Physiopathologie et classifications moléculaires des LAM

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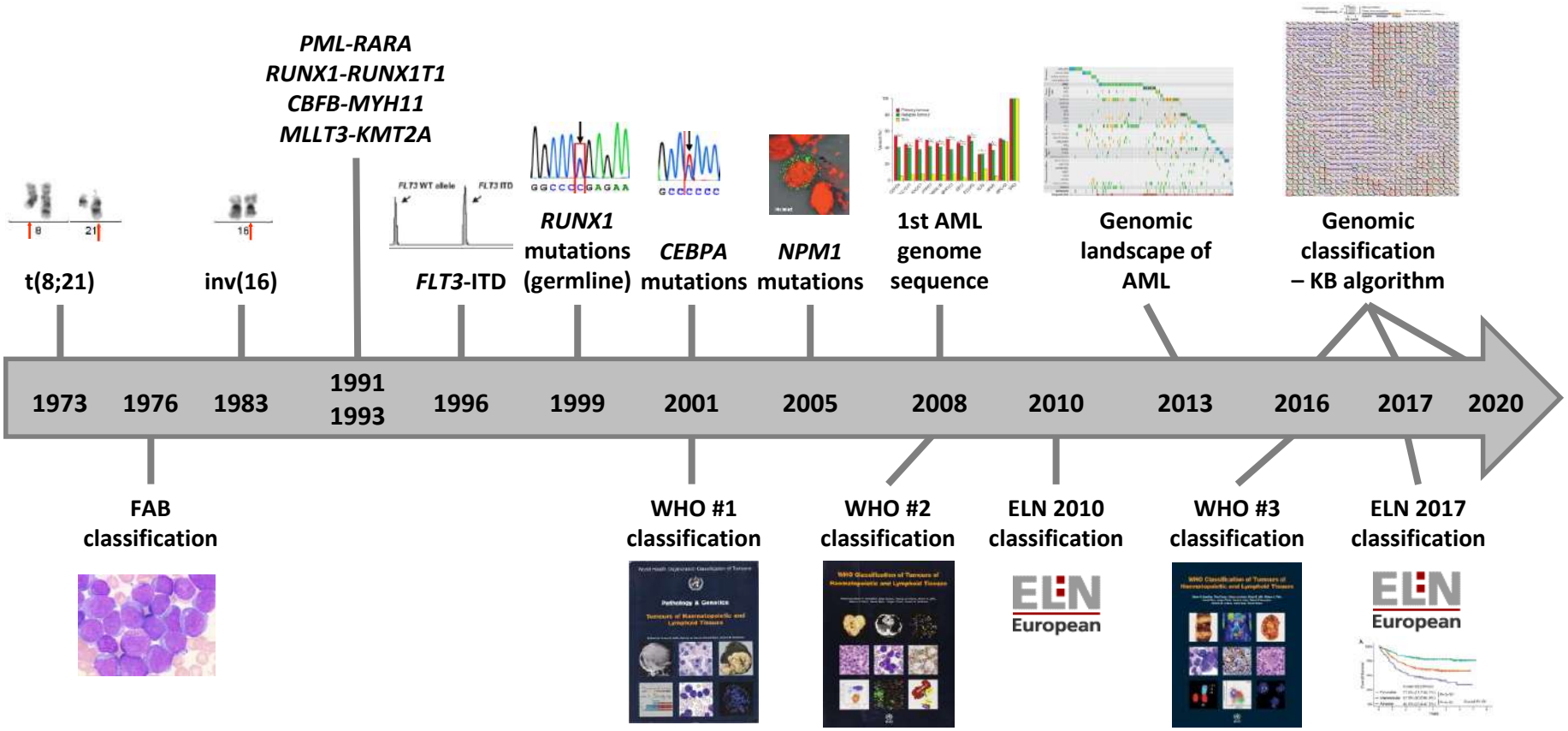
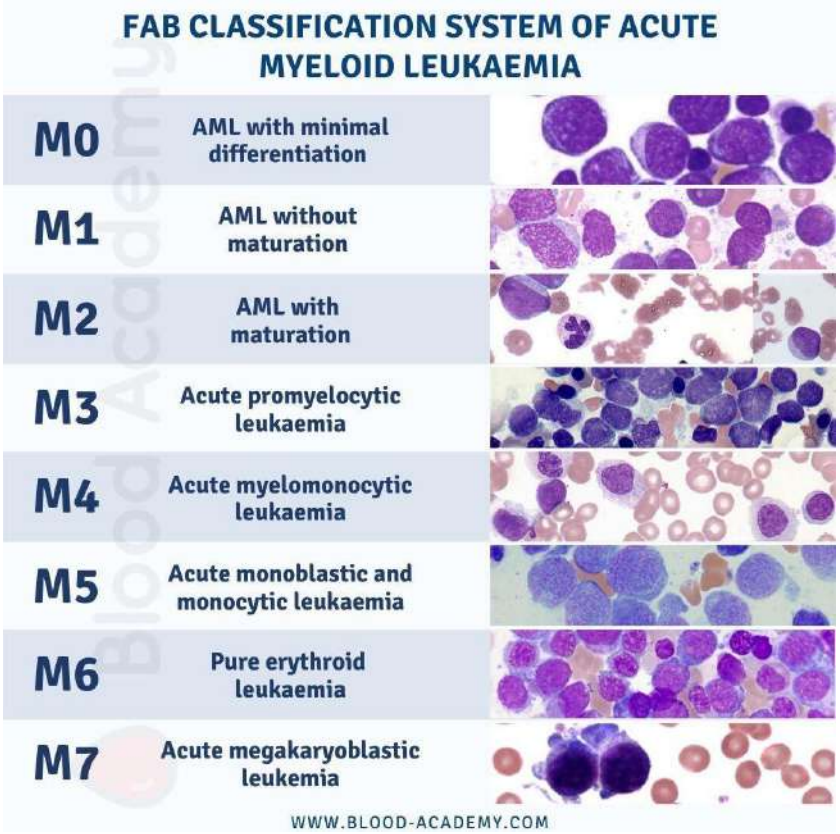
Biologie moléculaire des hémopathies

45 ans de classifications des LAM



I – Classification cytologique des LAM



British Journal of Haematology, 1976, **33**, 451.

Proposals for the Classification of the Acute Leukaemias

FRENCH–AMERICAN–BRITISH (FAB) CO-OPERATIVE GROUP

J. M. BENNETT,* D. CATOVSKY,† MARIE-THERÈSE DANIEL,‡ G. FLANDRIN,‡ D. A. G. GALTON,† H. R. GRALNICK§ AND C. SULTAN¶

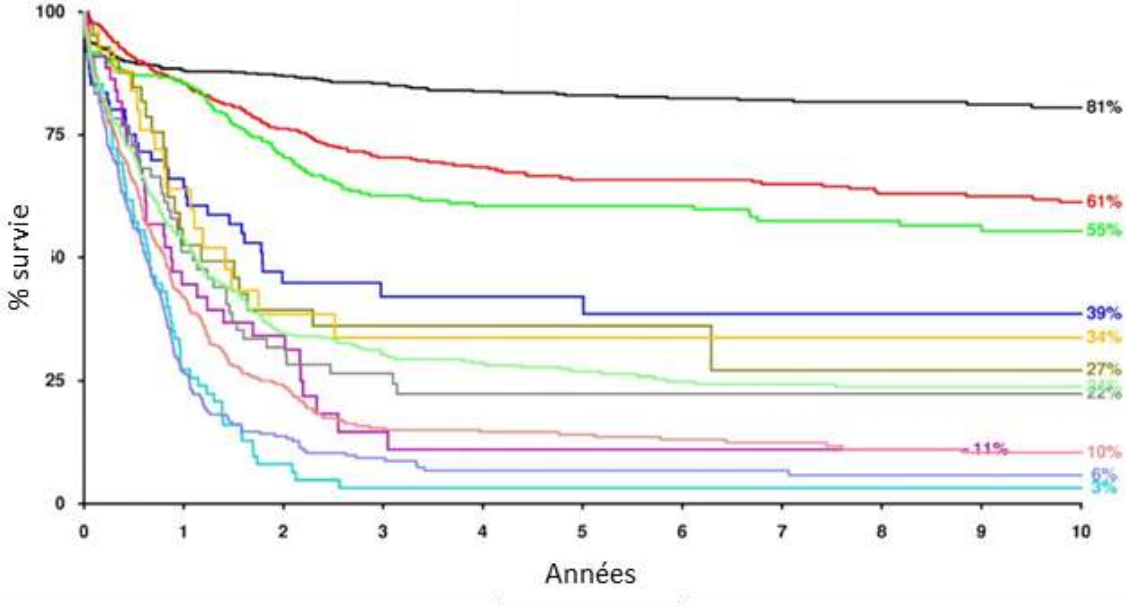
1976 (M1 à M6), **1985** (M7), **1987** (M0)

Chromosomal translocations	FAB classification	Relative prognosis
t(8;21)(q22;q22)	M2	fair to good
t(15;17)(q22;q21)	M3	fair to good
inv(16)(p13;q22)/t(16;16)(p13;q22)	M4eo	good
t(9;11)(p21;q23)	M5	poor
t(11q23)	M4–M5	poor
t(6;9)(p23;q34)	M2, M4	poor
t(8;16)(p11;p13)	M5	undetermined
inv(3)(q21;q26)/t(3;33)t(1;3)(p36;q21)	M4	undetermined
t(1;22)(p13;q13)	M7	undetermined

Segeren CM, van 't Veer MB. Neth J Med. 1996;49(3):126–131.

II – Classification cytogénétique des LAM

Rowley J D. Identification of a translocation with quinacrine fluorescence in a patient with acute leukemia. *Ann. Génét. Paris* 16:109-12, 1973.
[Department of Medicine, Pritzker School of Medicine, University of Chicago, and Argonne Cancer Research Hospital, Chicago, IL]



LAP t(15;17)

LAM-CBFa t(8;21)
LAM-CBFb inv(16)

→ **Low-risk**

LAM t(9;11)
Normal

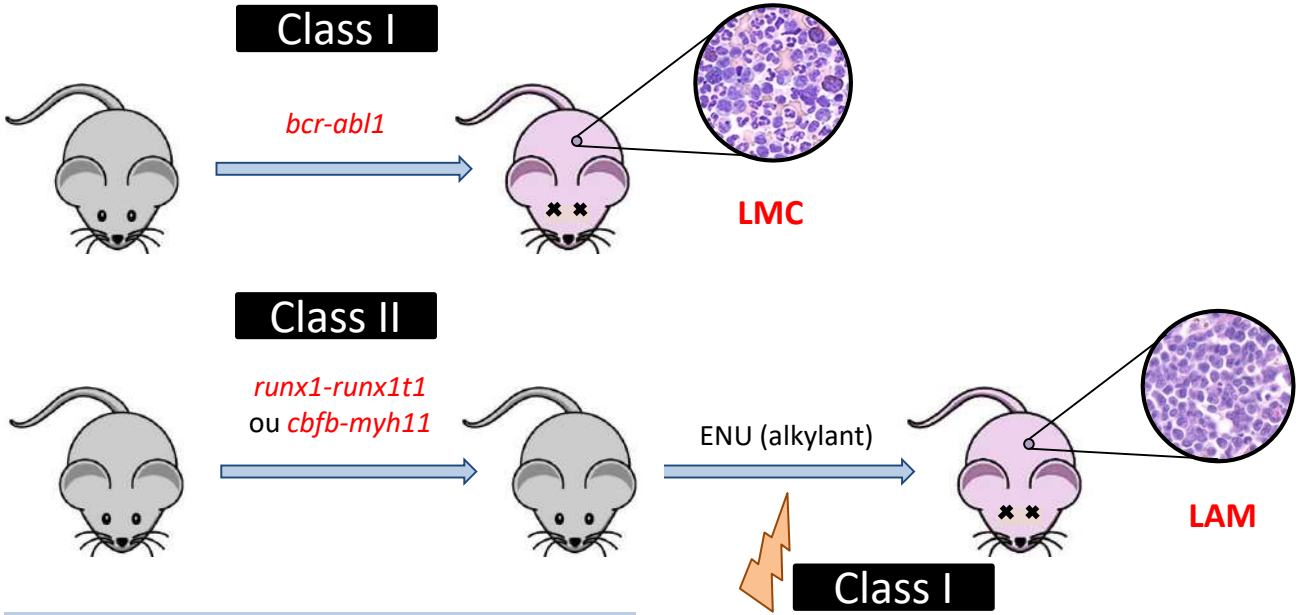
→ **Intermediate**

LAM -7/del7q
LAM -5/del5q
LAM inv(3)

→ **High-risk**

Grimwade D, et al. (UK MRC) Blood. 2010;116(3):354–365.

Physiopathologie des LAM : *multistep model*



Chez l'Homme :

- ❑ Persistance en RC prolongée
- ❑ Détection chez des nouveau-nés sains

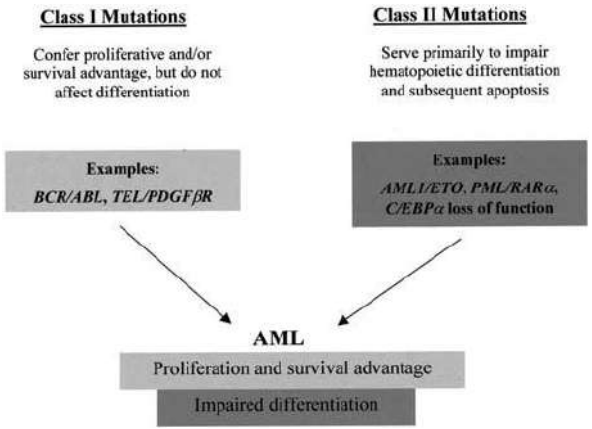
Miyamoto T, et al. Blood. 1996;87(11):4789–4796.
Wiemels JL, et al. Blood. 2002;99(10):3801–3805.

Downing JR. Current Opinion in Genetics & Development. 2003;13(1):48–54.

Physiopathologie des LAM : *multistep model*

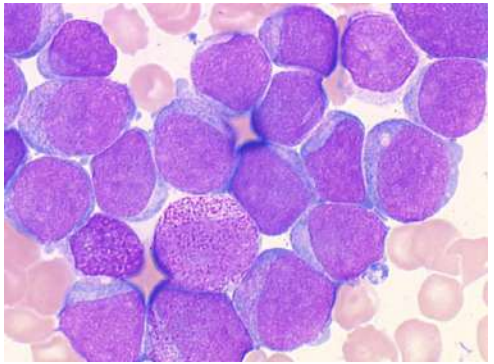
LAM = Prolifération clonale incontrôlée de cellules hématopoïétiques **bloquées dans leur différenciation** (blastes)

①



« two-hit » model

②

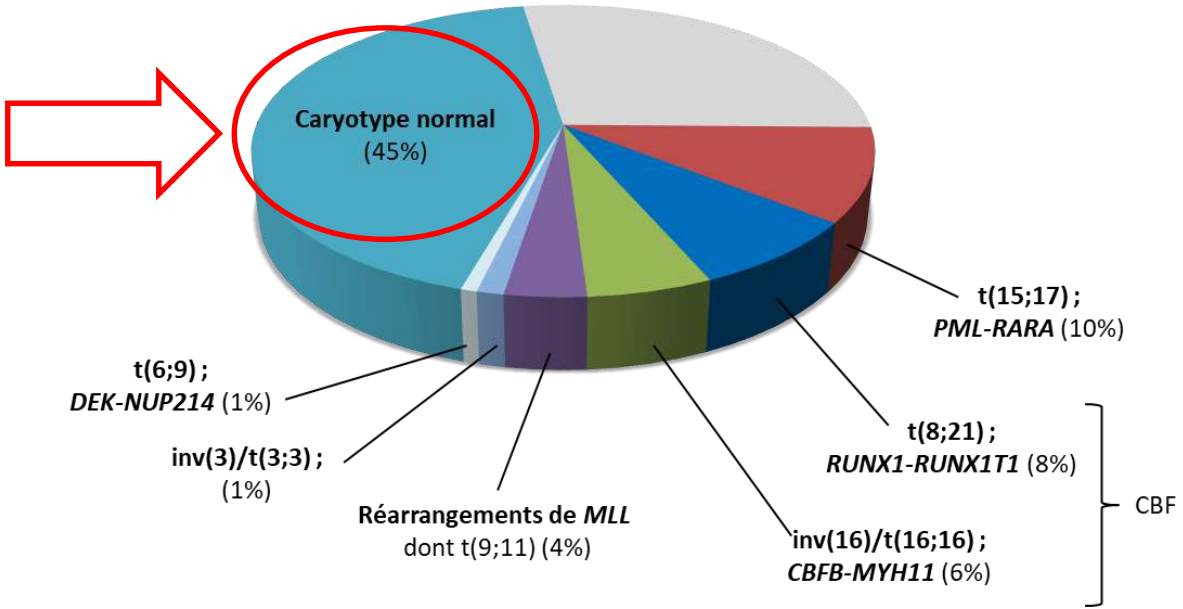


Accumulation « multi-étape » d'anomalies génétiques

- Induites (chimiothérapie, toxiques …)
- Constitutionnelles (thrombopénies familiales …)
- de novo

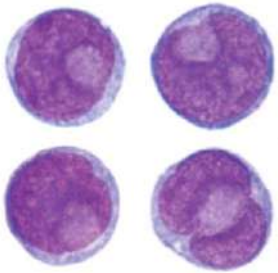
Gilliland DG. Molecular genetics of human leukemias: New insights into therapy. Seminars in Hematology. 2002;39(4):6–11.

III – Vers une classification moléculaire des LAM

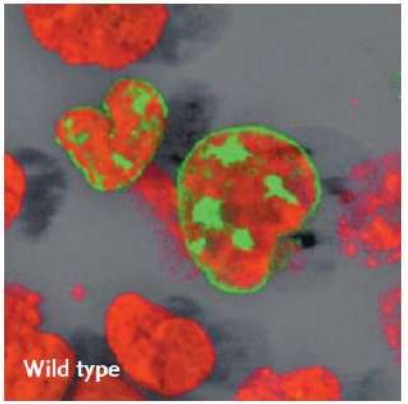


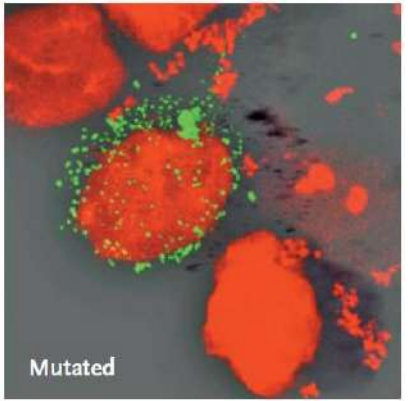
a) Mutations de *NPM1*

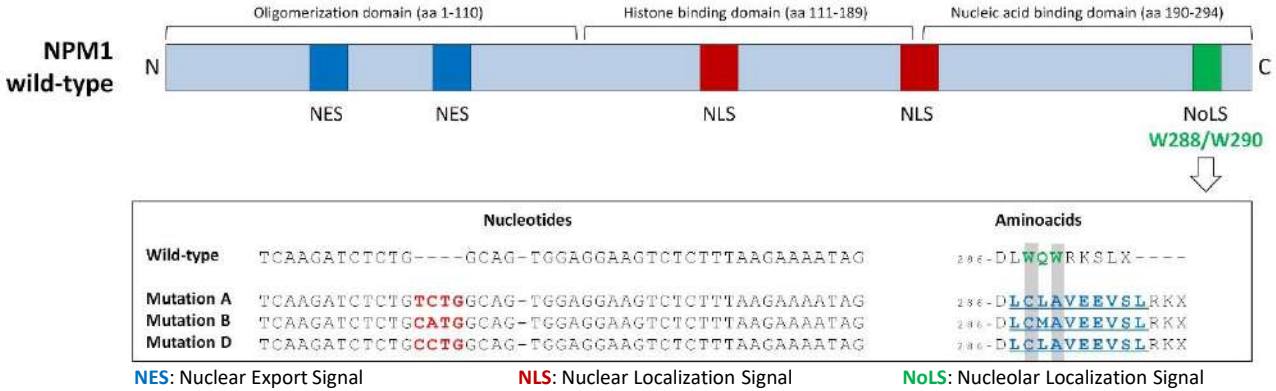
- **Nucléophosmine**
- **~ 30% des LAM de novo**
  - Délocalisation cytoplasmique de NPM1
  - M1, M2, M4, M5, morphologie « cup-like »
  - Caryotype normal, CD34-, souvent *FLT3*-ITD
  - Bonne réponse à la chimiothérapie
    - Modulé par *FLT3*-ITD



Jost E, et al. AJH. 2015;90(9):847–848.



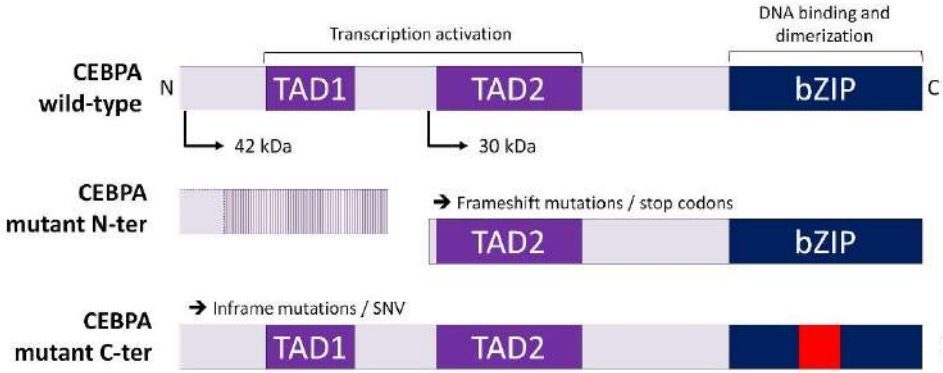


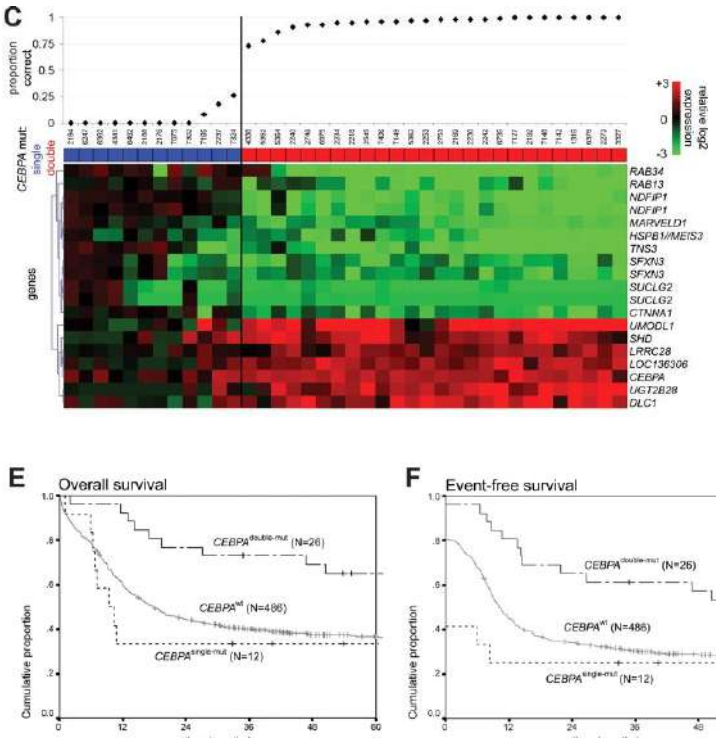


Falini B, et al. NEJM. 2005;352(3):254–266.

b) Mutations de *CEBPA*

- **CEBPA :** facteur de transcription myéloïde (class II)
- **~ 5% des LAM de novo**
  - Caryotype normal, FLT3-ITD négatif
  - Pronostic favorable restreint aux LAM avec double mutation *CEBPA*

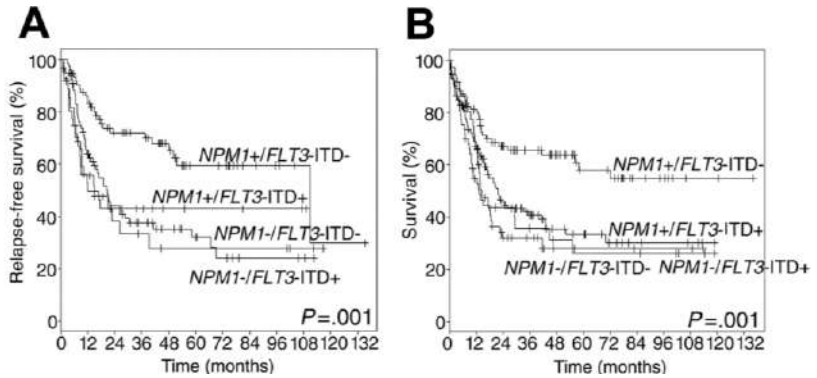




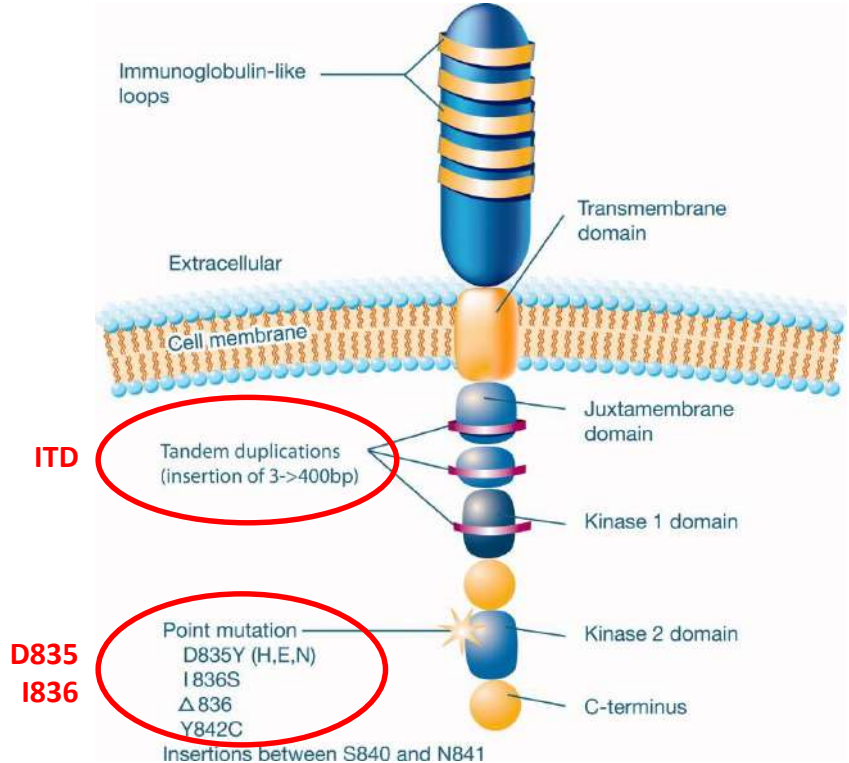
Pabst T, et al. Nature Genetics. 2001;27(3):263–270.
Wouters BJ, et al. Blood. 2009;113(13):3088–3091.

c) Mutations de *FLT3*

- **FLT3 :** RTK (class I)
- **~ 25-30% des LAM de novo**
  - Association +++ aux mutations de *NPM1, PML-RARA, CBF*
  - Pronostic défavorable de *FLT3*-ITD

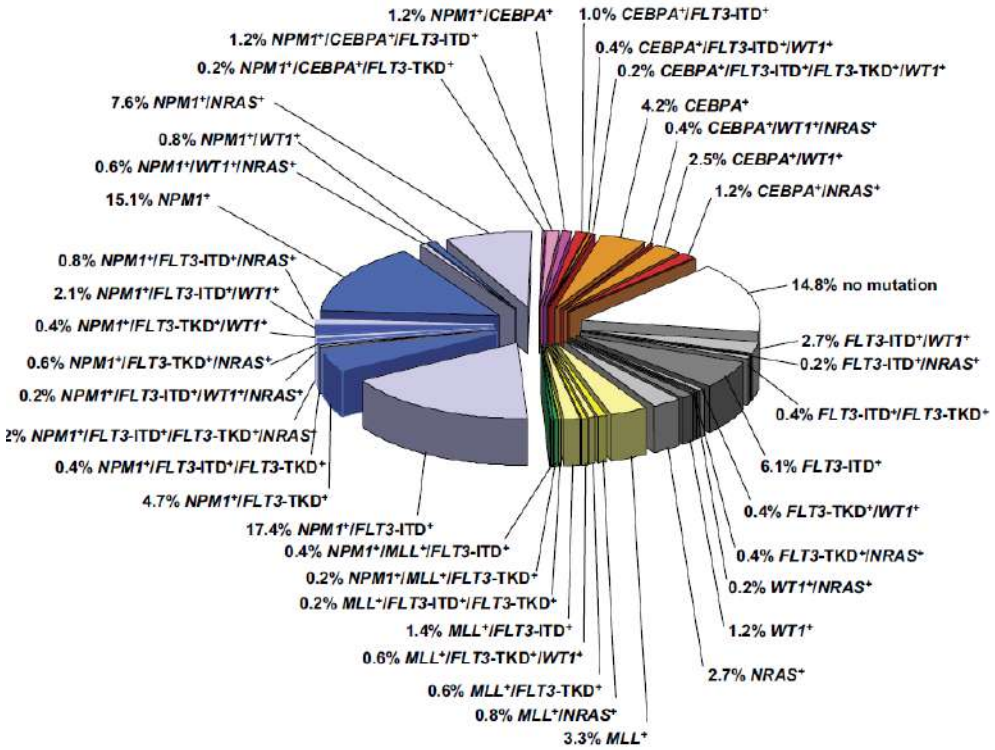


Döhner K, et al. Blood. 2005;106(12):3740–3746.



Nakao M, et al. Leukemia. 1996;10(12):1911–1918.

Anomalies moléculaires des LAM à caryotype normal



NPM1
CEBPA
FLT3

Pronostic

MLL
NRAS
WT1

Döhner H, et al. Blood. 2009;115(3):453–474.

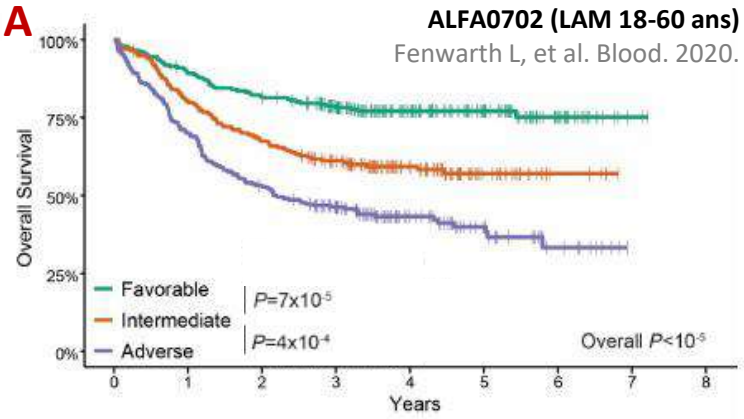
Classification pronostique ELN 2017

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Döhner H, et al. Blood. 2017;129(4):424–447.

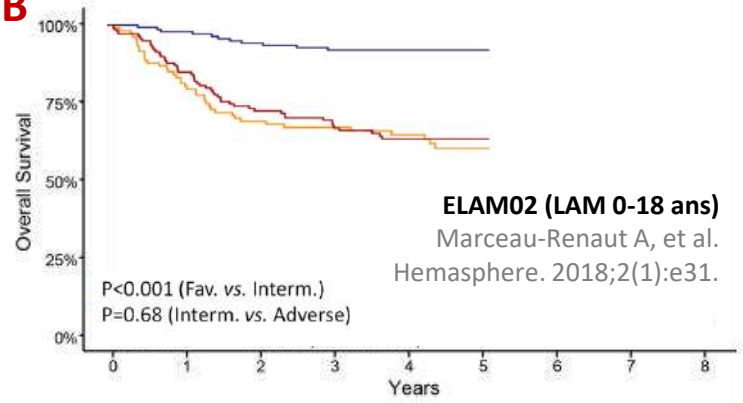
CC only
Mol. Only (standard/NGS)
Mol. or CC

A



ALFA0702 (LAM 18-60 ans)
Fenwarth L, et al. Blood. 2020.

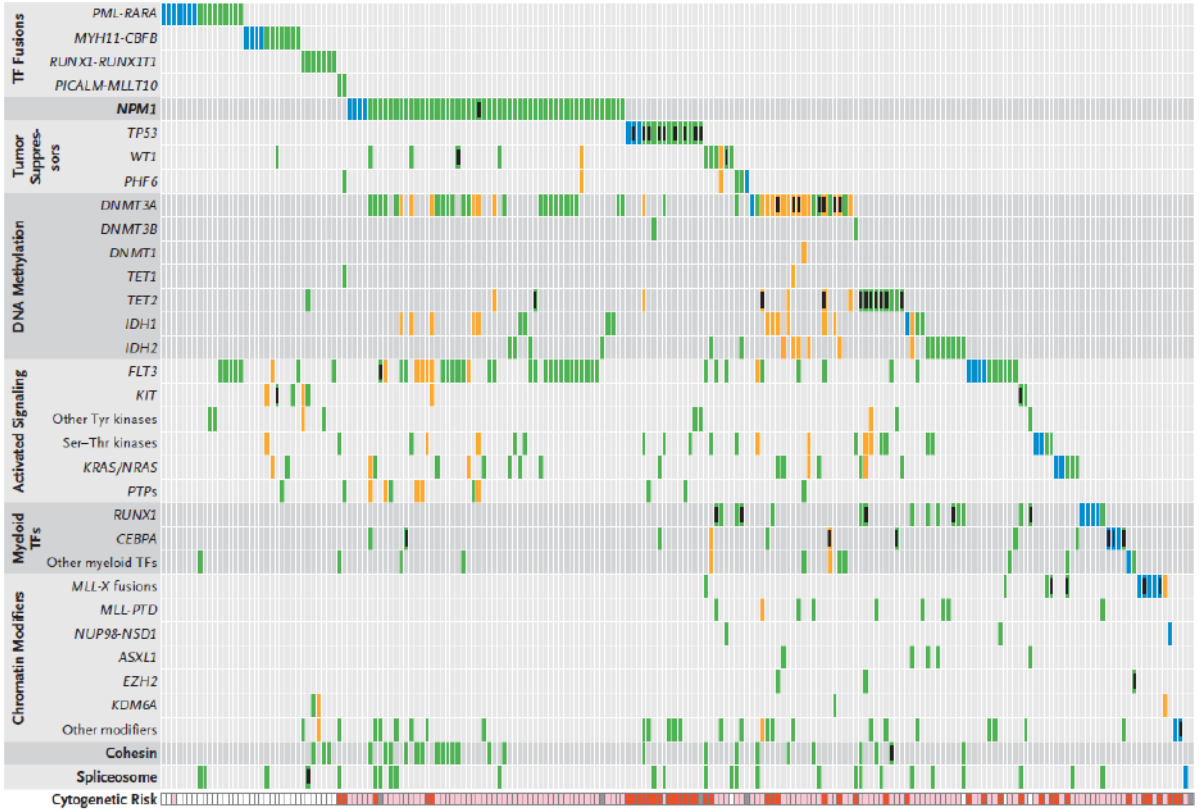
B



ELAM02 (LAM 0-18 ans)
Marceau-Renaut A, et al. Hemasphere. 2018;2(1):e31.

IV – Paysage mutationnel et leucémogenèse

* 1er génome de LAM publié en 2008 (Ley et al, NEJM)



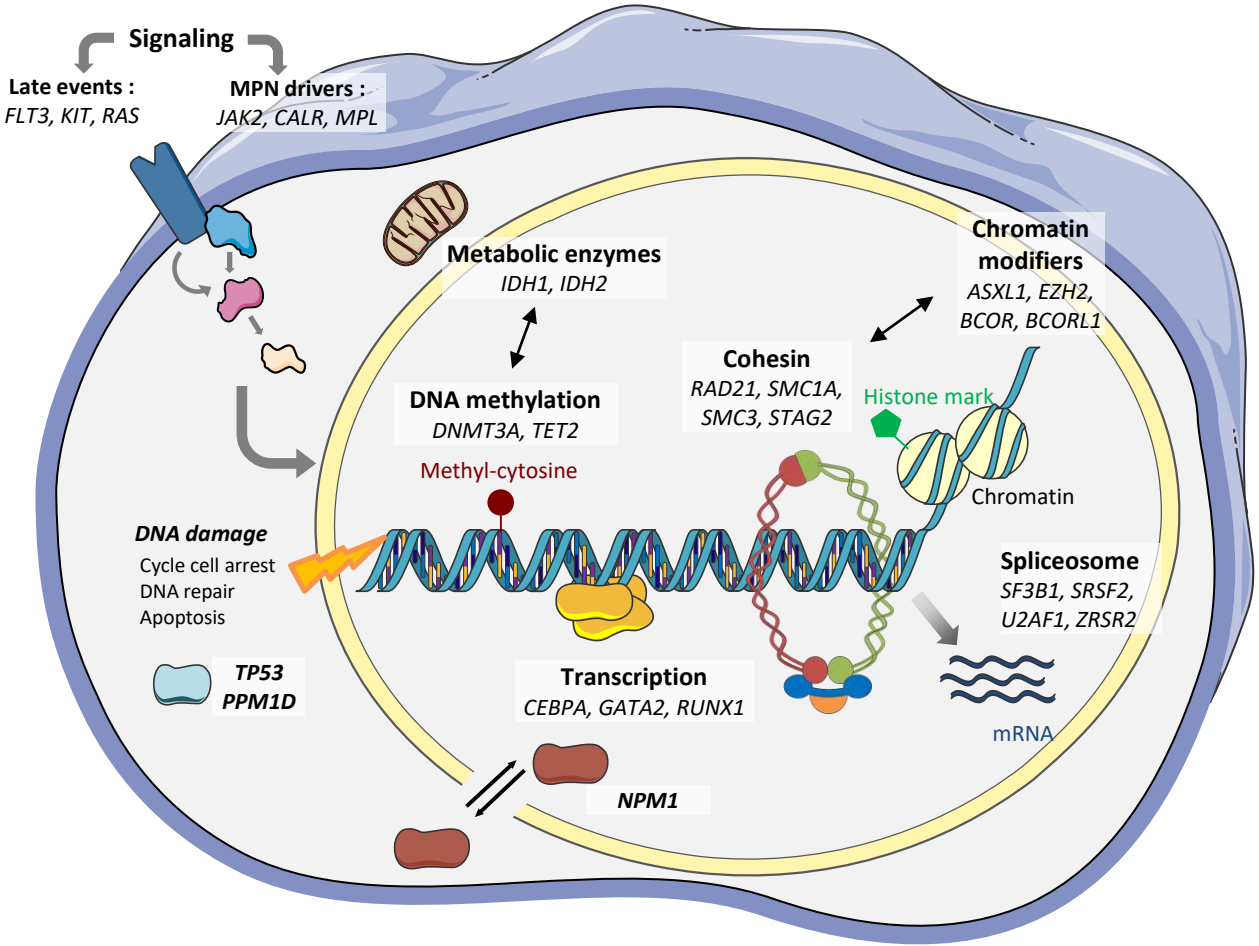
Whole genome sequencing
200 LAM de novo

- 23 gène mutés de manière récurrente
- Mutations classes en catégories fonctionnelles
  ➔ Physiopathologie

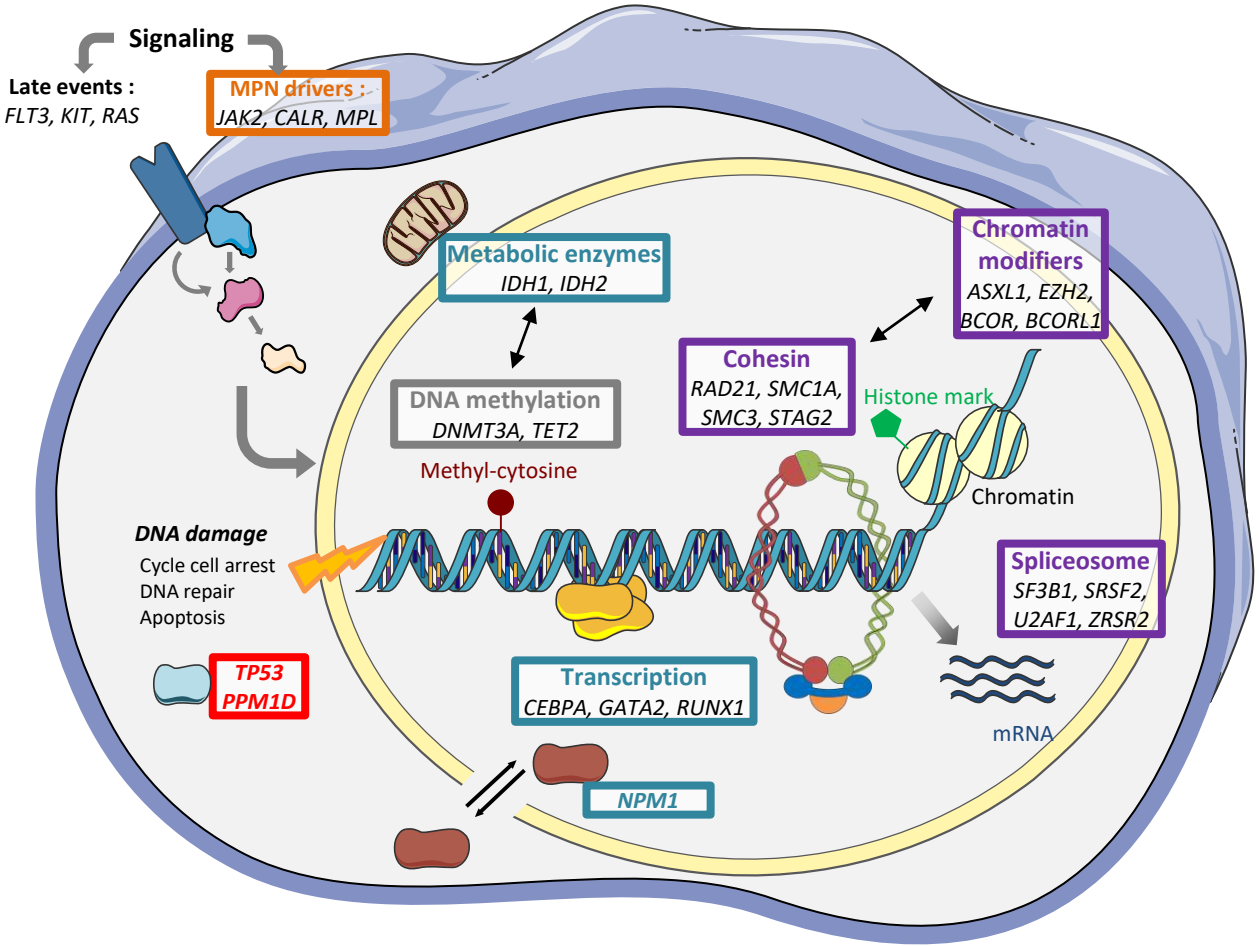
TCGA

The Cancer Genome Atlas Research Network. NEJM 2013;368(22):2059–2074.

IV – Paysage mutationnel et leucémogenèse



IV – Paysage mutationnel et leucémogenèse



Potentiel leucémogène « fort »

- **Transcription** (mutations & fusions)
- **NPM1**
- **Metabolic enzyme**

Potentiel leucémogène « modéré »

- **Chromatin modifiers**
- **Cohesin**
- **Spliceosome**

Potentiel leucémogène « faible »

- DNA methylation

Mutations voie TP53

Mutations JAK2/CALR/MPL

V – Ontogénétique des LAM

LAM sans antécédent (de novo AML)

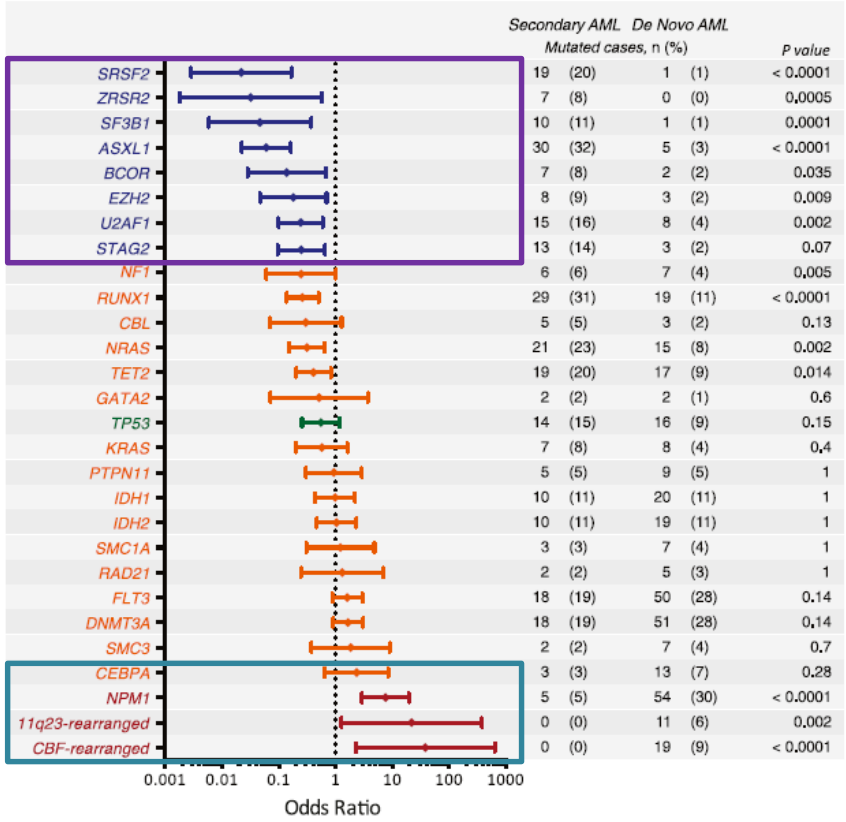
- Mutations **NPM1** et translocations **CBF et MLL**
- Plus fréquentes chez le sujet **< 60 ans**
- Meilleure **chimiosensibilité**

LAM après une hémopathie myéloïde (**secondary AML**)

- Mutations **spliceosome** /**chromatin modifiers**
- Plus fréquentes chez le sujet **> 60 ans**
- Plus **mauvaise réponse** à la chimiothérapie

LAM après chimiothérapie (**therapy-related AML**)

- Groupe très **hétérogène**
- Inhibiteurs de topo II → translocation CBF et MLL
- Alkykants → Mutations TP53, caryotype complexe



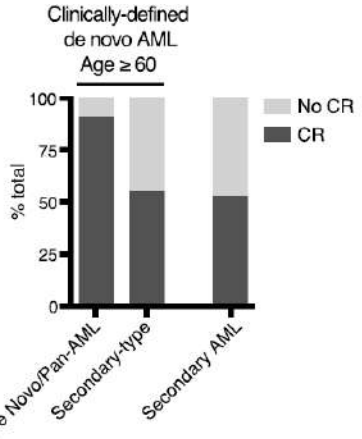
Lindsley RC, et al. Blood. 2015;125(9):1367–1376.

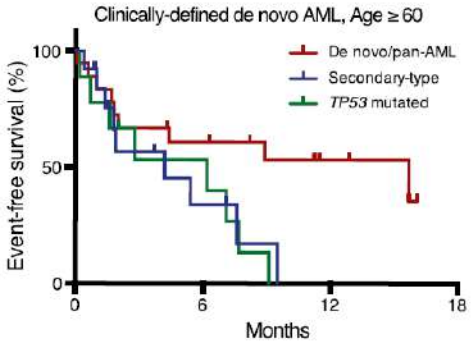
V – Ontogénétique des LAM

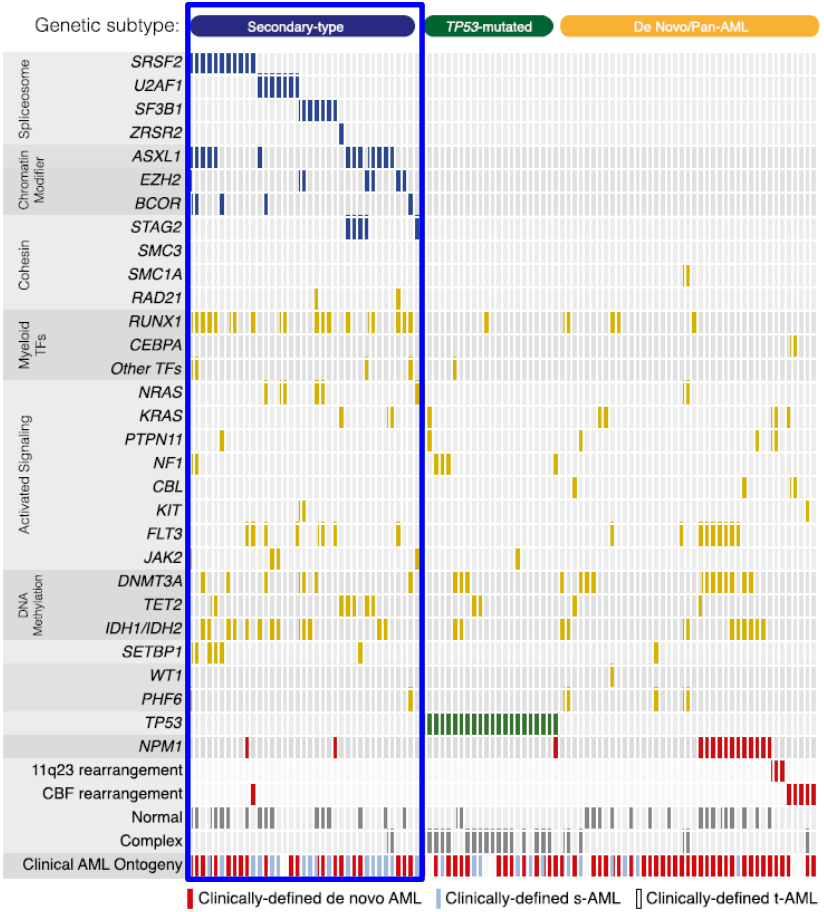
Cas des LAM de novo des sujets ≥ 60 ans :

→ ~ 35% ont des mutations « **secondary AML** » sans ATCD

→ ~ 20% ont des mutations ***TP53***







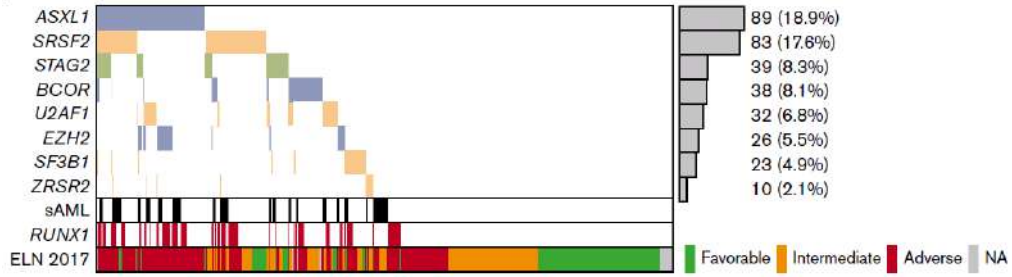
Lindsley RC, et al. Blood. 2015;125(9):1367–1376.

Cohorte ALFA-1200

	All patients	sAML-like mutations*			
		Present†	Absent†	P†	Not tested
Patients	509	226	245	—	38
Sex, male/female	289/220	156/70	111/134	<.001	22/16
Median age (range), y	68 (60-85)	69 (60-85)	67 (60-80)	<.001	69 (61-83)
ECOG-PS 0/1/2+/na	219/219/66/5	99/91/34/2	106/109/27/3	.22	14/19/5/0
HCT-CI 0/1/2/3+/na	226/92/66/115/10	90/41/35/55/5	115/44/29/53/4	.51	21/7/2/7/1
Median WBC (range), $\times 10^9$/L	4.9 (0.25-547)	4.8 (0.25-547)	5.9 (0.48-358)	.43	2.9 (0.5-122)
WBC ≥50 × 10^9/L	80	31 (41)	45 (59)	.21	4
sAML‡	74	56 (82)	12 (18)	<.001	6
ELN-2017 subgroups				<.001	
Favorable	136	33 (25)	100 (75)	—	3
Intermediate	157	49 (38)	80 (62)	—	28
Adverse	200	141 (72)	54 (28)	—	5
Not classified	16	3 (21)	11 (79)	—	2

n = 509 patients > 60 ans
Chimiothérapie intensive

48% LAM *secondary-like*



14% LAM **secondaires** à SMD/LMMC

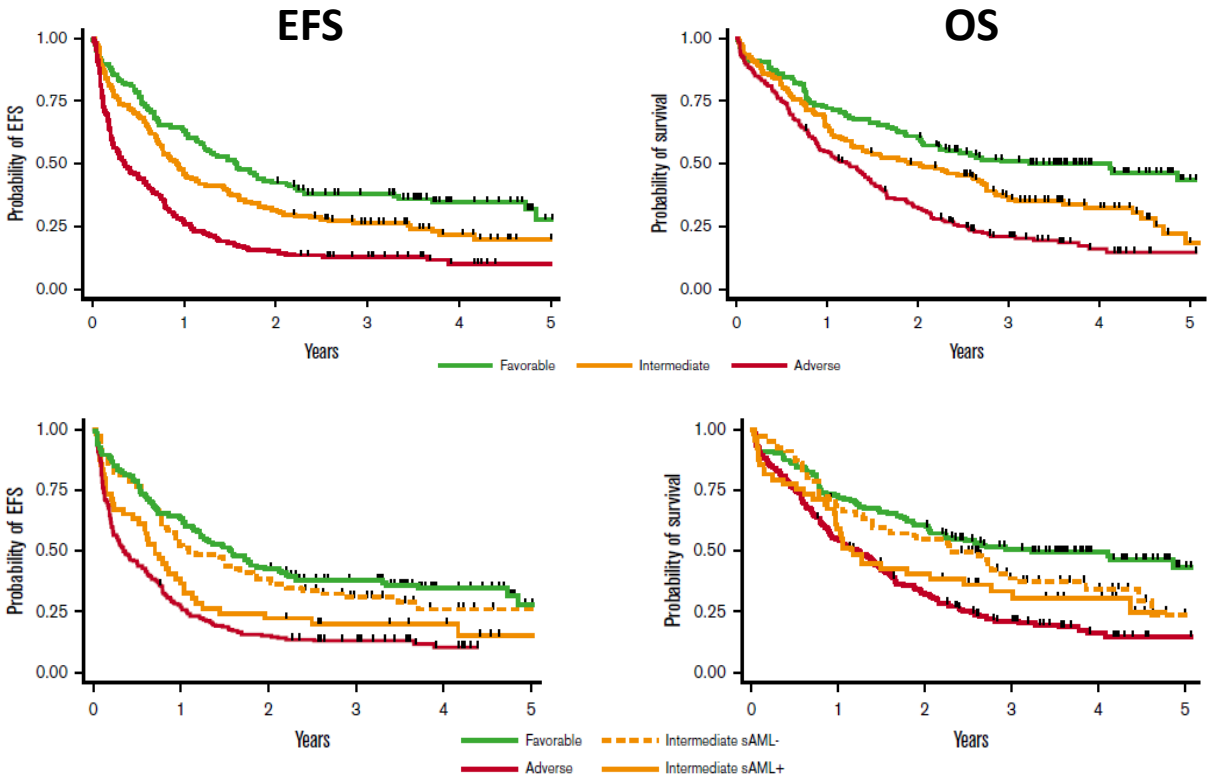
~ 30% ELN2017 **favorables**
~ 30% ELN2017 **intermédiaires**
~ 40% ELN2017 **défavorables**

Gardin C, Pautas C, Fournier E, et al. Blood Adv. 2020;4(9):1942–1949.

Cohorte ALFA-1200

ELN 2017

Secondary-like classification



Gardin C, Pautas C, Fournier E, et al. Blood Adv. 2020;4(9):1942–1949.

V – Ontogénétique des LAM

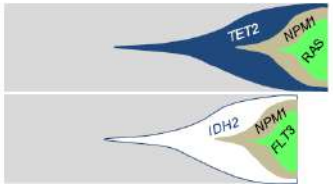
LAM de novo ou « de novo-like »

Facteurs de transcription +++
→ Blocage de différenciation, instabilité génomique

Potentiel leucémogène « fort »

Fusion de gènes :
RUNX1-RUNX1T1
PML-RARA
MLL-AF9

Mutations *NPM1*



Mutations *CEBPA*

Enfants, adultes jeunes +++

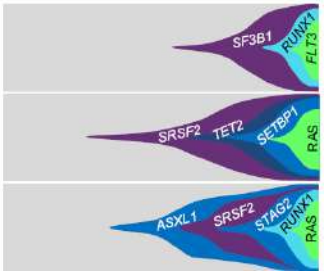
LAM secondaire ou « secondaire-like »

Modif. chromatine, cohésine +++
Epissage ARN +++

Potentiel leucémogène « modéré »

LAM post-SMD
- Précédées ou non d'un SMD « clinique »

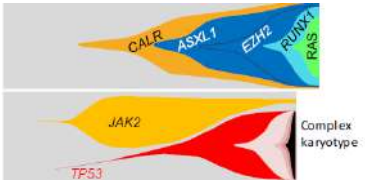
Adultes âgés +++



LAM mutées *TP53*

***post-traitement* +++**
Caryotypes complexes +++

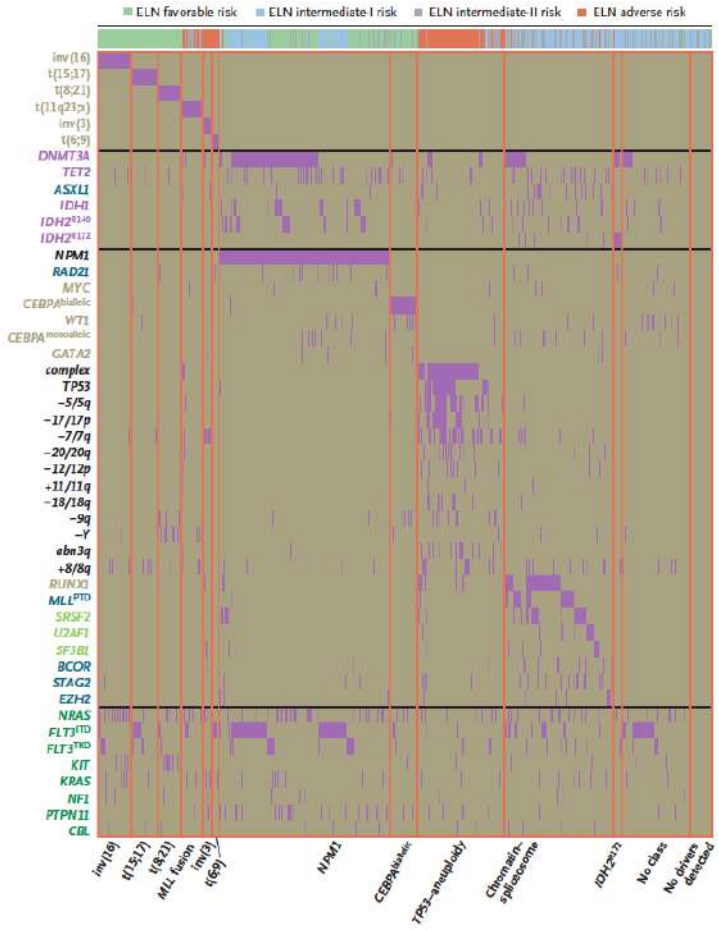
LAM post-SMP

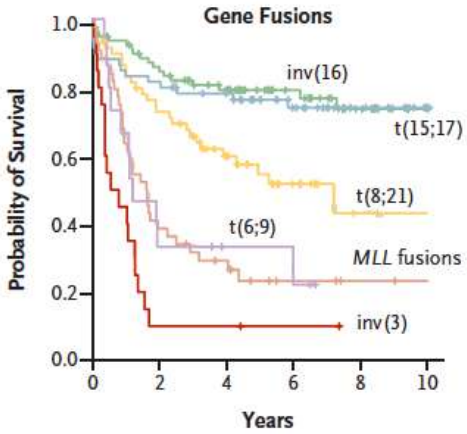


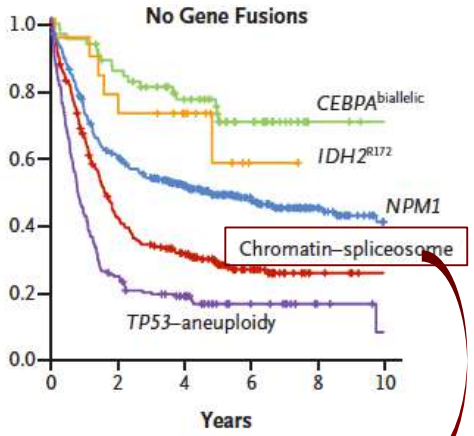
Mutations drivers : *JAK2/CALR*

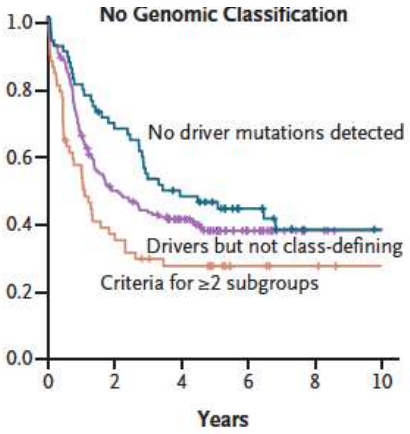
Martignoles J-A et al. IJMS. 2018;19(12):3850.

V – Au-delà des classifications moléculaires …









= mutations “secondary-like” + RUNX1

111 genes / 1,540 AML patients
(AMLSG trials 1993 -2004)

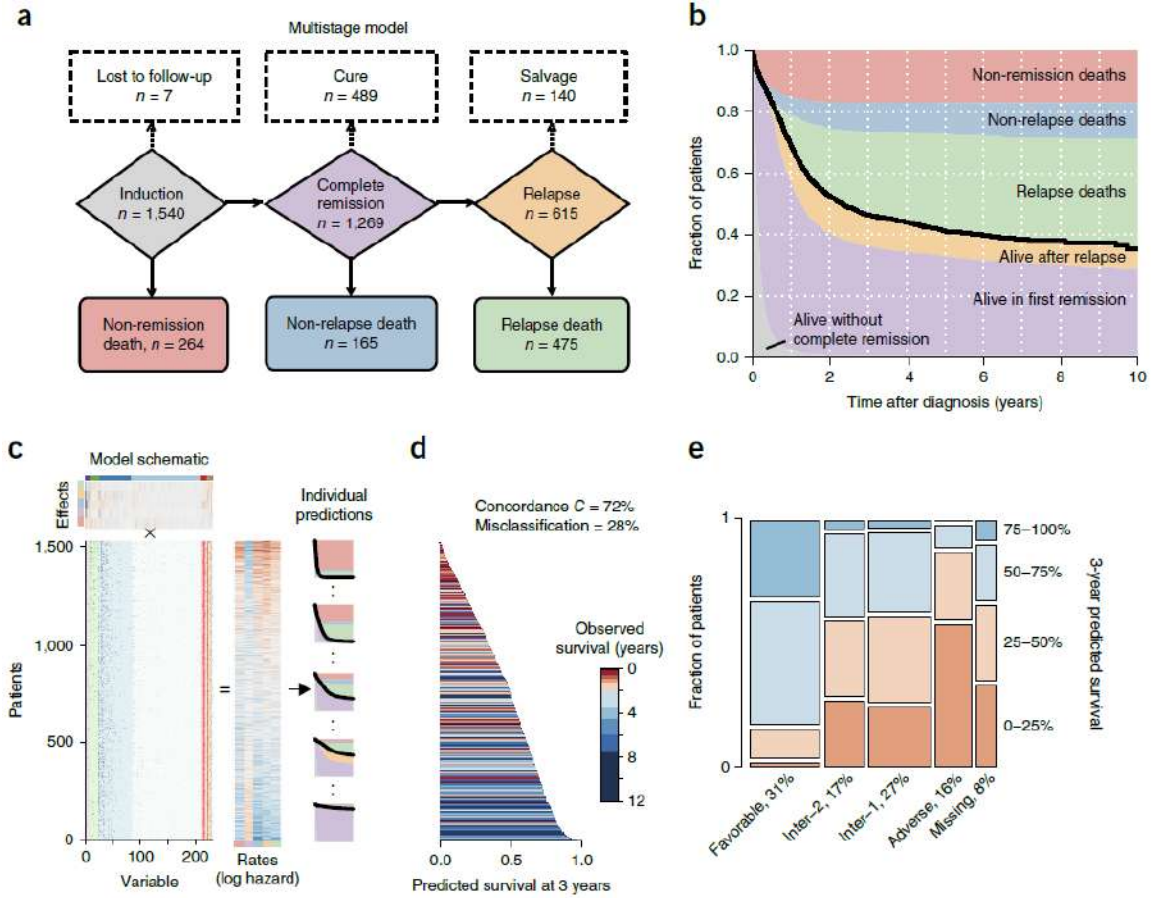
Papaemmanuil E, Gerstung M, Bullinger L, et al. NEJM. 2016;374(23):2209–2221.

V – Au-delà des classifications moléculaires …

- **Knowledge-bank algorithm**
  - Données cliniques
  - Données cytogénétiques
  - Données moléculaires
  - Données thérapeutiques (HSCT)

~ 230 variables

Prédiction « personnalisée »



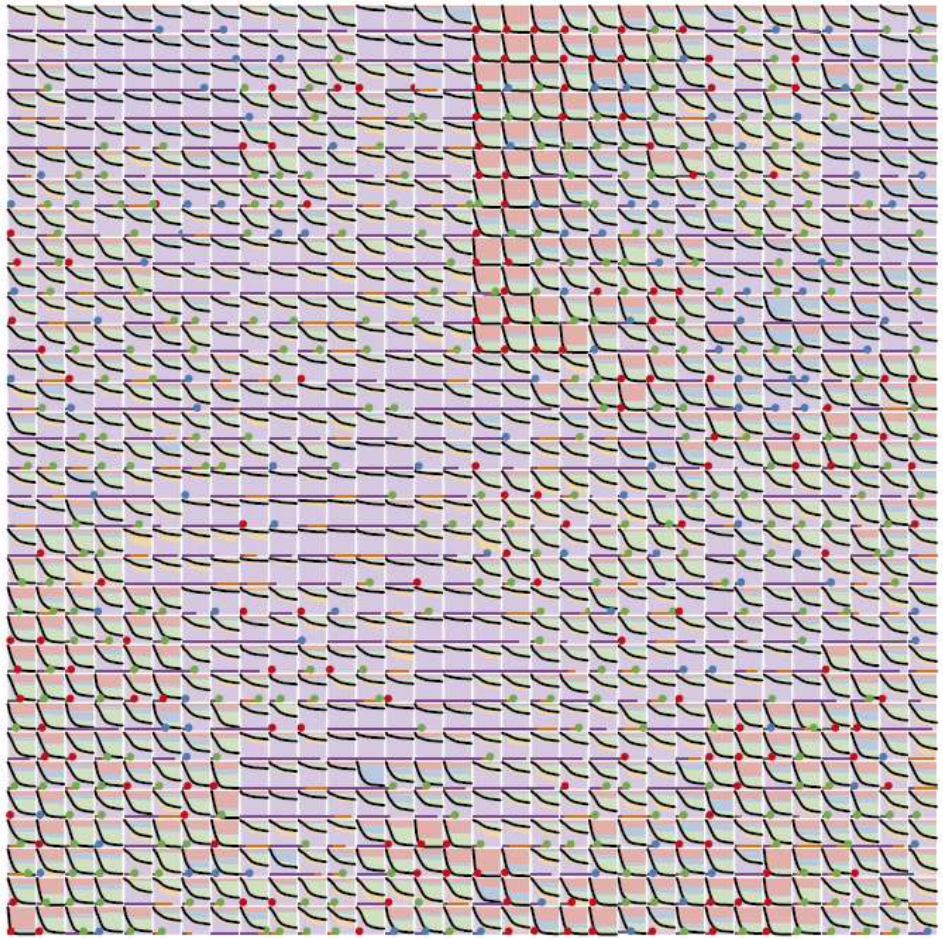
Gerstung M, Papaemmanuil E, Martincorena I, et al. Nature Genetics. 2017;49(3):332–340.

V – Au-delà des classifications moléculaires …

- **Knowledge-bank algorithm**
  - Données cliniques
  - Données cytogénétiques
  - Données moléculaires
  - Données thérapeutiques (HSCT)

~ 230 variables

Prédiction « personnalisée »



Gerstung M, Papaemmanuil E, Martincorena I, et al.
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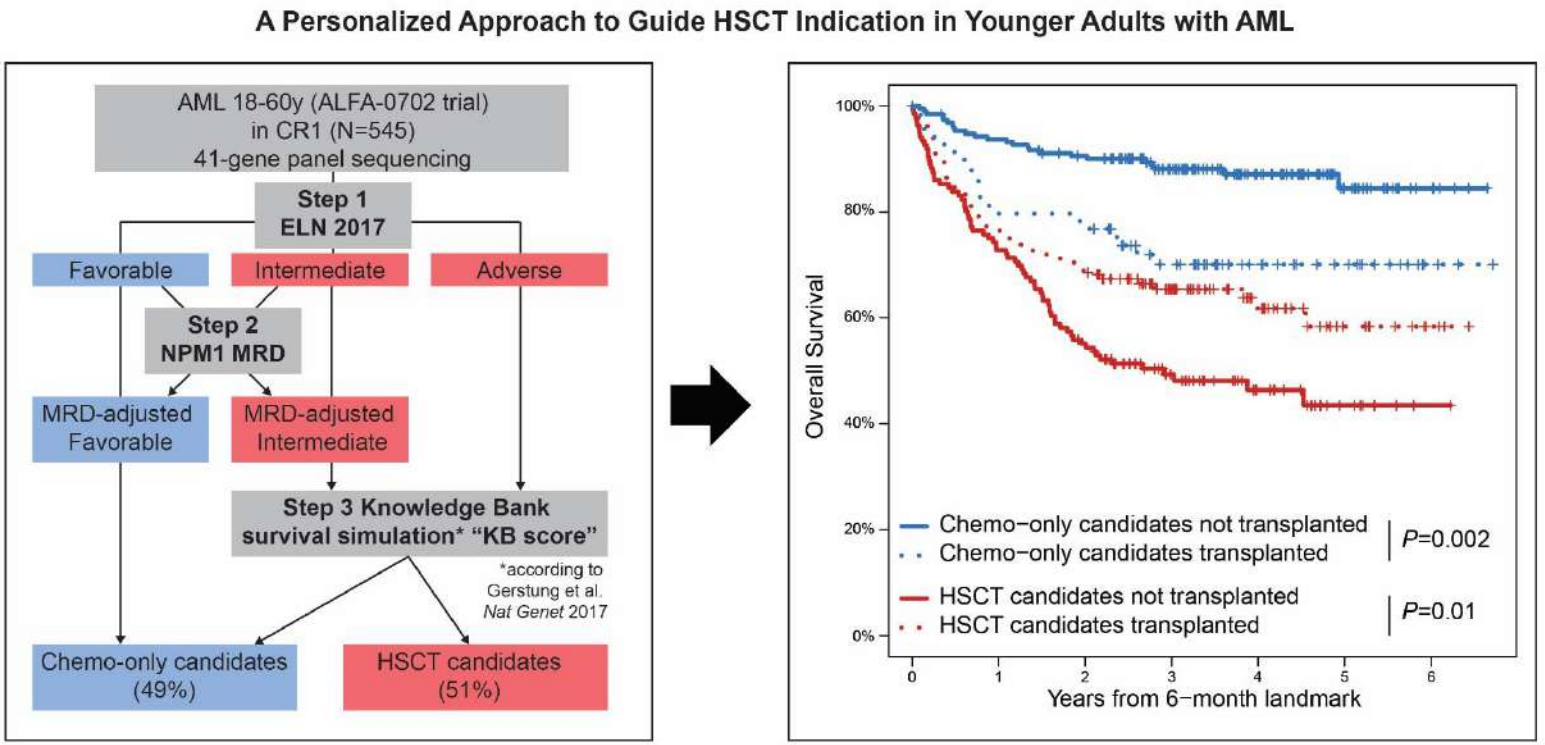
V – Au-delà des classifications moléculaires …



ALFA App

Fenwarth L., Thomas X., de Botton S., Duployez N., Bourhis J.-H., Lesieur A., Fortin G., Meslin P.-A., Yakoub-Agha I., Sujobert P., Dumas P.-Y., Recher C., Lebon D., Berthon C., Michallet M., Pigneux A., Nguyen S., Chantepie S., Vey V., Raffoux E., Celli-Lebras K., Gardin C., Lambert J., Malfuson J.-V., Caillot D., Maury S., Ducourneau B., Turlure P., Lemasle E., Pautas C., Chevret S., Terré C., Boissel N., Socié G., Dombret H., Preudhomme C., Itzykson R. **Blood. 2020.**

Conclusion : classification des LAM