Facteurs Pronostiques des LAM

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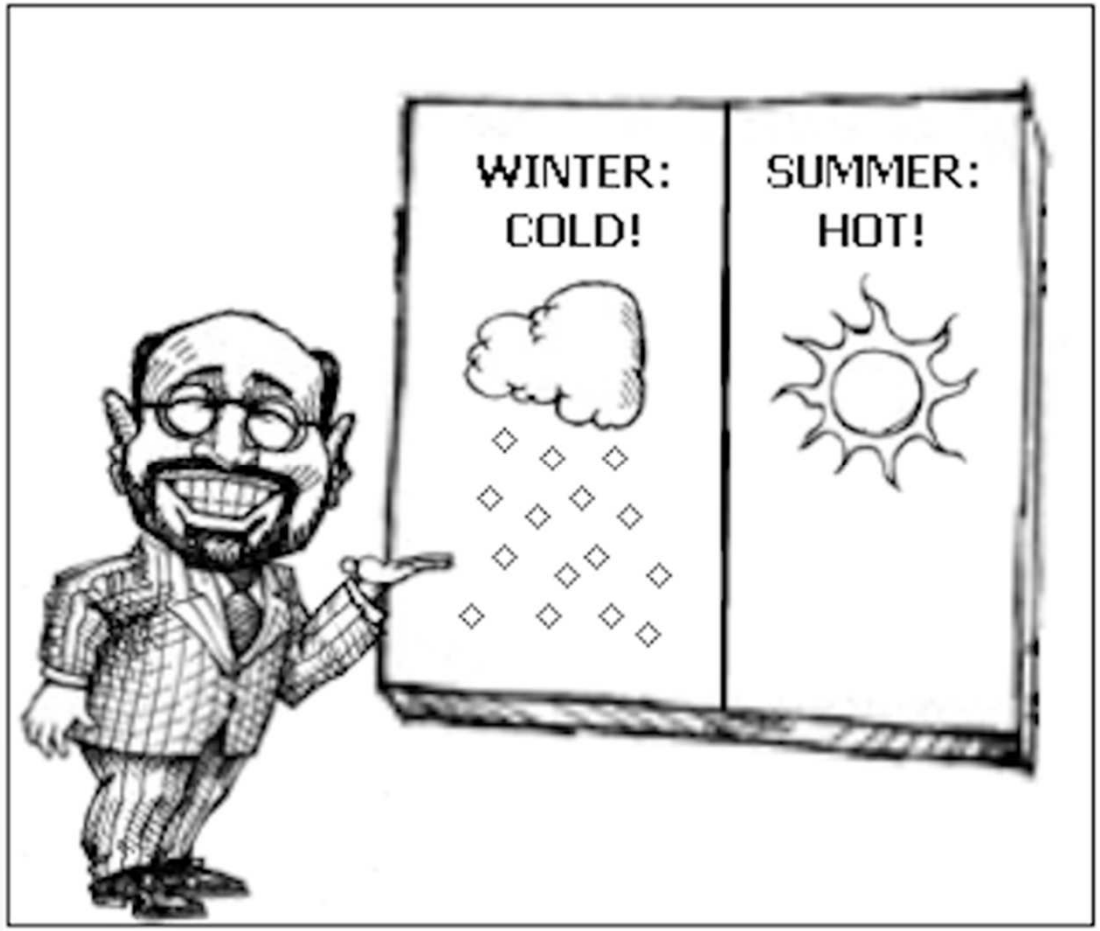
Prognostic factor



Prognostic factors

Prédit statistiquement le devenir

Patient	AML	Response
Age	WBC, LDH	Late CR
Comorbidités	Multilineage dysplasia	Day 14 bone marrow
ECOG-PS	Cytogenetics	Minimal Residual Disease (blasts, LSC)
Prior hematologic disorder (MDS, MPD)	Genetic profile (mutation, expression)	
Prior CTx, RTx	SNP-array lesions	

Prognostic scores

- *Additive scores*
  - *MD-Anderson, older pts (Kantarjian, 2006)*
    - *Age 75y, ECOG-PS, cytogenetics, AHD, laminar airflow, organ dysfunctions.*
  - *ALFA, older pts (Malfuson, 2008)*
    - *Age 75y, WBC, ECOG-PS, cytogenetics*
  - *German SAL, older pts (Röllig, 2010)*
    - *Age, WBC, LDH, CD34 expression, cytogenetics, NPM1 mutation*
  - *German AMLCG/SAL, CR and ED in older pts (Krug, 2010)*
    - *Age, body temperature, secondary AML, Hb, platelets, Fg, LDH*
- *Weighted scores*
  - *UK NCRI, older pts (Wheatley, 2009)*
    - *Age, WBC, ECOG-PS, secondary AML, cytogenetics*
  - *German SAL, post-remission treatment in younger pts (Pfirrmann, 2012)*
    - *Age, secondary AML, CD34-positive blast %, FLT3-ITD ratio, cytogenetics*

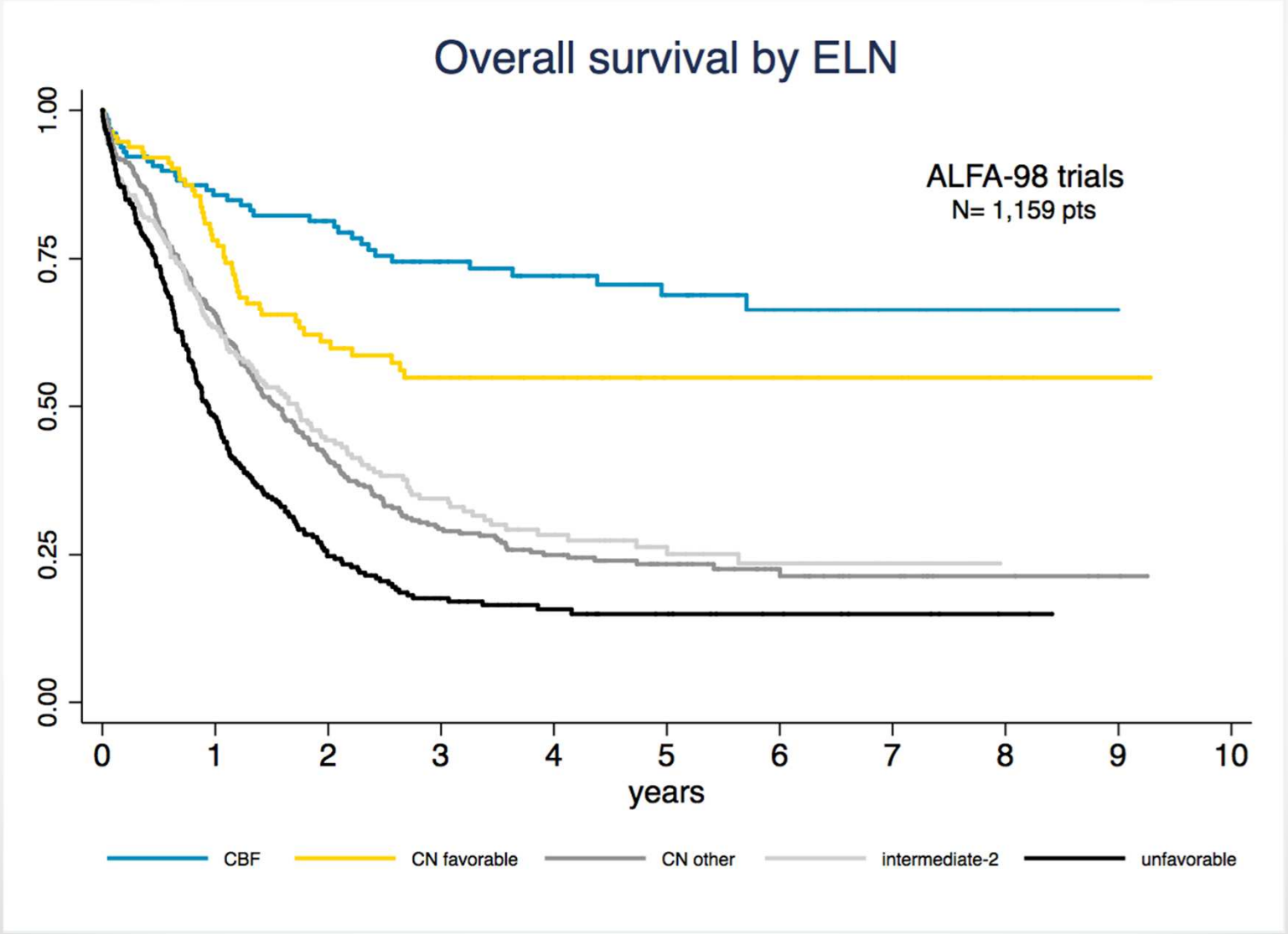
AML prognostic groups

Subgroup	Cytogenetics	Molecular genetics
Favorable	t(15;17)(q22;q21)	*PML-RARA*
	t(8;21)(q22;q22)	*RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	*CBFB-MYH11*
	Normal karyotype	Mutated *NPM1* without *FLT3*-ITD
	Normal karyotype	Mutated *CEBPA*
Intermediate-1	Other normal karyotypes	
Intermediate-2	t(9;11)(p22;q23)	*MLLT3-MLL*
	Other non-adverse non-favorable abns.	
Adverse	t(6;9)(p23;q34)	*DEK-NUP214*
	inv(3)(q21q26.2) or t(3;3)(q21;q26.2)	*RPN1-EVI1*
	t(v;11q23)	*MLL* rearranged
	-5, del(5q), -7	
	17p abns.	
	Complex karyotype (3+ abns.)	

ELN European LeukemiaNet

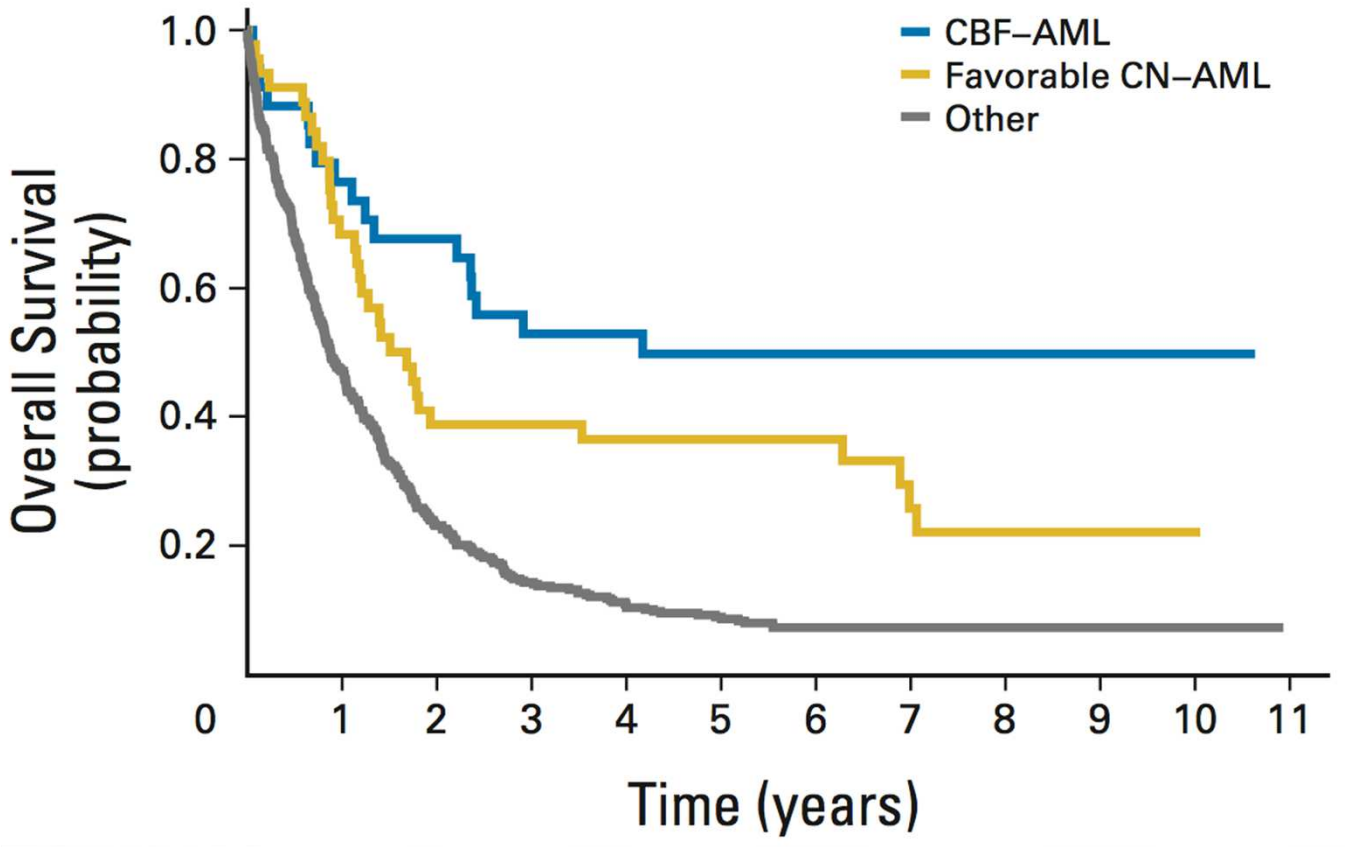
Döhner et al. Blood 2010

ELN groups


Overall survival by ELN
ALFA-98 trials
N= 1,159 pts
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
years
CBF
CN favorable
CN other
intermediate-2
unfavorable

ELN groups

- *N= 452 older patients (median age, 66y)*



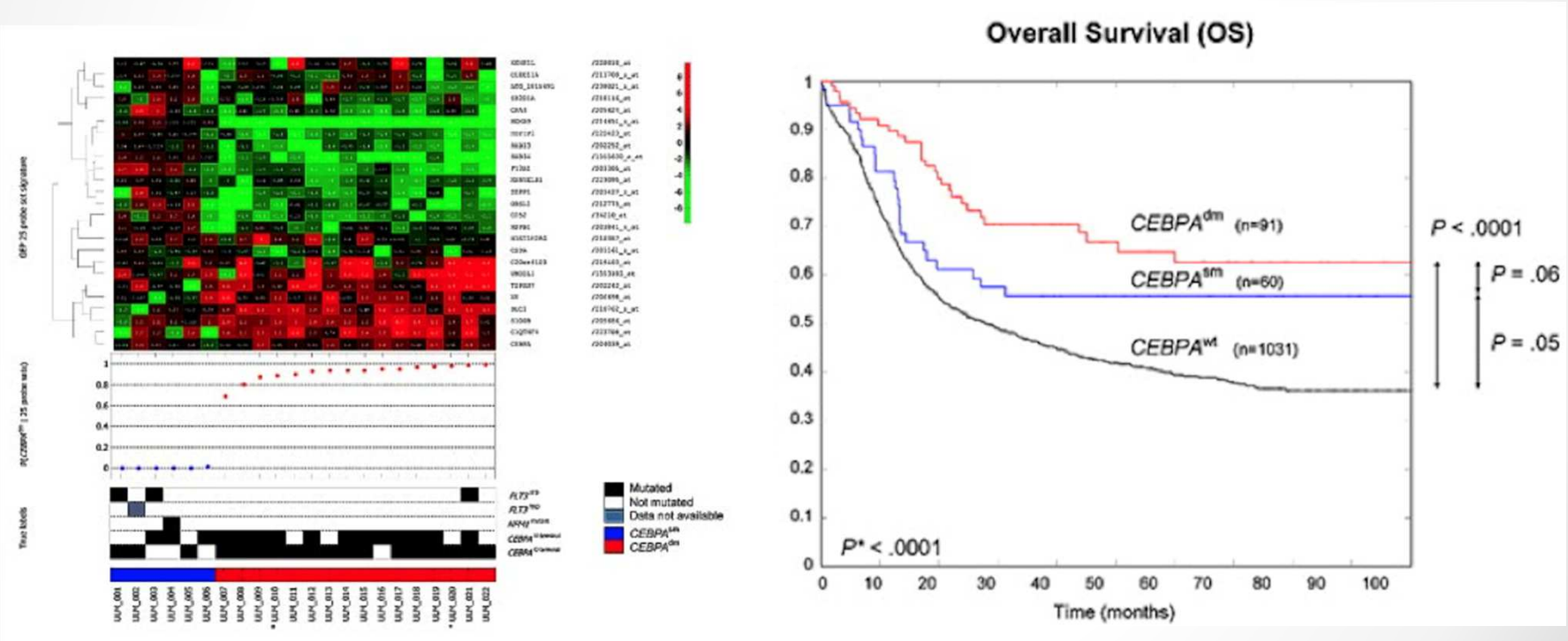
Cure rates

- CBF, 52.7%
- Favorable CN-AML, 27%
- Others, 8%

C. Gardin et al. JCO 2013

Favorable genotype

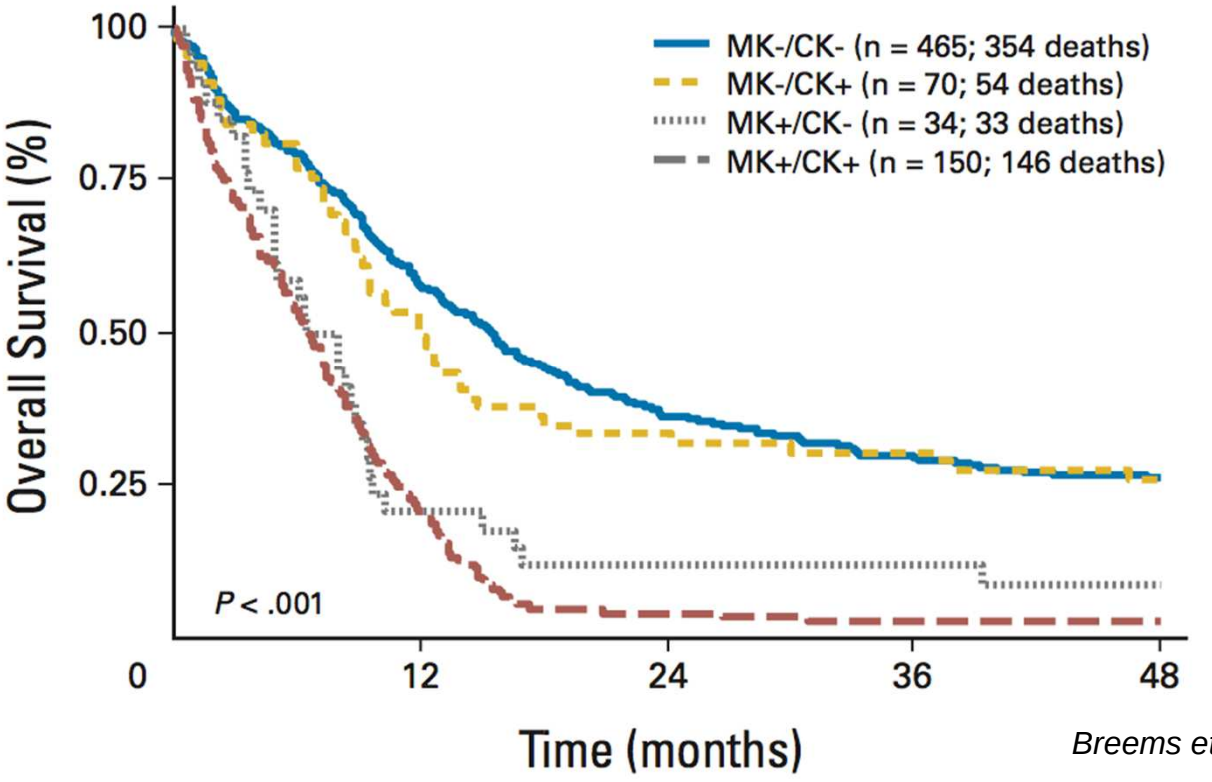
- *CEBPA double mutant*



Taskesen et al. Blood 2011

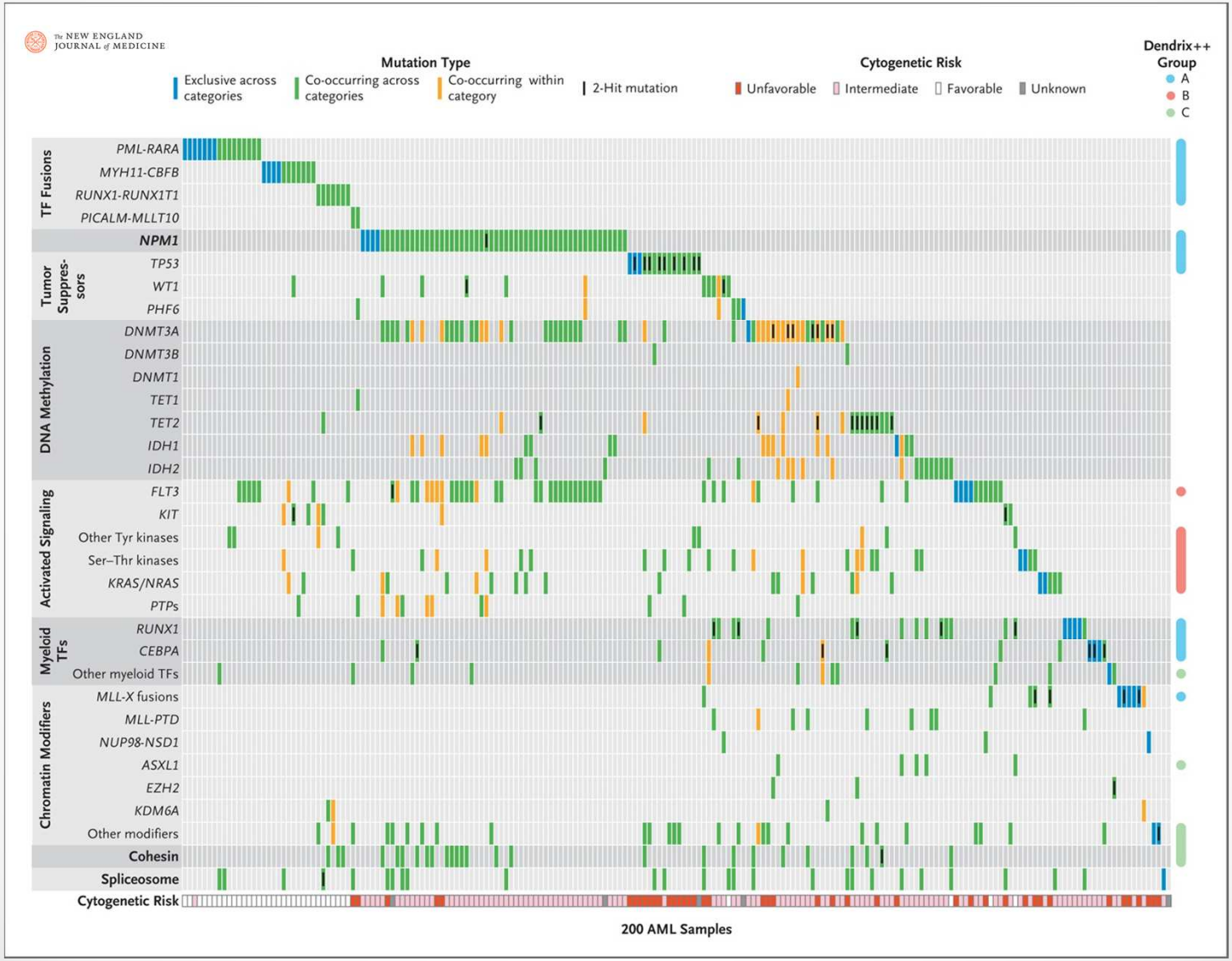
Unfavorable cytogenetics

- *Monosomal karyotypes*
  - *Two or more distinct autosomal chromosome monosomies*
  - *One single autosomal monosomy in the presence of structural abns.*



Breems et al. JCO 2008

Genomic landscape



The Cancer Genome Atlas Research Network. N Engl J Med 2013;368:2059-2074

Impact pronostique (1 à 1)

Favorable	*Contreversé*	*Défavorable*	
CEBPA dm	FLT3-TKD	FLT3-ITD	RUNX1 ?
NPM1	IDH2R172	MLL-PTD	ASXL1 ?
IDH2R140	IDH1R132	DNMT3A	WT1 ?
	GATA2	TP53	TET2 ?
		KIT	BCOR ?
	NEUTRE	EVI1	PHF6 ?
			ERG ?
	N-RAS		BAALC ?
	K-RAS	SNP-A ?	MN1 ?

Dans les LAM CEBPA dm

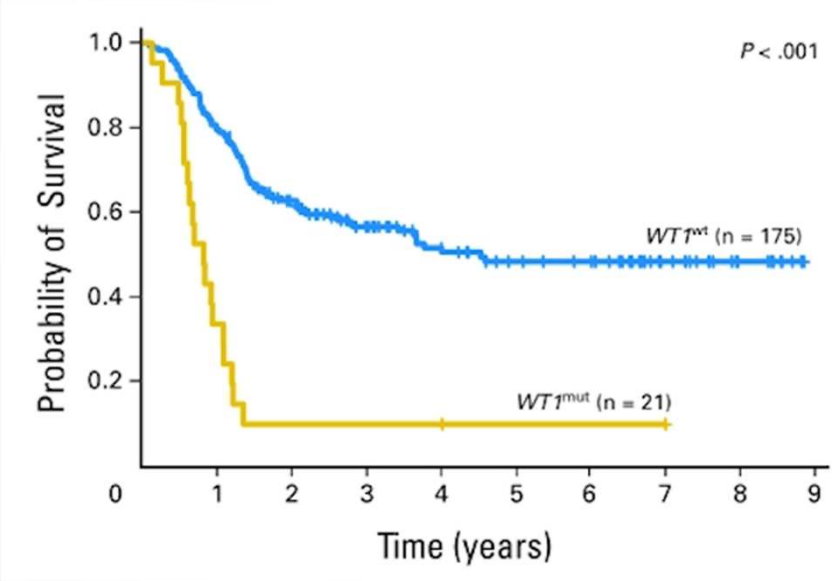
Dans les LAM CBF

Dans LAM à caryo complexe

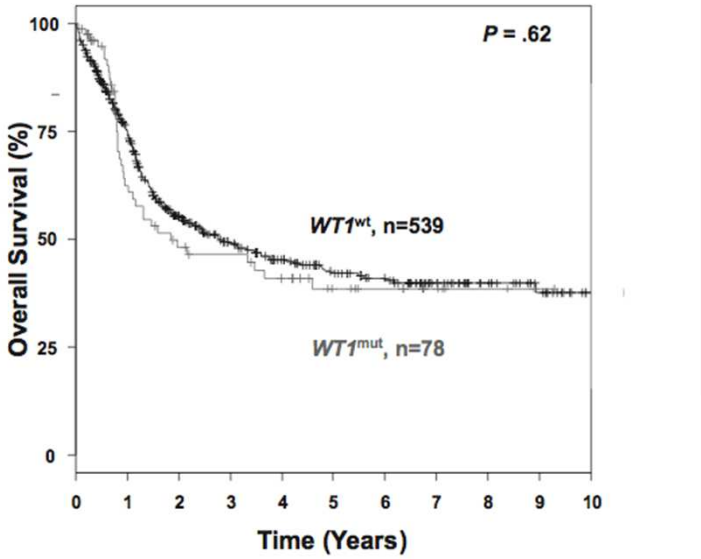
Caractère pronostique indépendant à confirmer pour la plupart de ces marqueurs

Discordant results

- *WT1 gene mutation in CN-AML*



JCO 2008 (CALGB)



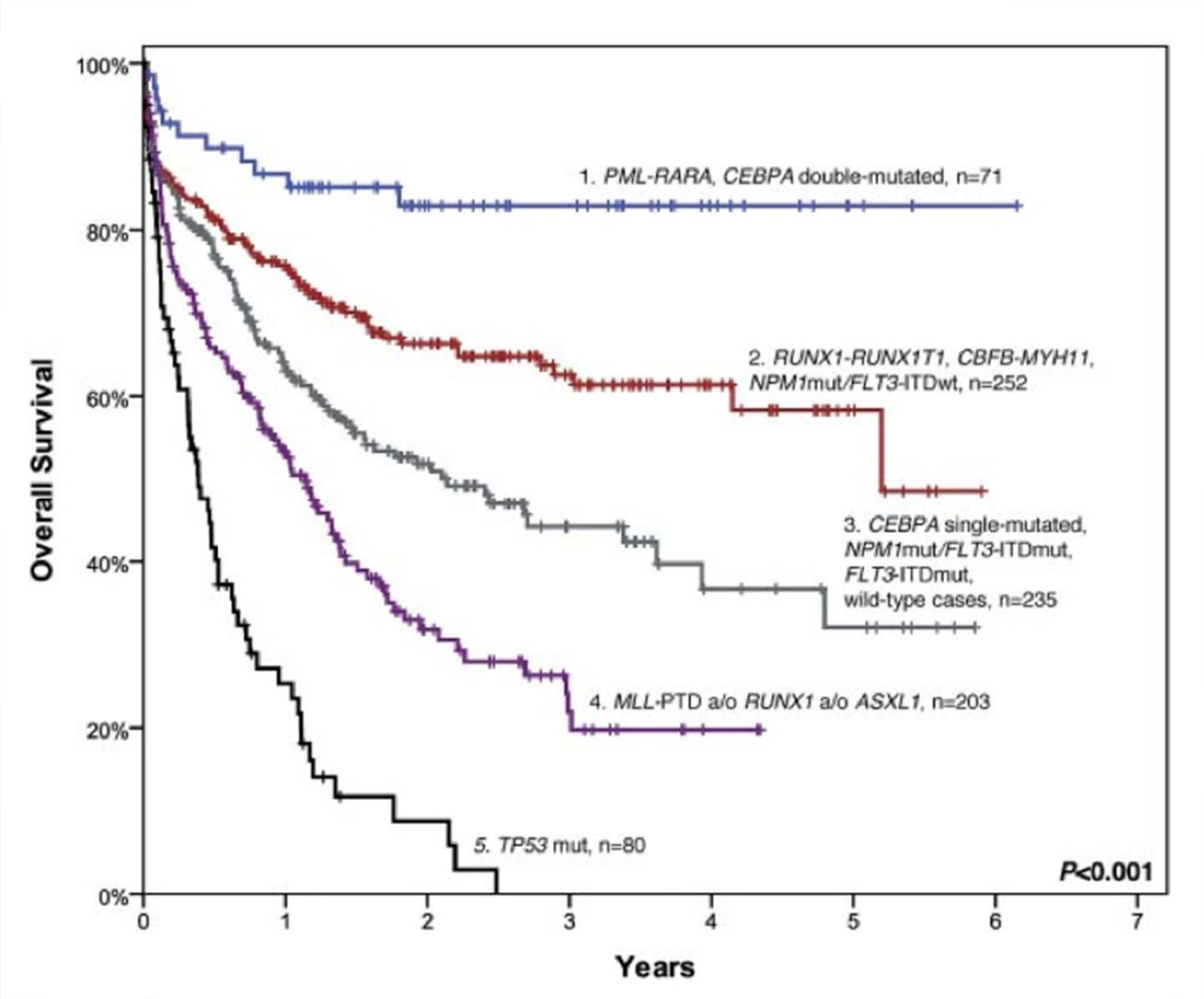
Blood 2008 (AMLSG)

How to integrate so many factors?

Multivariate analysis

Big dataset
Collilenarity
Additive or synergic independency
Role of treatment protocols

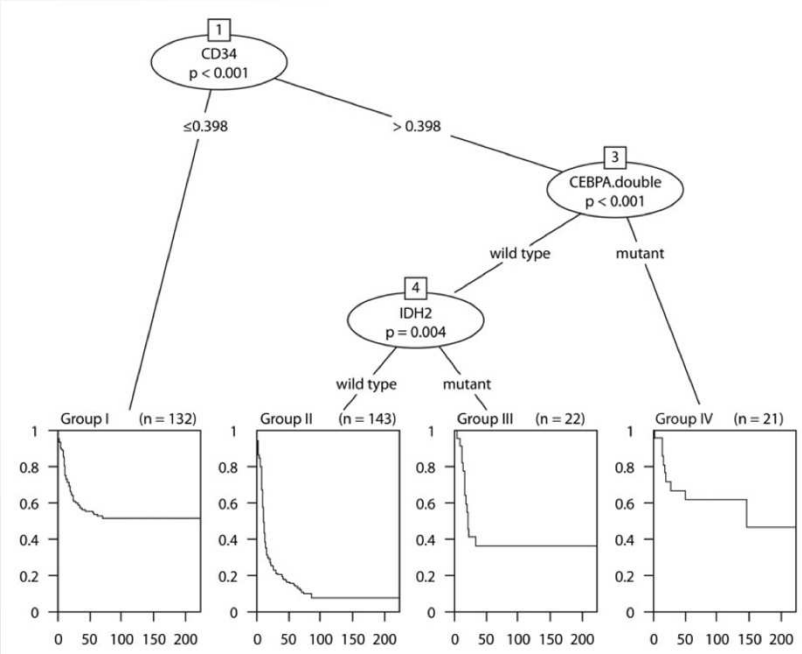
Integrated classifications



Grossmann et al. Blood 2012 (MLL Munich)

Integrated classifications

Intermediate-risk group



Rockova et al. Blood 2011 (HOVON)

Cytogenetic Classification	Mutations		Overall Risk Profile
Favorable	Any		Favorable
Normal karyotype or intermediate-risk ctyogenetic lesions	*FLT3*-ITD-negative	Mutant *NPM1* and *IDH1* or *IDH2*	
	FLT3-ITD-negative	Wild-type *ASXL1*, *MLL*-PTD, *PHF6*, and *TET2*	Intermediate
	FLT3-ITD-negative or positive	Mutant *CEBPA*	
	FLT3-ITD-positive	Wild-type *MLL*-PTD, *TET2*, and *DNMT3A* and trisomy 8–negative	
	FLT3-ITD-negative	Mutant *TET2*, *MLL*-PTD, *ASXL1*, or *PHF6*	Unfavorable
	FLT3-ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A*, or trisomy 8, without mutant *CEBPA*	
Unfavorable	Any		

Patel et al. NEJM 2012 (ECOG)

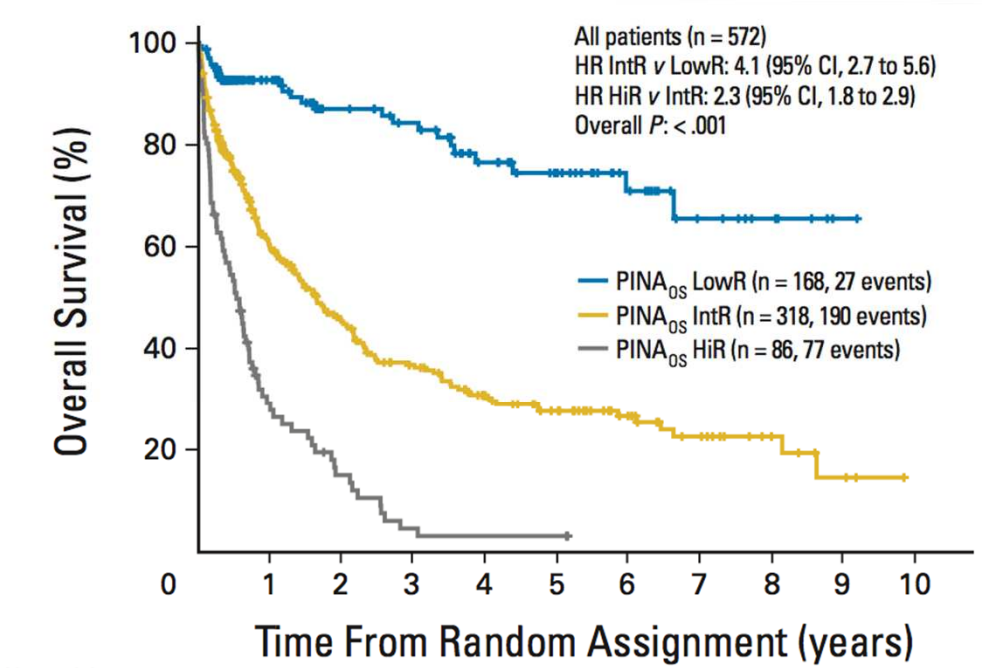
Integrated score

CN-AML group

$PINA_{OS}$ score =

-1.20 (if *NPM1*+, otherwise 0)-0.26 (if *FLT3*-ITD+, otherwise 0)
+0.89 (if *NPM1*+ and *FLT3*-ITD+, otherwise 0)-1.30 (if bi*CEBPA*, otherwise 0)
+0.57 x $\log_{10}$WBC [10^6/L]+0.044 x age [years]+0.40 (if ECOG 2-4, otherwise 0)

LowR $PINA_{OS}$	$PINA_{OS}$ score	< 4.0
IntR $PINA_{OS}$	$PINA_{OS}$ score	≥ 4.0 and < 5.4
HiR $PINA_{OS}$	$PINA_{OS}$ score	≥ 5.4



No. at risk

$PINA_{OS}$ LowR	168	89	67	60	42	32	20	10	6	1	0
$PINA_{OS}$ IntR	318	148	98	71	51	38	25	15	8	3	0
$PINA_{OS}$ HiR	86	21	10	3	2	2	0				

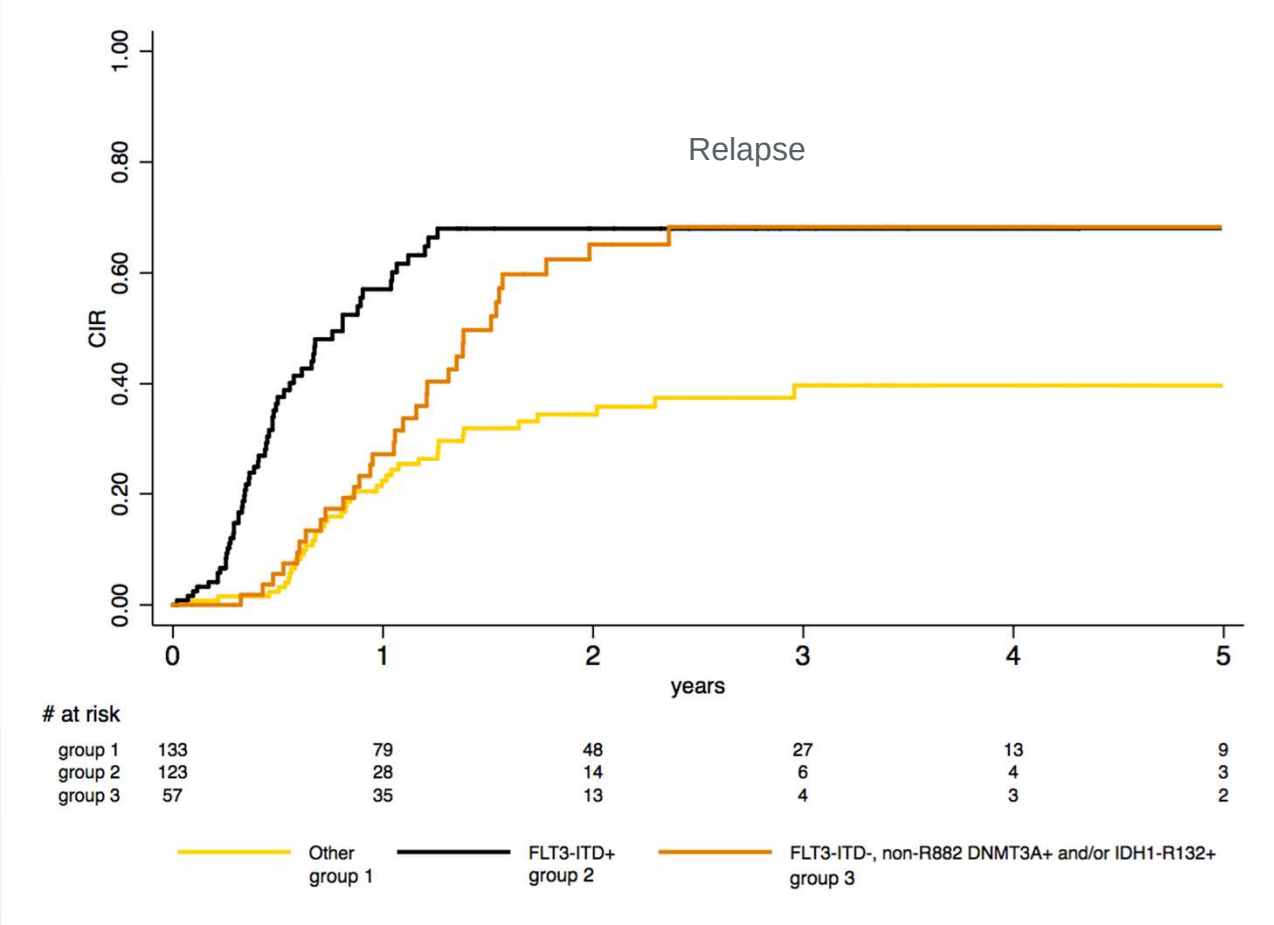
Pastore et al. JCO 2014 (AMLSG & CALGB)

Genetically-defined subsets

- *Isolate a subset defined by a given founding mutation*
  - *PML-RARA*
  - *RUNX1-RUNX1T1, CBFB-MYH11*
  - *NPM1*
  - *…*
- *Then study the prognostic impacts of additional mutations*
  - *For instance, FLT3-ITD does not have the same value in APL as compared to NPM1+ CN-AML*

NPM1+ CN-AML

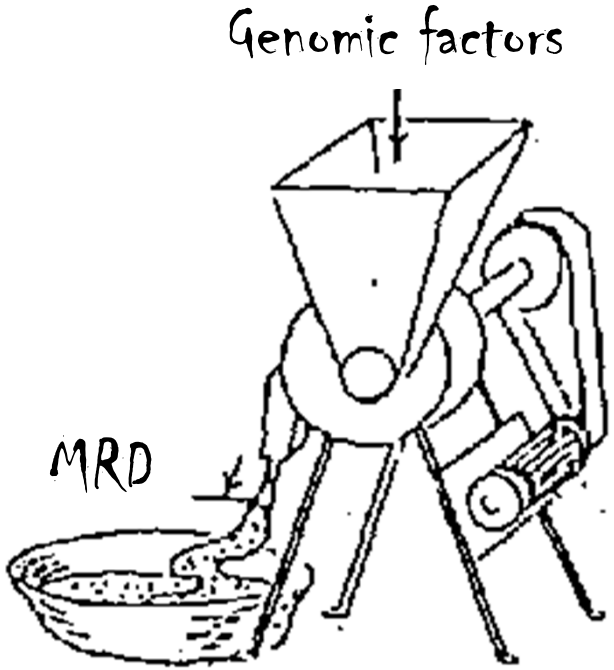
- *Impact of FLT3-ITD, IDH1 and DNMT3A mutations*



P. Peterlin et al. (in preparation)

Minimal residual disease

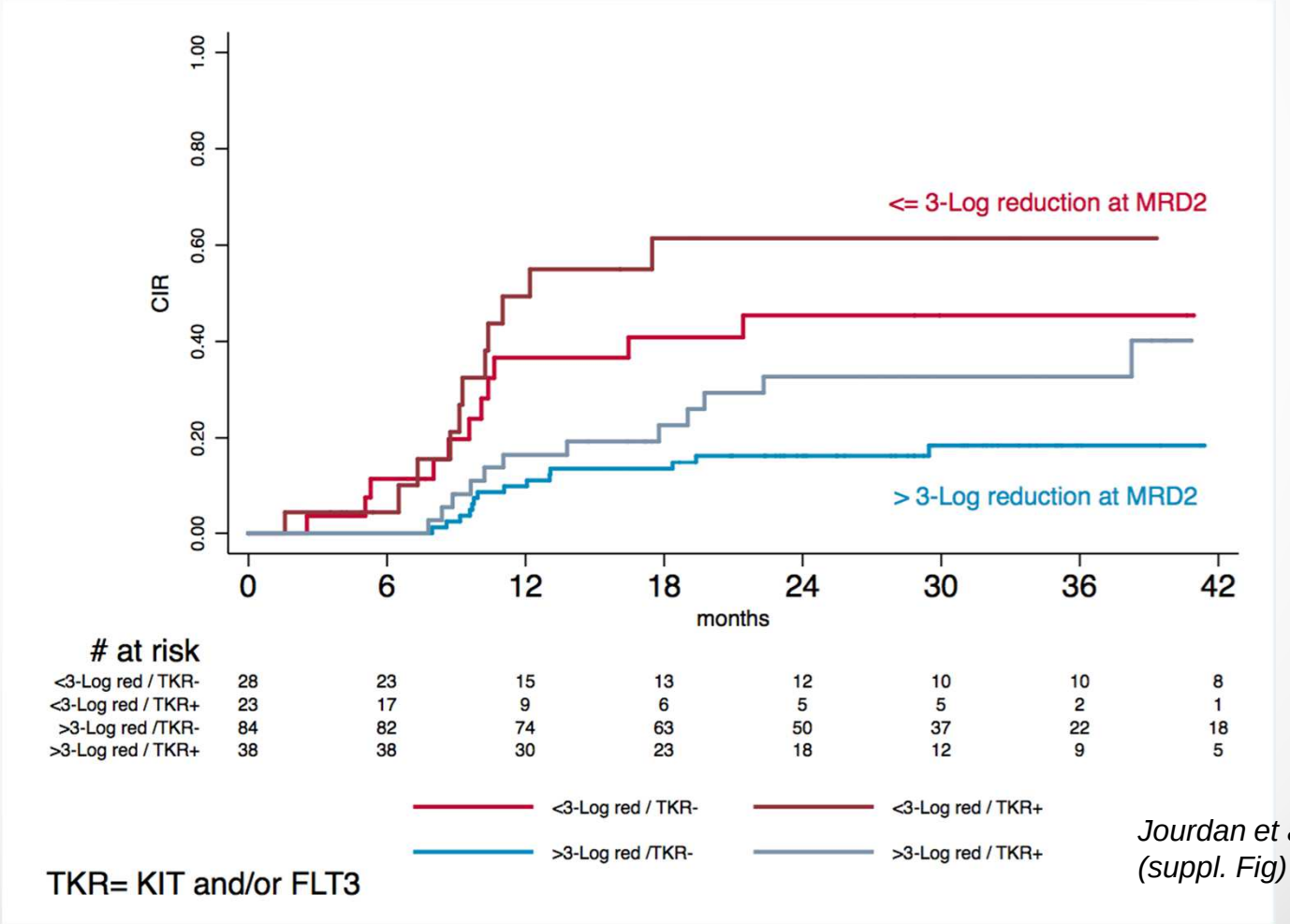
the magic integrator?



Best technique, cutoff threshold, and time-point
Sensitivity
Leukemic subclones, leukemic stem cells
Role of treatment protocol

MRD – CBF

- *French CBF-2006 study*

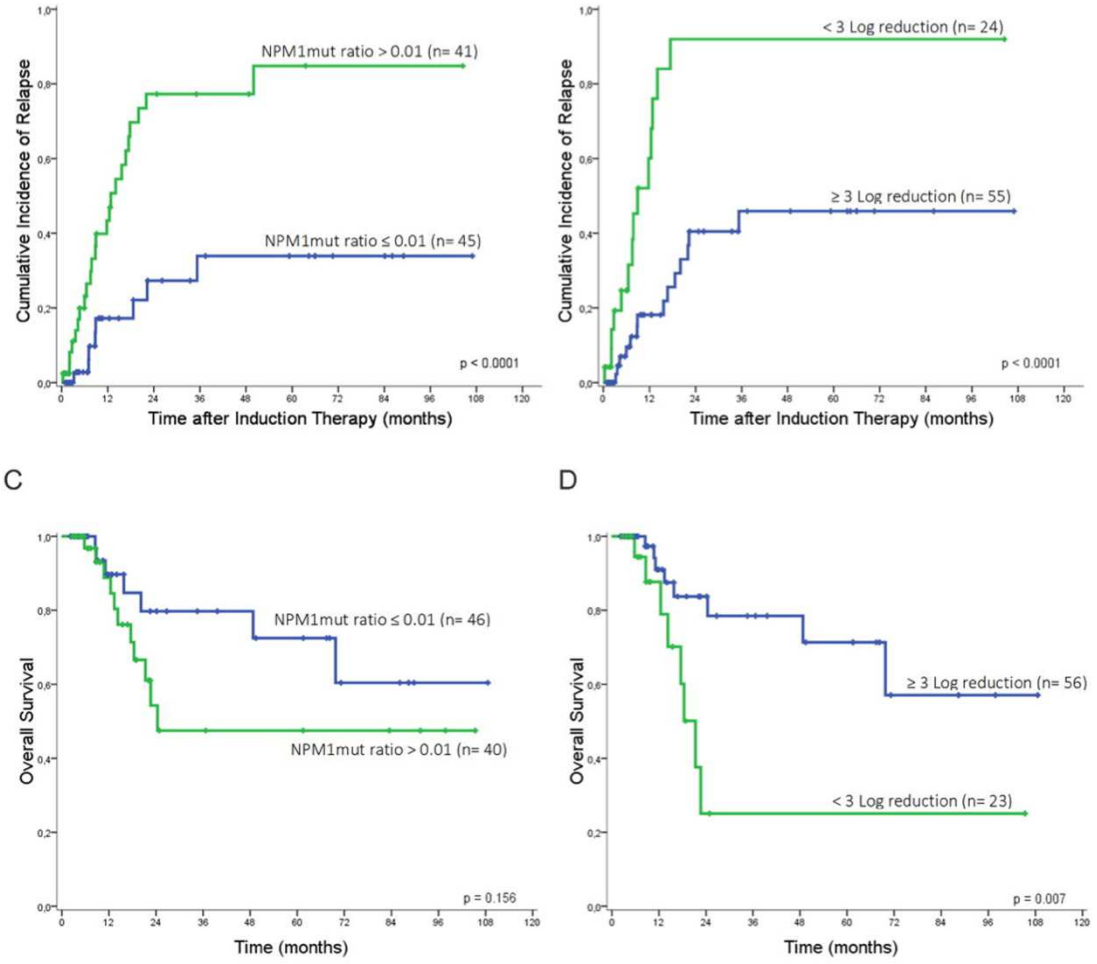


Jourdan et al. Blood 2013 (suppl. Fig)

MRD – *NPM1*

- *AMLCG study*

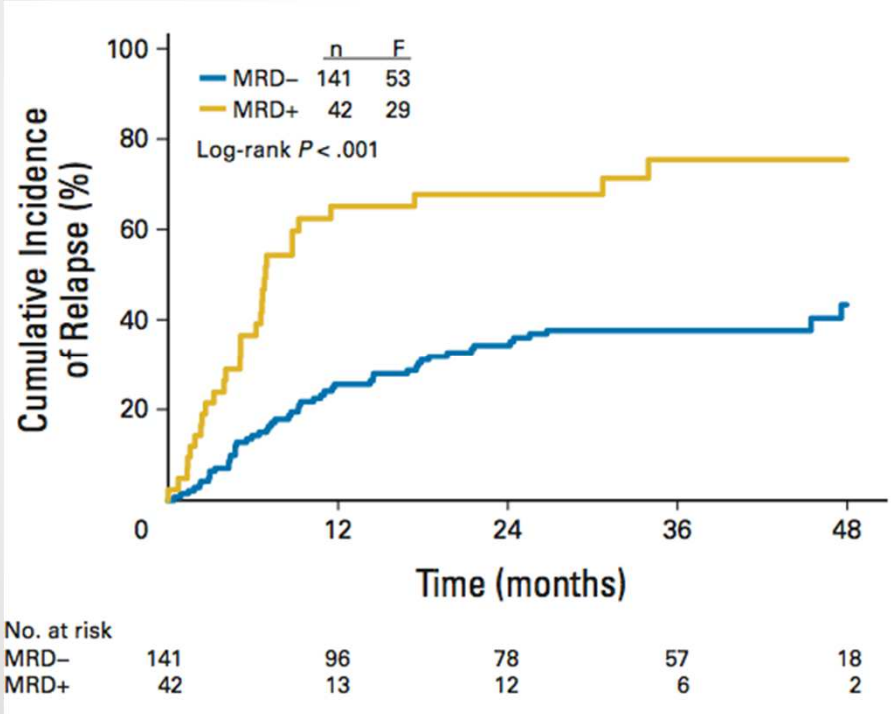
*NPM1*mut ratio after induction



Hubmann et al. Haematologica 2014

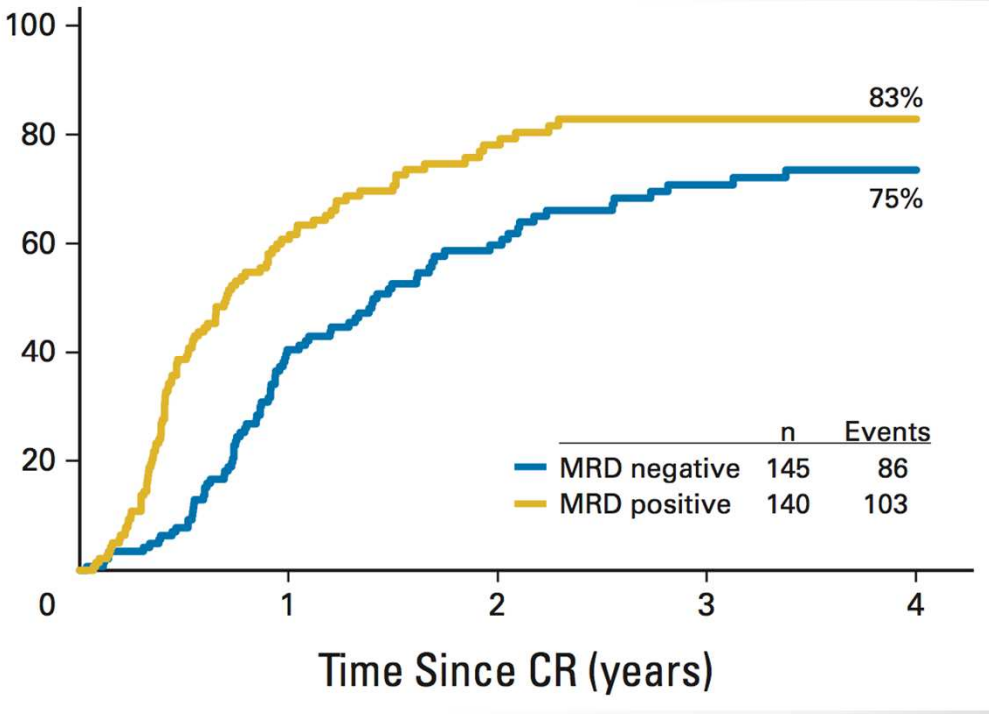
MRD – Flow

- *Younger pts*



Terwijn et al. JCO 2013 (HOVON)

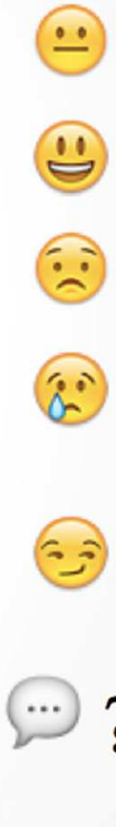
- *Older pts*



Freeman et al. JCO 2013 (NCRI)

Individual risk

Patient	AML	Response
Female 25y ECOG 0	WBC, 25 G/L	-
Female 25y ECOG 0	WBC, 25 G/L t(8;21)	-
Female 25y ECOG 0	WBC, 25 G/L t(8;21), del(9q)	-
Female 25y ECOG 0	WBC, 25 G/L t(8;21), del(9q) KIT+	-
Female 25y ECOG 0	WBC, 25 G/L t(8;21), del(9q) KIT+	MRD Log-red, 3.0
Female 25y ECOG 0 Sibling donor +	WBC, 25 G/L t(8;21), del(9q) KIT+	MRD Log-red, 3.0



Predictive factor

Outil de stratification thérapeutique

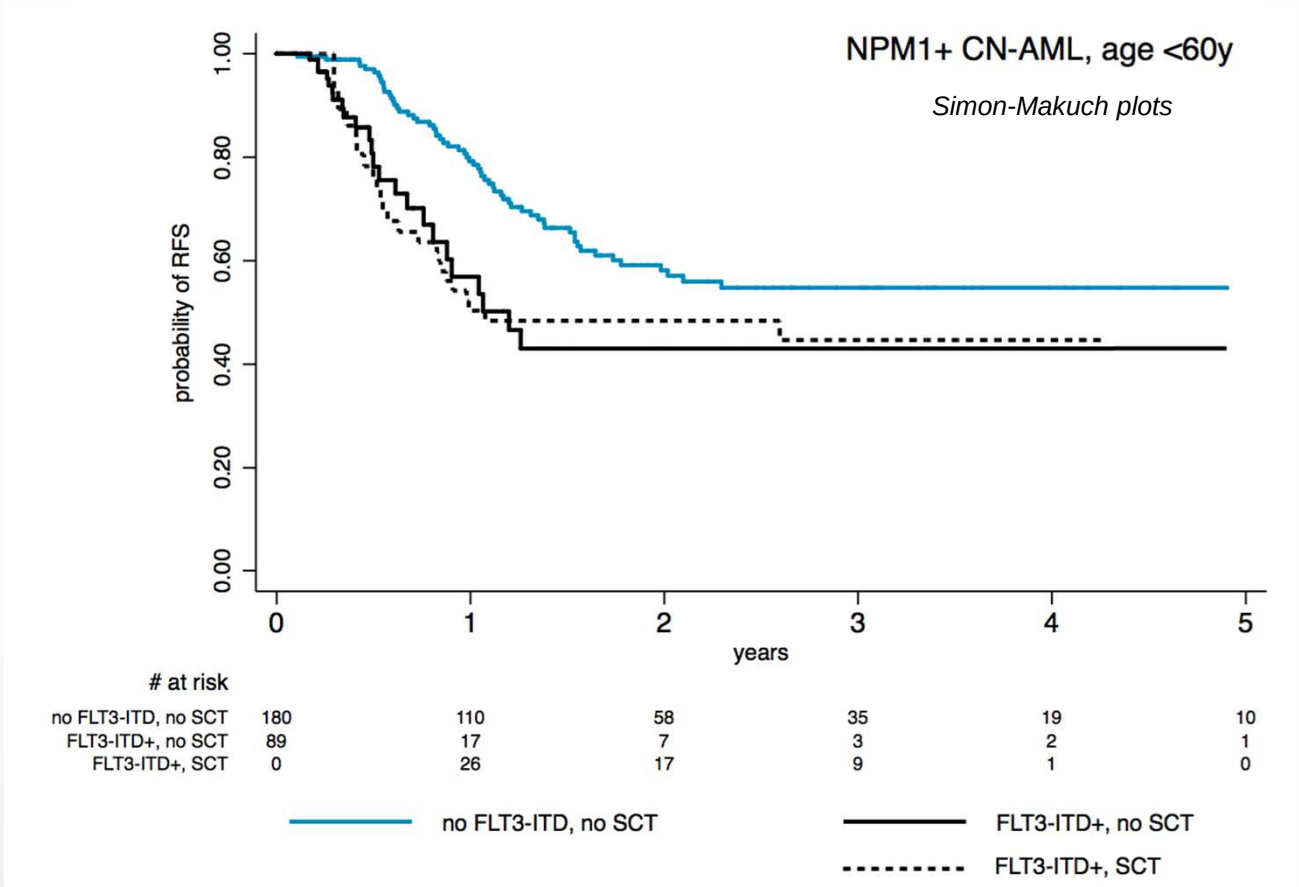
- *Interaction significative entre la présence ou l'absence de ce factor et l'effet d'une intervention thérapeutique.*

- *Quelle(s) décision(s) thérapeutique(s) sont réellement stratifiée(s) à ce jour ?*

  - *Allogreffe en RC1, OUI/NON (sujets jeunes)*
  - *Chimiothérapie intensive, OUI/NON (sujets âgés)*
  - *Traitement intensif d'une rechute, OUI/NON (tous)*

Predictive factor

L'allogreffe n'est pas la réponse univoque à tout facteur de mauvais pronostic



P. Peterlin et al. (in preparation)

The best way to predict the future is to invent it

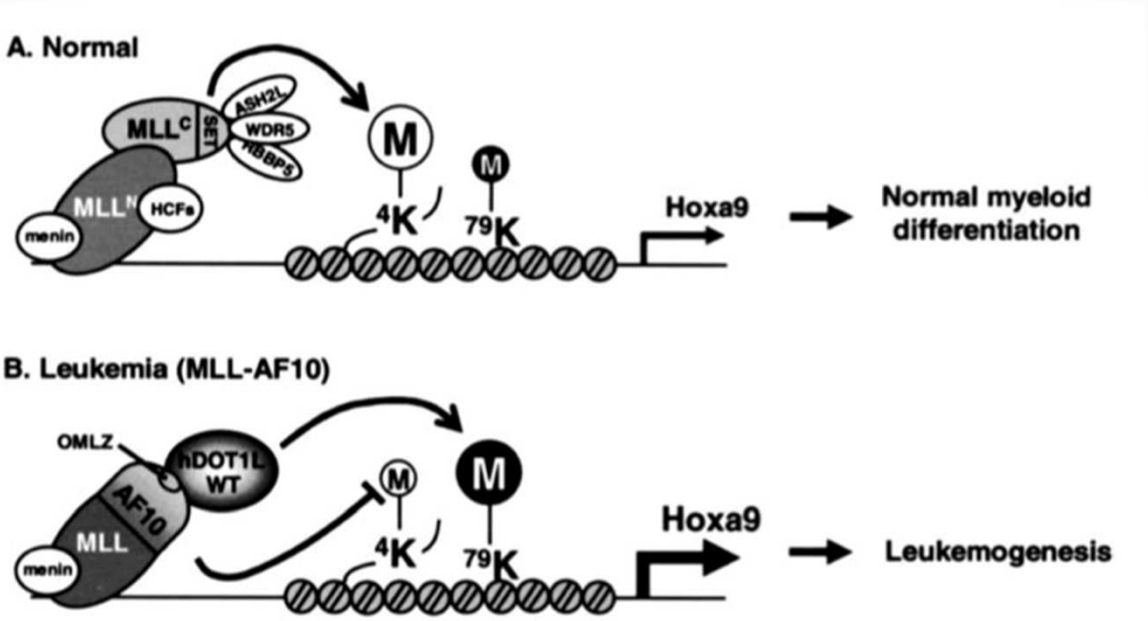
Alan Kay

FLT3 inhibitors

- *Tandutinib*
- *Sorafenib*
- *Sunitinib*
- *Midostaurin*
- *Lestaurtinib*
- *KW-2449*
- *Quizartinib*
- *Crenolanib*

- *Mostly induce blast clearance*
- *Few true CR as single agent (if any)*
- *Efficacy in combination or after transplantation under investigation*

DOT1L inhibitors / *MLL*



Okada et al. Cell 2005

blood

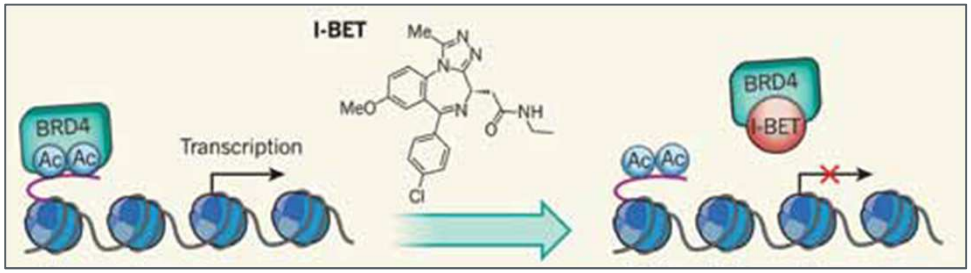
2013 122: 1017-1025
doi:10.1182/blood-2013-04-497644 originally published online June 25, 2013

Potent inhibition of DOT1L as treatment of MLL-fusion leukemia

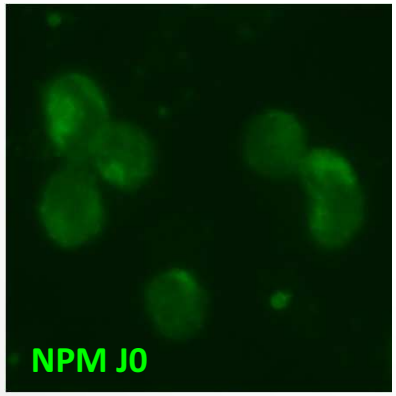
Scott R. Daigle, Edward J. Olhava, Carly A. Therkelsen, Aravind Basavapathruni, Lei Jin, P. Ann Boriack-Sjodin, Christina J. Allain, Christine R. Klaus, Alejandra Raimondi, Margaret Porter Scott, Nigel J. Waters, Richard Chesworth, Mikel P. Moyer, Robert A. Copeland, Victoria M. Richon and Roy M. Pollock

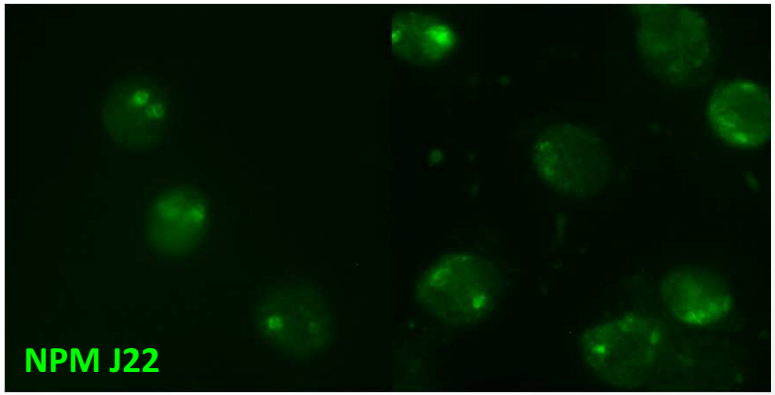
BRD4 inhibitors / *NPM1*

- *BRD4 = epigenetic reader*
- *BRD4 inhibitors = new class of epigenetic treatment*

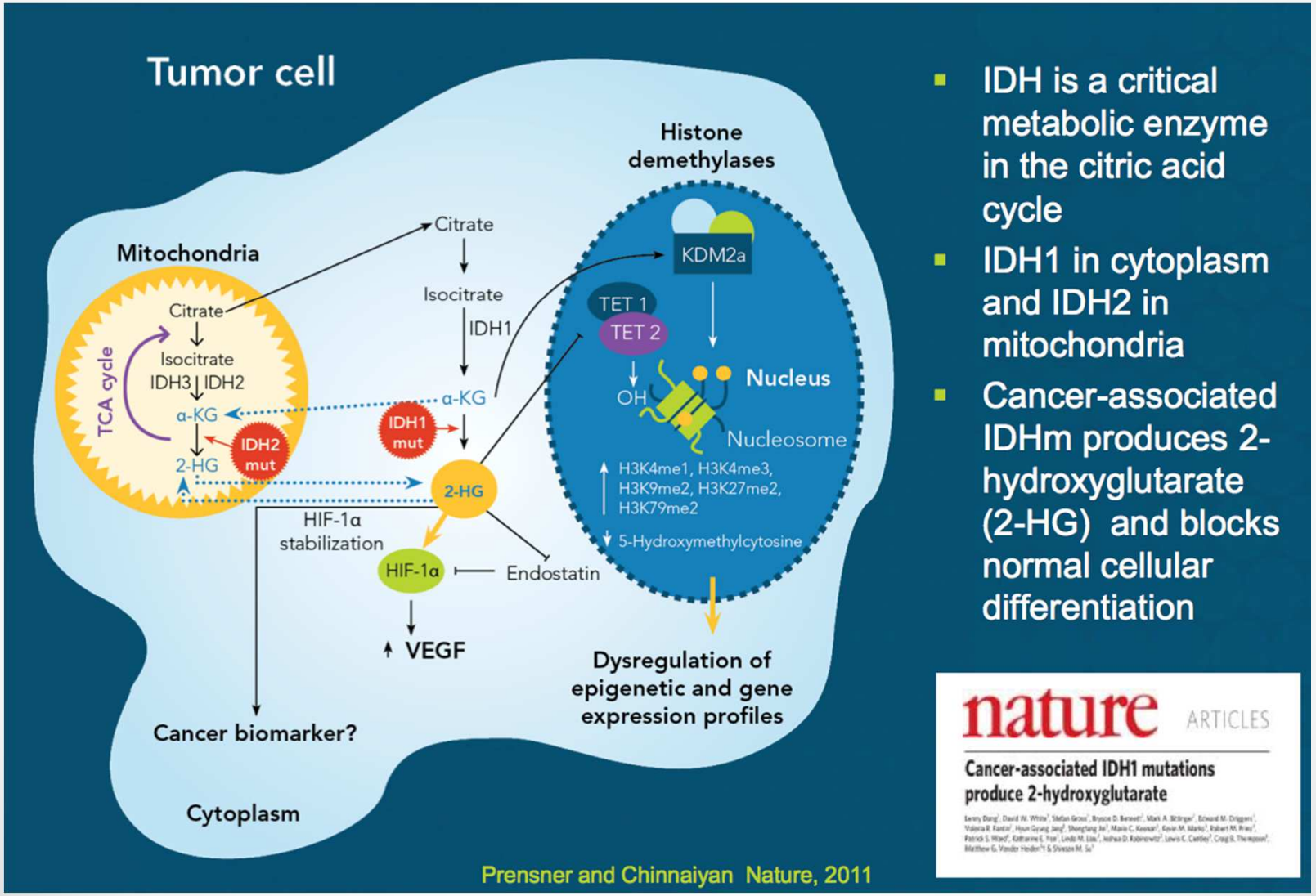


Ongoing OTX015 Phase 1 study





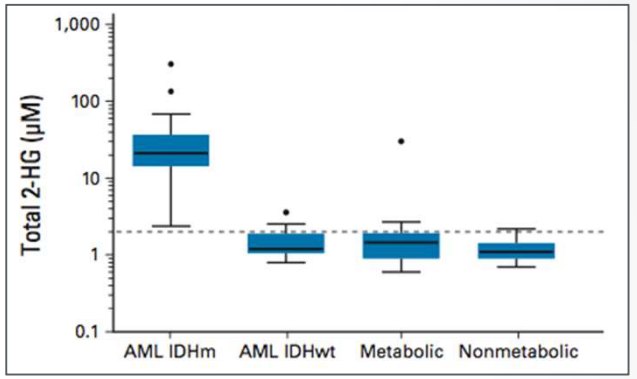
Role of IDH in cancer



- IDH is a critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Serum 2HG levels

- *Diagnosis tool*
- *Correlation with MRD levels*



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JOURNAL OF CLINICAL ONCOLOGY

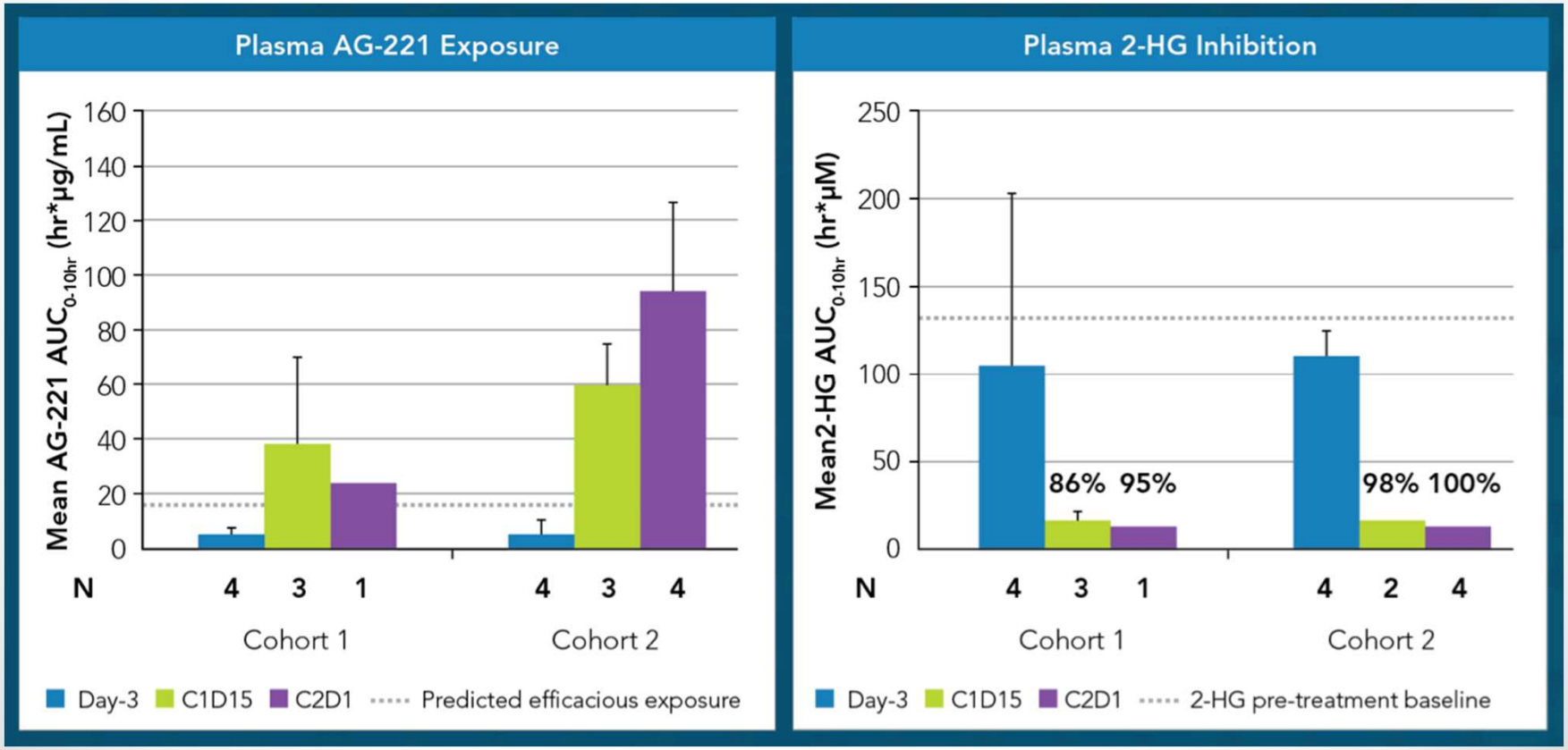
ORIGINAL REPORT

Serum 2-Hydroxyglutarate Production in *IDH1*- and *IDH2*-Mutated De Novo Acute Myeloid Leukemia: A Study by the Acute Leukemia French Association Group

Maxime Janin, Elena Mylonas, Véronique Saada, Jean-Baptiste Micol, Aline Renneville, Cyril Quivoron, Serge Koscielny, Laurianne Scourzic, Sébastien Forget, Cécile Pautas, Denis Caillot, Claude Preudhomme, Hervé Dombret, Céline Berthon, Robert Barouki, Daniel Rabier, Nathalie Auger, Frank Griscelli, Elisabeth Chachaty, Edwige Leclercq, Marie-Hélène Courtier, Annelise Bennaceur-Griscelli, Eric Solary, Olivier Adrien Bernard, Virginie Penard-Lacronique, Chris Ottolenghi, and Stéphane de Botton

IDH2m inhibitor

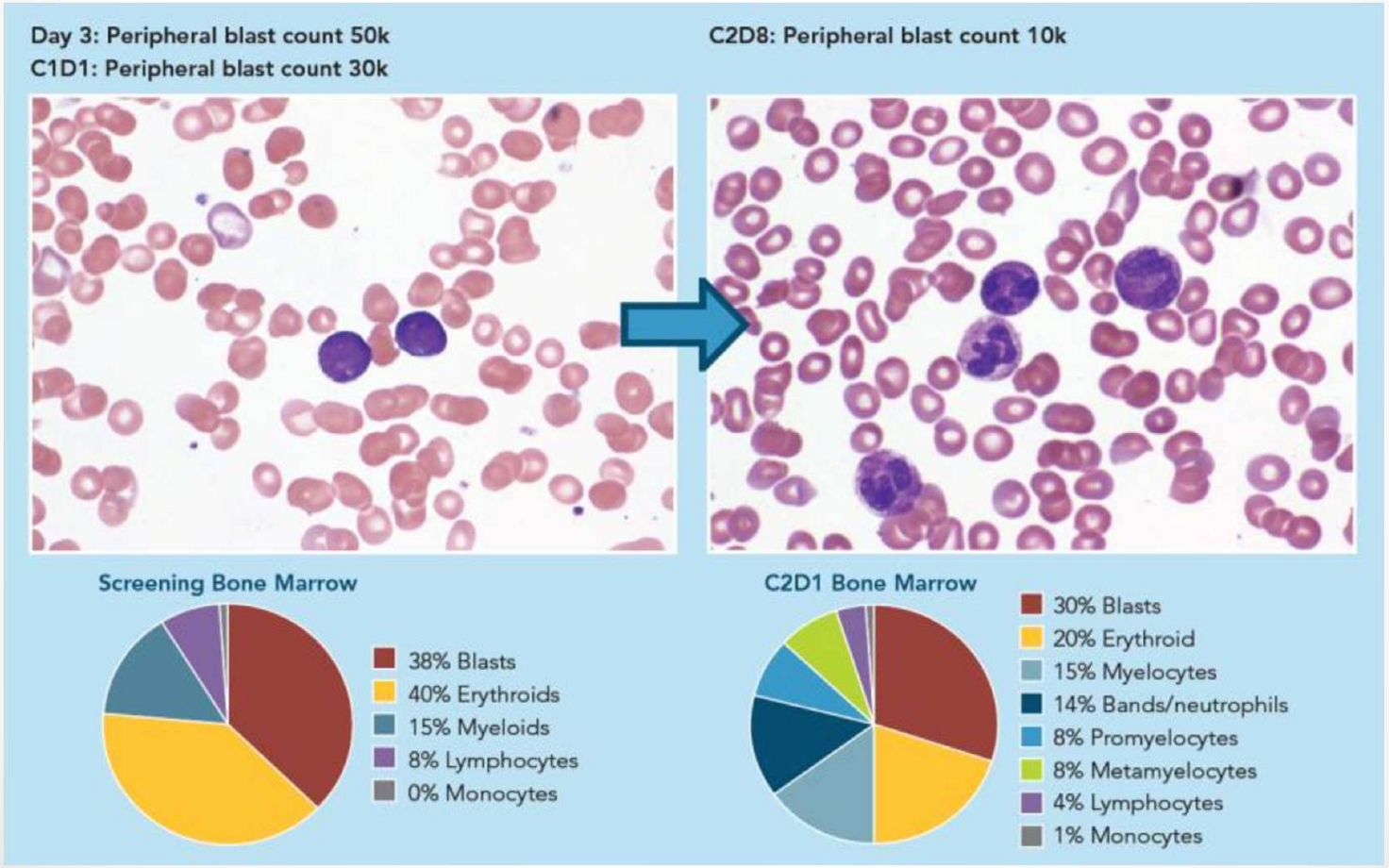
- AG-221 Phase 1 study



EM. Stein et al. AACR 2014

IDH2m inhibitor

- One patient who achieved a CR after 3 cycles



EM. Stein et al. AACR 2014

Conclusions

- *L'étude de la valeur pronostique des mutations oncogénétiques doit sans doute tenir compte de leur hiérarchie au sein du clone leucémique.*

- *La MRD devient un outil décisionnel important dans la LAM, qui peut toutefois d'avérer insuffisant dans certains sous-types.*

- *Le ciblage thérapeutique des mutations fondatrices arrive… à l'instar de ce qui a été accompli dans la leucémie aiguë promyélocytaire.*