Le point sur une pathologie : la LAM

Apport des classifications OMS et ELN

CHU Hôpitaux de Bordeaux

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GFCH 03 06 2020

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

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CHAPITRE 8 :

Acute myeloid leukemia (AML) and related neoplasms

AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
- APL with *PML-RARA*
- AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
- AML with t(6;9)(p23;q34.1);*DEK-NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM* NEW
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
- *Provisional entity: AML with BCR-ABL1* NEW
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA* NEW
- *Provisional entity: AML with mutated RUNX1* NEW

AML with myelodysplasia-related changes = AML-MRC

Therapy-related myeloid neoplasms

AML , NOS

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

MECOM passe sous le contrôle de l'enhancer du gène *GATA2* => hyperexpression de MECOM et haploinsuffisance de GATA2

<u>Mutations bialléliques de *CEBPA* :</u>

4~9% des LAM (enfants, jeunes adultes)(↓ sujets âgés)
Pronostic favorable ~ inv(16),t(8;21)
Mutations de *GATA2* fréquemment associées ~40%
⚠ Recherche anomalie constit

<u>Entité provisoire : *BCR-ABL1*</u>

< 1% des LAM
p210 le plus souvent
Profil génétique distinct de transformation de LMC: *FLT3-ITD, NPM1* (peu fréquent), délétions *IKZF* et *CDKN2A*, délétions cryptiques *IGH* et *TCR* (Nacheva et al., BJH, 2013)
Pronostic défavorable

<u>Entité provisoire : *RUNX1*</u>

4~16% des LAM (↑ sujets âgés)
Exclusion: LAM therapy-related, LAM avec autre anomalie génétique récurrente , LAM MRC , *NPM1* et *CEBPa*
Pronostic plutôt défavorable surtout si associé à *ASXL1*
⚠ Recherche anomalie constit

LAM –MRC : la définition

Le diagnostic de LAM-MRC requiert la présence des 3 critères suivants :

≥ 20 % de blastes dans le sang et/ou la moelle

Présence d'un des items suivants :

- ATCD de SMD ou SMD/SMP
- Présence d'**une anomalie cytogénétique associée aux myélodysplasies**
- **Dysplasie multilignée***

Absence des 2 items suivants :

- Thérapeutique (cytotoxique ou radiation) préalable
- Translocations ou inversions récurrentes désignées par l'OMS

Table 18. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded

Cytogenetic abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
−7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
−13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p36.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
t(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

Toutes les anomalies [illegible] associées aux myélodysplasies son[illegible] défavorable

FAUX

Le myélogramme se[illegible] une LAM en LAM-MRC

FAUX

Astérisque sur la DML : exclusion des cas avec *NPM1*mut ou bi*CEBPA*mut ⇒ **Allongement du délai pour conclure à une LAM-MRC sur les bases de la morphologie**

LAM –MRC : la vraie vie

Selon la littérature = 25 à 35% des LAM

LAM de l'adulte – CHU de Bordeaux – mars 2018 à août 2019

Présence d'un des items suivants :

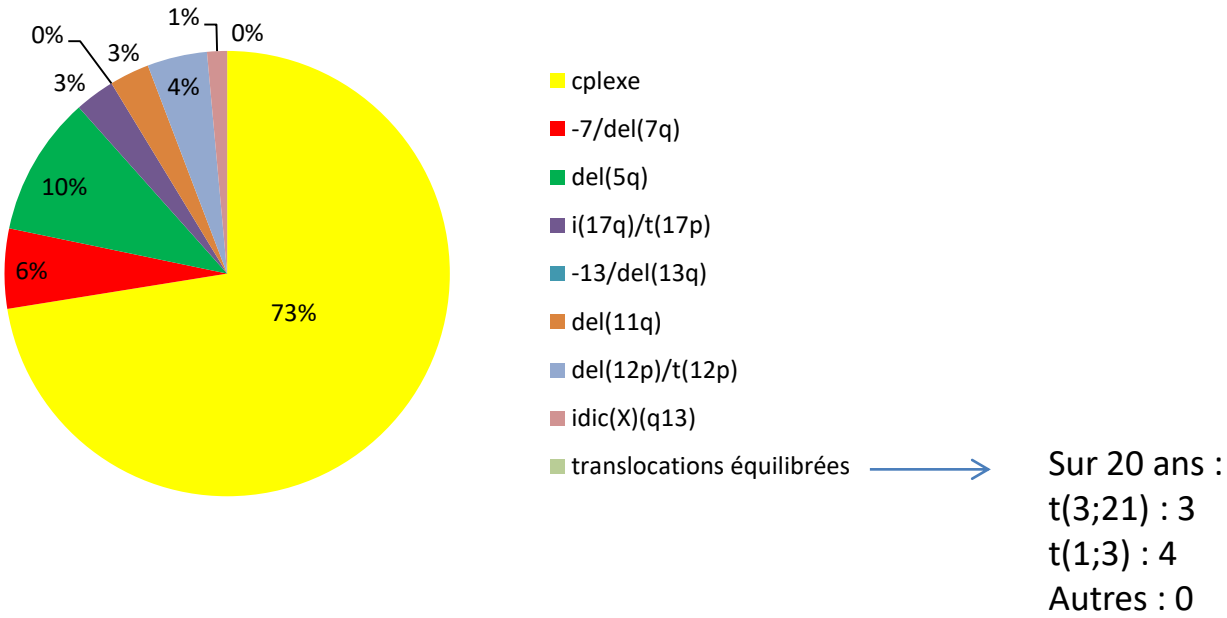
- **ATCD de SMD ou SMD/SMP** : **12%**
- **Dysplasie multilignée * : 17%**

Mais si on exclut *NPM1mut* et *biCEBPAmut* : 12%

- Présence d'**une anomalie cytogénétique associée aux myélodysplasies : 30%**

Mais si on exclut ceux qui ont déjà un des deux 1ers items : **12%**

Au total : 12%+12%+12% = 36%



Sur 20 ans :
t(3;21) : 3
t(1;3) : 4
Autres : 0

Hémopathies myéloïdes avec prédisposition germinale

Table 17. Classification of myeloid neoplasms with germ line predisposition

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

*Lymphoid neoplasms also reported.

Rien qui ne le laissait présager

Hémopathies myéloïdes « pures »

thrombopenie

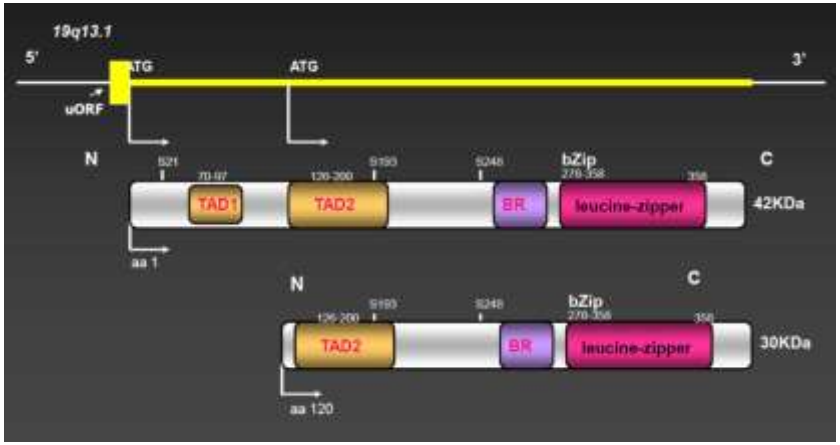
Hémopathies myéloïdes avec thrombopénie préalable

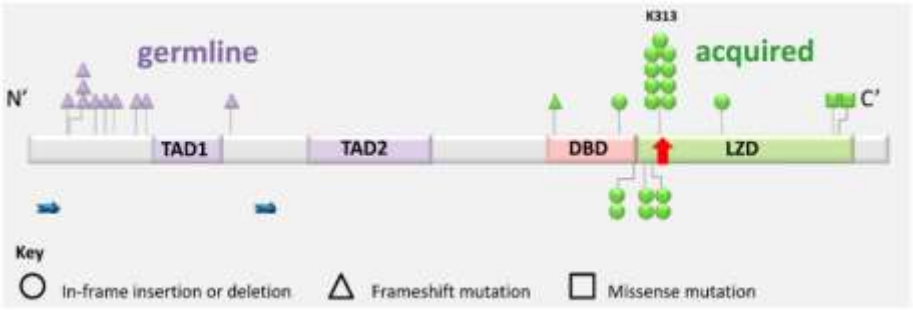
Signes cliniques préalables

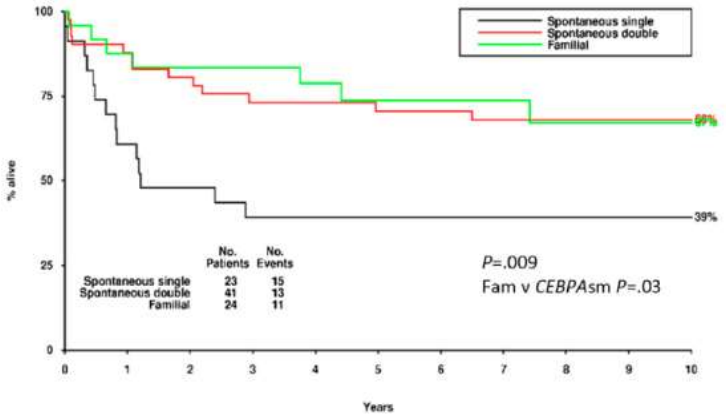
Hémopathies myéloïdes « syndromiques »

Mutations germinales de *CEBPa*

- Transmission Autosomique Dominante
- Mutations Nter >> Cter
- Pénétrance >95% (Nter) vs 50% (Cter)
- Profil LAM : LAM1,M2, caryo N, CD7+
- Age médian = 24 ans (2-50)
- Parmi les LAM *CEBPA* double mutées : 5 à 10%
- Bon pronostic mais récurrences +++





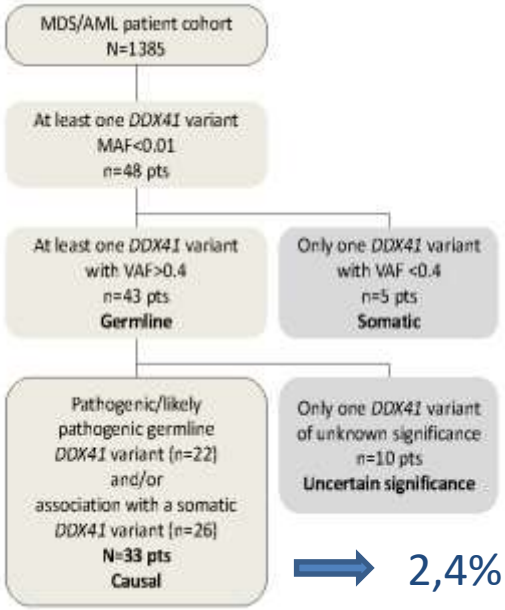


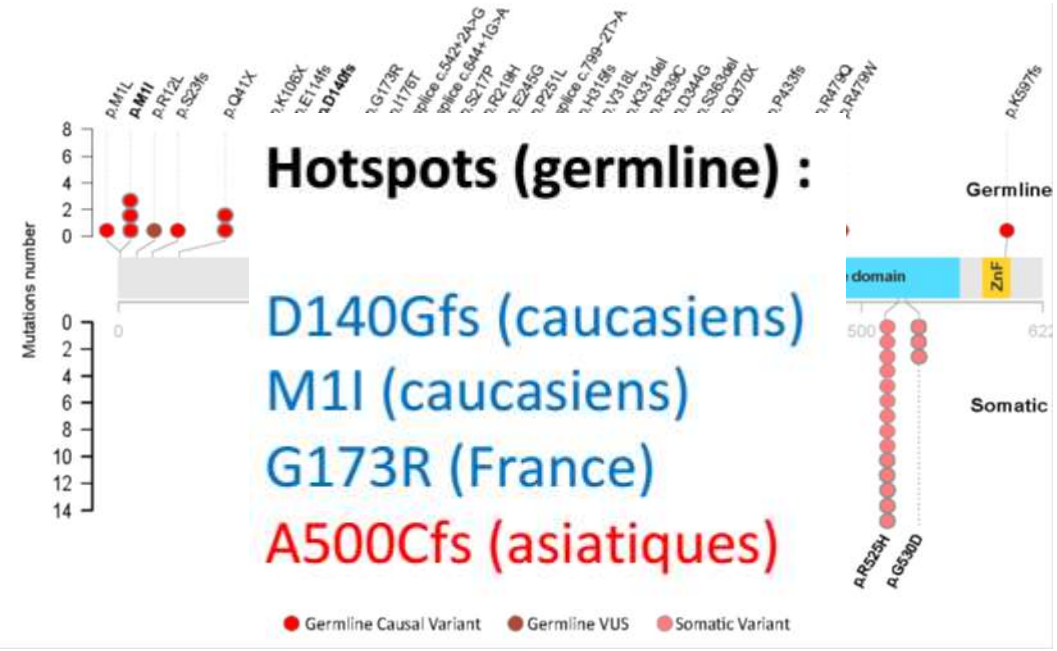
OS in sporadic and familial patients < 45 years.

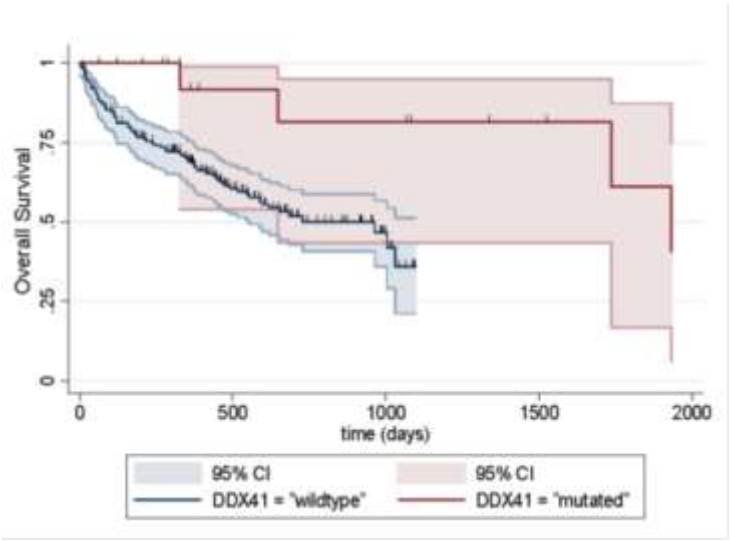
(Tawana et al, Blood 2015)

Mutations germinales de *DDX41*

- Transmission Autosomique Dominante
- Pénétrance >50%
- Age médian = 69 ans (36-88)
- SMD/LAM, caryo N
- Acquisition mutations somatiques de *DDX41 : 80%* (R525H+++)
- Bon pronostic ?







Sébert et al., Blood 2019

Review Article

blood

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

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Karyotype is not dead !

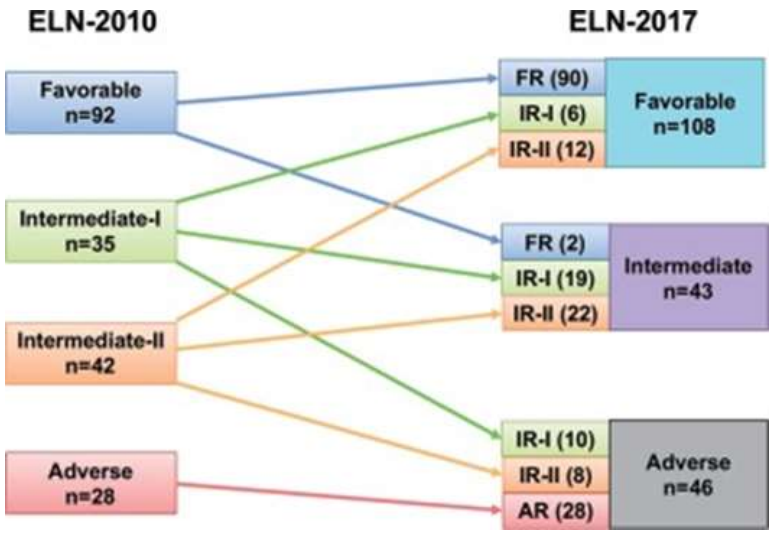
Suppression des groupes pronostiques intermédiaires I et II

ELN 2010

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype‡

ELN 2017

Risk Category[b]	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(c)] Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high(c)] Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] 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(c)] Mutated *RUNX1*[g] Mutated *ASXL1*[g] Mutated *TP53*[h]



Harada *et al,* Leukemia Research, 2018

Apparition de la notion de caryotype monosomique
Disparition de la notion de caryotype normal

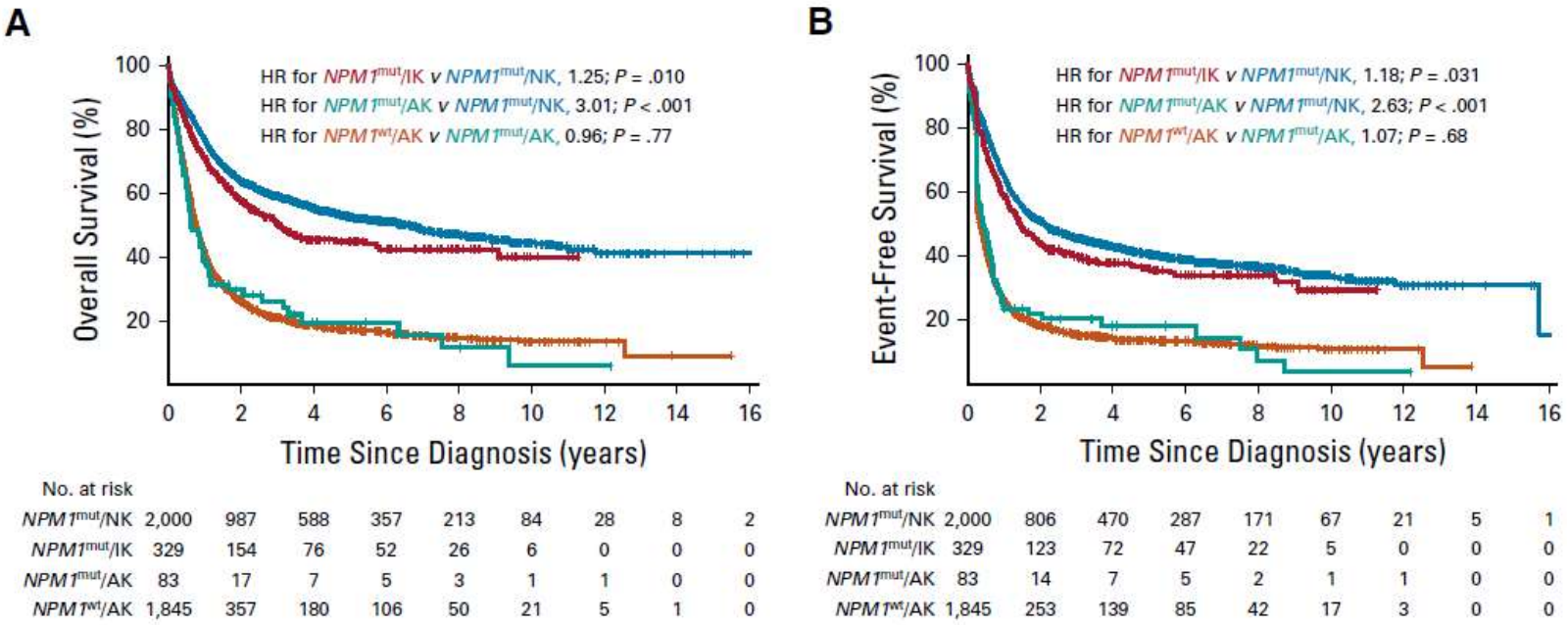
ELN 2010 → ELN 2017

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

Risk Category[a]	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(c)]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high(c)]
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[e]
	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,[g] monosomal karyotype[f]
	Wild type *NPM1* and *FLT3*-ITD[high(c)]
	Mutated *RUNX1*[g]
	Mutated *ASXL1*[g]
	Mutated *TP53*[h]

Caryotype monosomique :
1 monosomie (sauf –X ou –Y) + au moins une autre monosomie ou une anomalie de structure

Breems , JCO 2008



Impact des anomalies chr. chez 2426 patients *NPM1*mut/*FLT3-ITD*neg/low Tt intensif
9 groupes Européens, Australiens ou Américains

⇨ La valeur défavorable du caryotype l'emporte sur la valeur favorable de la mutation *NPM1.* Les patients avec cytogénétique défavorable devraient rester en défavorable même si *NMP1* est muté.

Angenendt et al., JCO, oct 2019

FLT3-ITD low : <0,5

FLT3-ITD high : ≥0,5

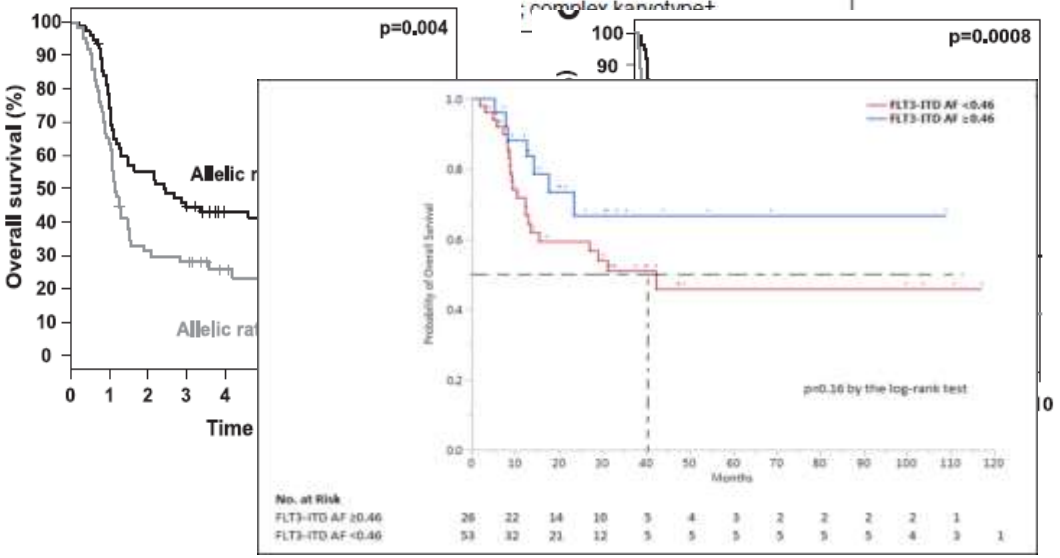
ELN 2010

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2)

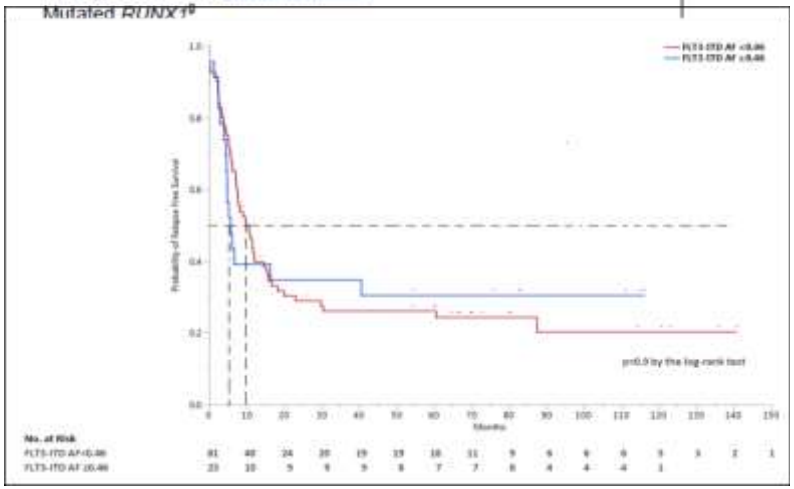
ELN 2017

Risk Category[b]	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$^{low(c)}$
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD$^{high(c)}$
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	A rearranged
	; *BCR-ABL1*
	or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype,[e] monosomal karyotype[f]
	Wild type *NPM1* and *FLT3*-ITD$^{high(c)}$
	Mutated *RUNX1*[g]

Est-ce que les ITK FLT3 changent la donne ?



Schlenk et al., Blood 2014



Yalniz et al, AJH, 2019

Les nouveautés 2017

Mutations bialléliques de *CEBPA*
t(9;22) de type *BCR-ABL1*
3 nouveaux gènes d'intérêt : *ASXL1, RUNX1* et *TP53*

ELN 2010 → ELN 2017

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	−5 or del(5q); −7; abnl(17p); complex karyotype‡

Risk Category[b]	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(c)]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high(c)]
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d]
	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,[e] monosomal karyotype[f]
	Wild type *NPM1* and *FLT3*-ITD[high(c)]
	Mutated *RUNX1*[g]
	Mutated *ASXL1*[g]
	Mutated *TP53*[h]

MERCI pour votre attention !