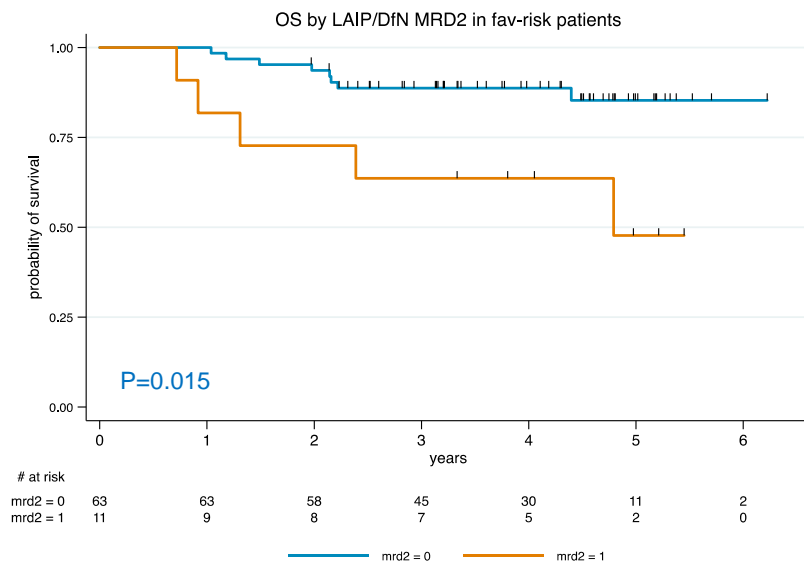
**MRD2, N= 180 pts**



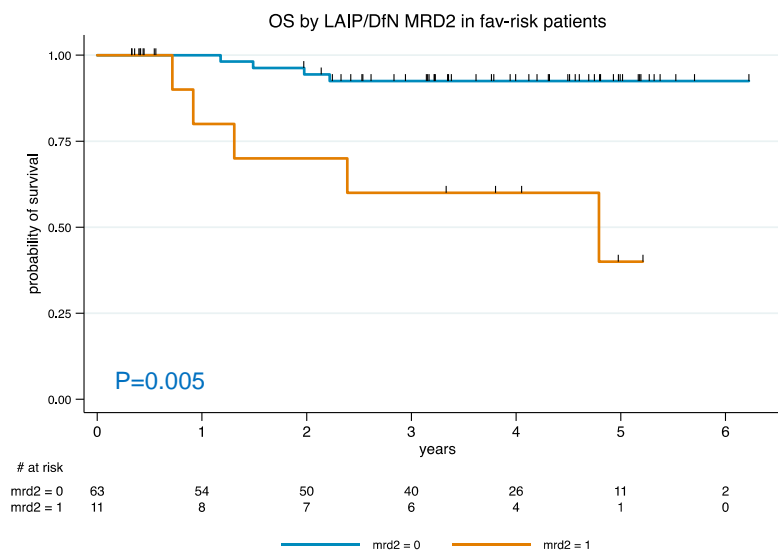
# V – Favorable-risk AML patients (no CBF-AML here)

- After adjustments in 74 FAV-risk AML patients who achieved CR/CRi, LAIP/DfN MRD2 appeared to be the most powerful tool to predict outcome (low LSC frequency in this subgroup)

No HSCT censoring



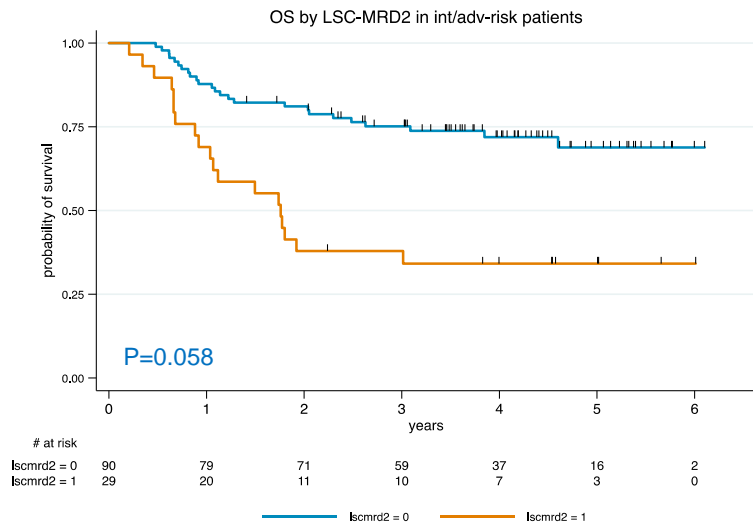
Censoring at HSCT in first CR



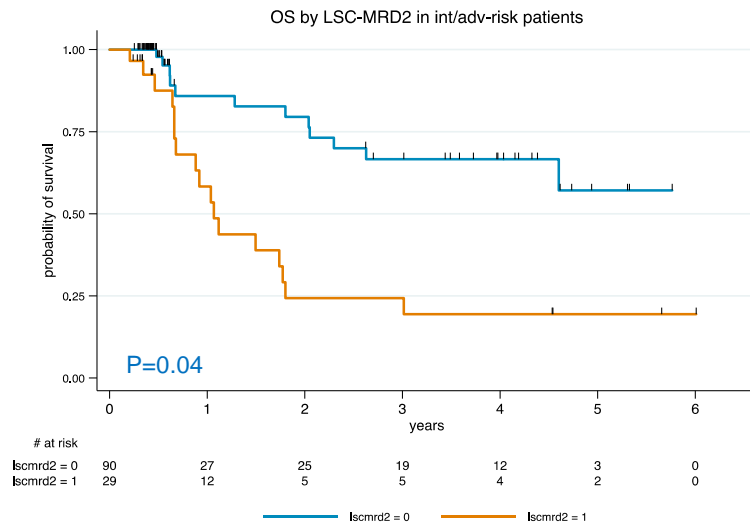
# VI – Intermediate/adverse-risk AML patients

- After adjustments in 119 INT/ADV-risk AML patients who achieved CR/CRI, LSC MRD2 appeared to be the most powerful tool to predict outcome (higher LSC frequency in these subgroups)

No HSCT censoring



Censoring at HSCT in first CR



# Conclusions

- Standardized Flow MRD LAIP/DfN and LSC monitoring is routinely feasible in a multicentric and multi-labs network
- Higher LSC level at baseline is associated with a worse outcome, mostly due to the contribution of adverse-risk AML patients
- After CR/CRi achievement, the most powerful MRD tools that may be used for treatment stratification appeared to be:
  - ✓ **LAIP/DfN MRD2 in the favorable-risk AML group**
  - ✓ **LSC MRD2 in the intermediate/adverse-risk AML groups**



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Biological coordinators: Claude Preudhomme, Eric Delabesse  
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## AML MRD French Flow Network

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Paris St Cloud: Valerie Bardet  
Paris Creteil: Oriane Wagner Ballon, Bouchra Badaoui  
Paris Versailles: Victoria Raggueneau , Jennifer Osman  
Paris IGR: Veronique Saada  
Paris Bobigny: Remi Letestu  
Paris St Antoine: Frederic Feger  
Lille St Vincent: Agnes Charpentier  
Amiens: Veronique Harrivel  
Rouen: Elsa Bera  
Caen: Veronique Salaun, Edouard Cornet  
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Toulouse: Francois Vergez  
Marseille IPC: Anne Catherine Lhoumeau  
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