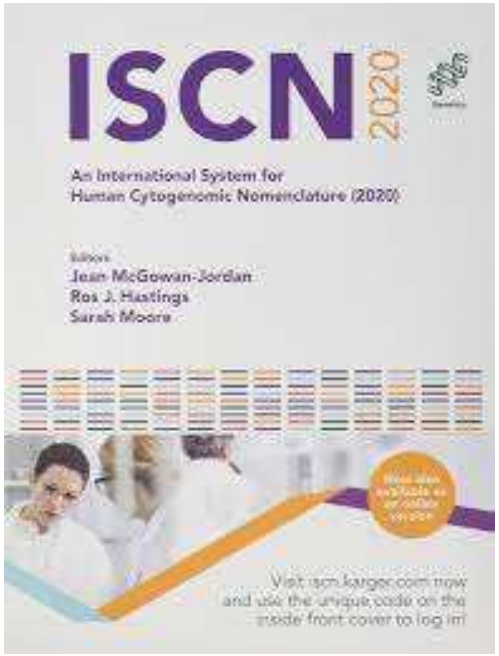
Caryotype complexe et impact pronostique dans les hémopathies malignes. Une revue du GFCH.

Audrey Bidet

Contexte

- ❑ Caryotype complexe (CK) : rôle +++ dans le pronostic et le traitement de nombreuses hémopathies
- ❑ Définition du CK peut connaître des variations selon les hémopathies
- ❑ Version révisée de l'ISCN 2020 : guidelines pour dénombrer les anomalies



Proposition d'une revue complète par le GFCH :

- définitions du CK et de sa valeur pronostique selon les hémopathies
- discussion de la complexité au regard d'autres techniques cytogénomiques
- Illustration à l'aide d'exemples des modifications entrainées par l'ISCN 2020 sur le décompte des anomalies

McGowan-Jordan et al., 2020

Panel d’experts

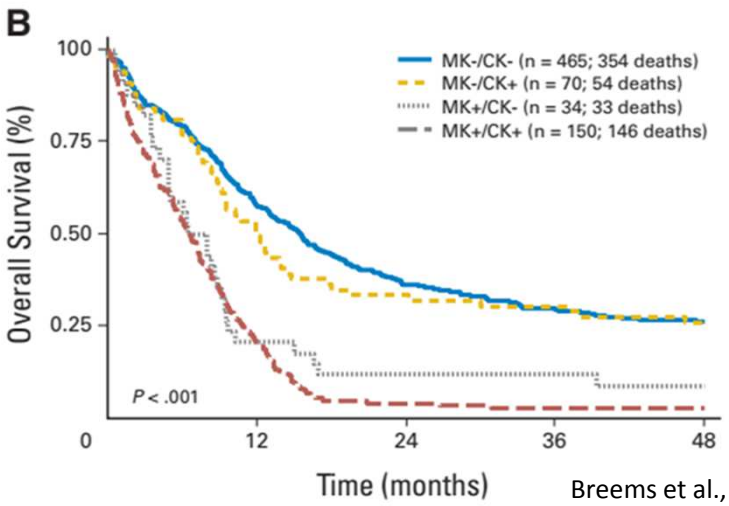
Hémopathies	Cytogénéticiens
SMD	MB Troadec, N Douet-Guilbert, V Eclache, M Lafage-Pochitaloff
LAM	A Bidet, I Luquet, C Terré, MA Collonge-Rame, M Lafage-Pochitaloff
SMP	L Véronèse, A Bidet, C Bilhou-Nabera, V Eclache, N Nadal
LAL	M Lafage-Pochitaloff, W Cuccuini, C Lefebvre,
LLC	F Nguyen-Khac, E Chapiro, L Veronese
Lymphomes	C Lefebvre, A Daudignon, D Penther
Myélomes	A Daudignon, D Penther, B Quilichini, L Michaux, W Cuccuiny, G Ameye, C Terré

Définition – Fréquence – Pronostic

Hematological malignancies		Definition	Frequency	Prognostic impact	References
MDS	***de novo* MDS**	**CK ≥ 3 abnormalities**	9-10%	OS, time to AML evolution	Schanz 2012 Greenberg 2012 Mauritzon 2002 Kantarjian, 2008
		CK >3 abnormalities	7%		
	Therapy-related MDS	**CK ≥ 3**	30-45%		
AML		**ELN : ≥ 3 abnormalities** **MRC : > 3 abnormalities** Excluding WHO designated recurring abnormalities as t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3), t(9;22)	All AML : 10-12% > 60 years: 23% secondary AML and t-AML : up to 25%	PFS,OS	Döhner 2017 Grimwade 2010 Byrd 2002 Daneshbod 2019 Schoch 2004 Bager 2018 Schoch 2005
MPN	**CML**	**CK ≥ 3 abnormalities**	1%	Blast crisis	Perez 2015 Bacher 2009 Such 2011 Wang blood 2014
	Other MPN		7.5%	OS, time to AML evolution	
	CMML		5-8%		
	aCML & U-MPN/MDS		3-8%		
Adult T-ALL		**CK≥ 5 abnormalities** Excluding cases with an established translocation	7-13%	EFS	Moorman 2007 Marks 2009 Lafage-Pochitaloff 2014
CLL		**CK ≥ 3 abnormalities** **HCK ≥ 5 abnormalities** Excluding +12,+19,+other abnormalities	CK: 11-19% HCK: 4-8% (treatment-naive)	TTFT, PFS, OS	Puiggros 2017 Rigolin 2017 Baliakas 2019
MCL		**CK ≥ 3 additional abnormalities to t(11;14)**	19-59%	TTFT, OS	Sarkozy 2014 Greenwell 2018 Obr 2018

Pronostic : scores pronostiques, sous-groupes de CK

Hematological malignancies		Prognostic Scoring System	Subgroup of CK	Nota Bene
MDS		IPSS, IPSS-R	***TP53* alterations** (Bersanelli et al., 2021, Bernard et al, 2020))	
AML		ELN 2017	**Monosomal Karyotype** (Breems et al, 2008; Döhner et al, 2017) « **typical CK** » (5q, 7q and or 17p abnormalities) vs « **atypical CK** » (Schoch et al, 2005; Mrozek et al, 2019)	
MPN	**CML**			High-risk ACA : CK, +8, +Ph, i(17q), +19,-7/7q- ,11q23, 3q26 (ELN 2020)
	PMF	IPSS, DIPSS-Plus, GIPSS, MIPSS70+ version 2.0		
	CMML	CPSS, CPSS-Mol		
CLL		Model by Baliakas et al, Blood,2019	**CK1** (balanced translocations, del, monosomy or trisomy) vs **CK2** (unbalanced translocations, add, ins, dup, r, dic, mar)(Rigolin et al, 2018)	



Breems et al., JCO, 2008

CK et myélome multiple : un concept difficile à définir ….

Cytogénétique conventionnelle :

Hyperdiploidie / trisomies de chr. impairs (HR-MM) vs Pseudodiploidie ou Hypodiploidie / translocations (t(14q32)-IGH) :
CK présents dans les 2 groupes

Limites +++

- Faible taux de plasmocytes souvent
- Guidelines recommandent la FISH interphasique sur plasmocytes triés
- Nombre limité et hétérogènes de marqueurs réalisés rendant difficile la caractérisation de la complexité

		Working groups				
Cytogenetic abnormality	Frequency	ISS-R 2015	EMN 2018	EMN and IMWG 2019 recommandations	Mayo Clinic 2020	IFM 2021
1p32 deletion (*CDKN2C - FAF1*)	7-17%		N	●		N (+0,8)
1q gain (*CKS1B*)	34-40%		N	●	N	N (+0,5)
t(4;14)(p16;q32) *FGFR3-MMSET*	15%	N	N	●	N	N (+0,4)
t(6;14)(p;q32)(p21;q32) *CCND3-IGH*	2%				S	
MYC rearrangement	20-47%			●		
t(11;14)(q13;q32) *IGH-BCL1*	20%		G	●	S	S
t(14;16)(q32;q23) *MAF-IGH*	2-3%	N	C	●	N	C
17p deletion (*TP53*)	5-15%	N	N	●	N	N (+1,2) (cut-off : 55%)
t(14;20)(q32;q12) *MAFB-IGH*	< 1%			●	N	
Ploidy (+5 /+9 /+ 15 /+21)	55-60%		S	●	S	Trisomy 5: G : (- 0,3) Trisomy 21 : N : (+0,3)
Additional data				Proposal of FISH targets to be performed according to national recommendations in European countries	double/triple hits : N (any 2 or >=3 high risk factors)	Low Risk <= 0 Intermediate Risk 0-1 High Risk > 1
References		Palumbo et al - JCO 2015	Caers et al - Haematologica 2018	Rack et al - Leukemia 2019	Rajkumar - Am J Hematol 2020	Perrot et al - JCO 2019 Corre et al - Blood 2021

N : Negative impact
G : Good prognosis
S : Standard prognosis
C : Controversial prognosis
IFM : Intergroupe Francophone du Myélome
EMN : European Myeloma Network
IMWG : International Myeloma Working Group

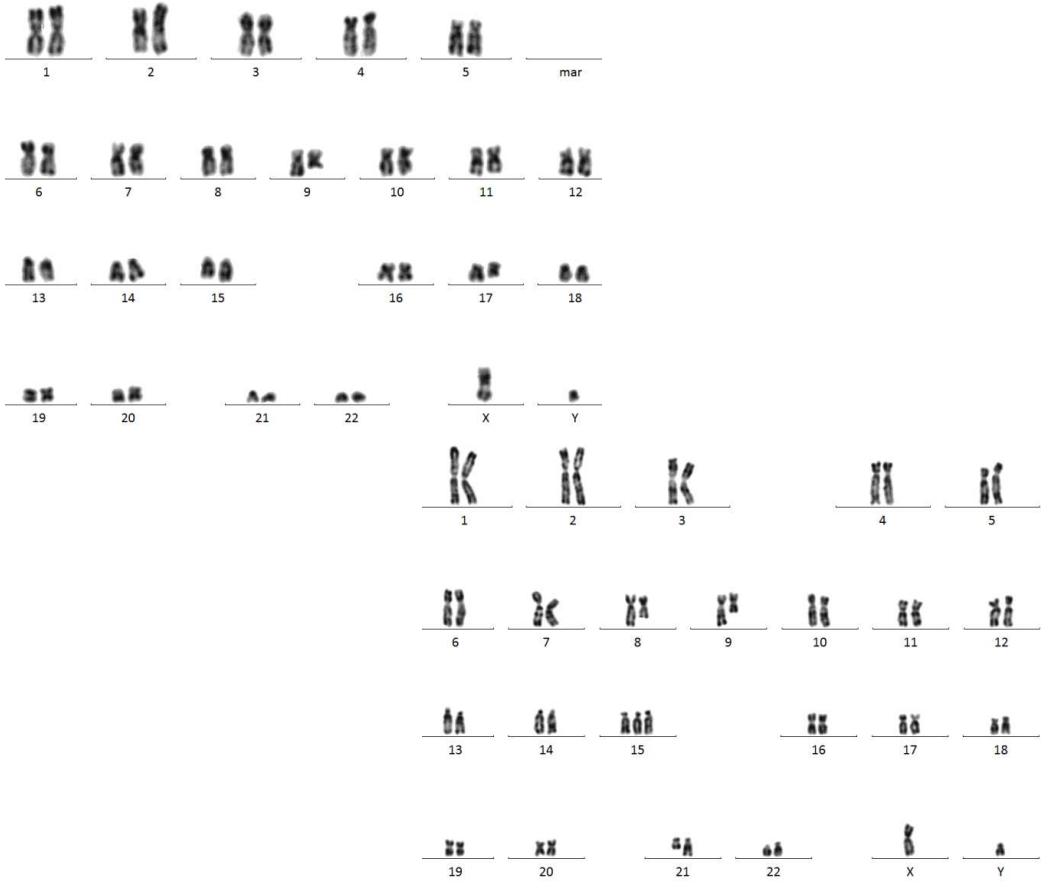
Exceptions à la règle

LAM:

Anomalies récurrentes définies par l'OMS :

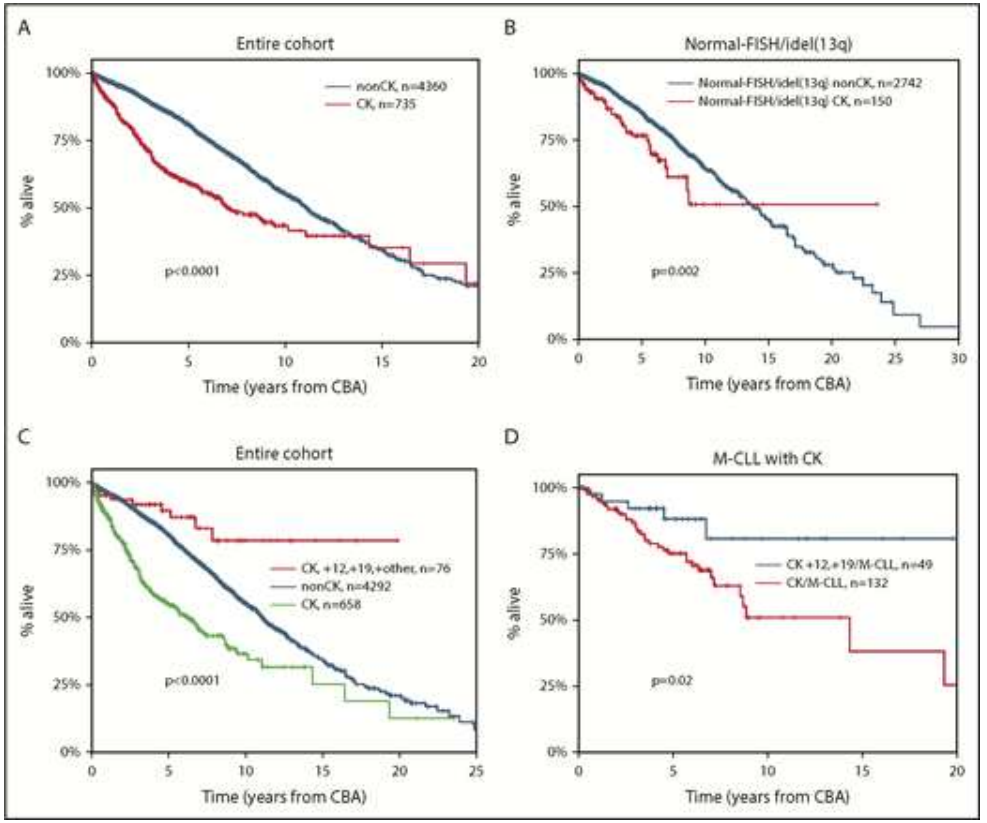
t(15;17), CBF: t(8;21), inv(16)/t(16;16)

t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3), t(9;22)



LLC :

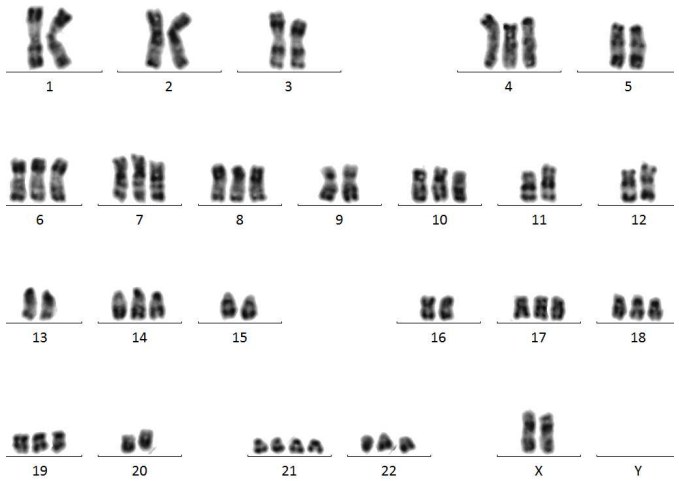
+12, +19

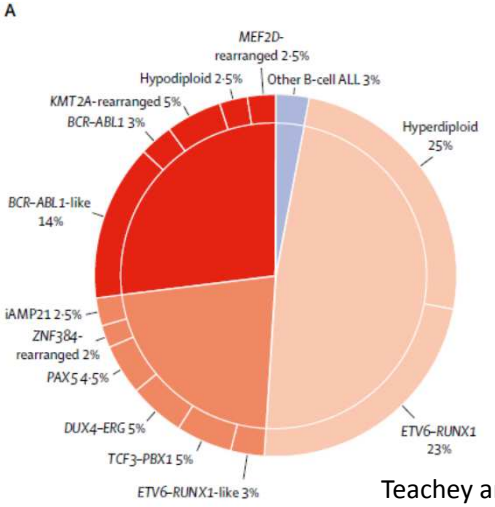


Baliakas et al., Blood, 2019

Exceptions à la règle

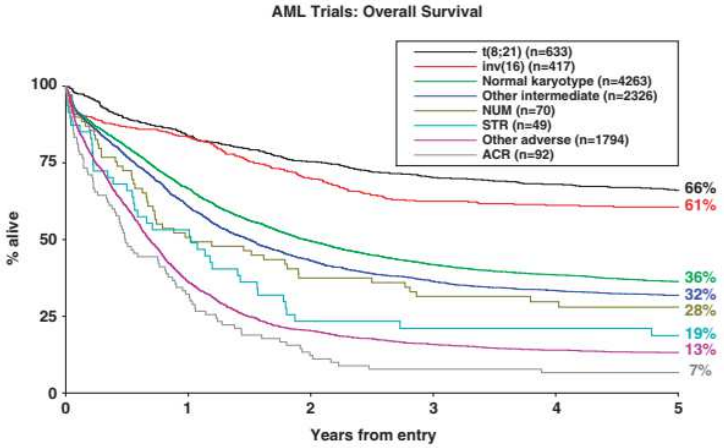
LALB: High Hyperdiploidy (51-67 chr.)





Teachey and Pui, 2019

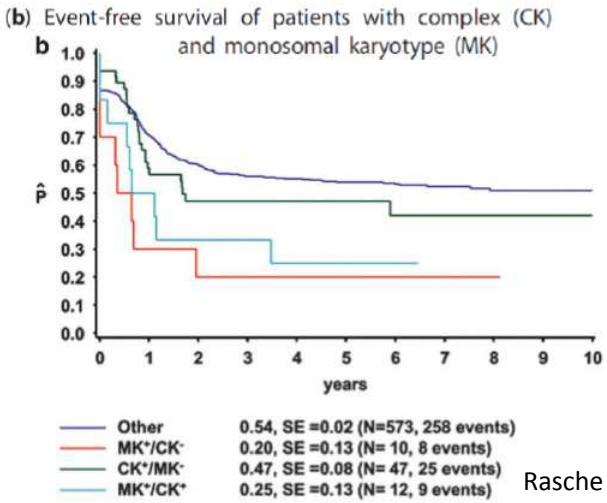
Hyperdiploidies dans les LAM



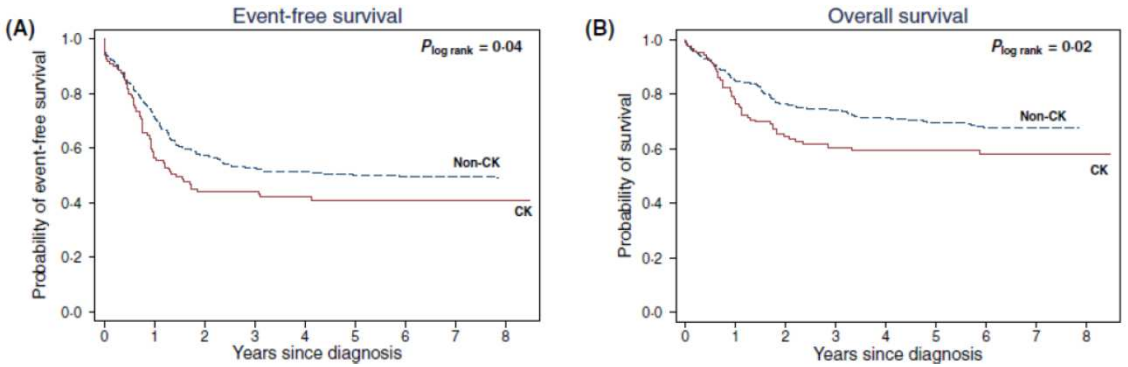
Chilton et al., Leukemia, 2013

CK en Pédiatrie : une catégorie de patients un peu à part

LAM : CK < 10% / jeune enfant / LAM 7

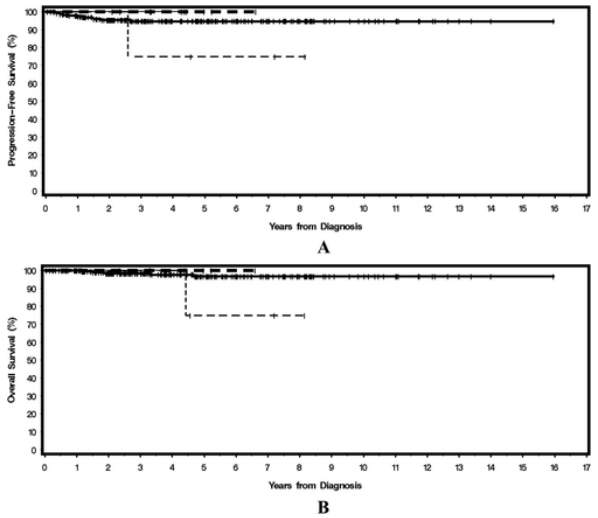


Rasche et al., Leukemia, 2017



Bager, et al., BJH, 2018

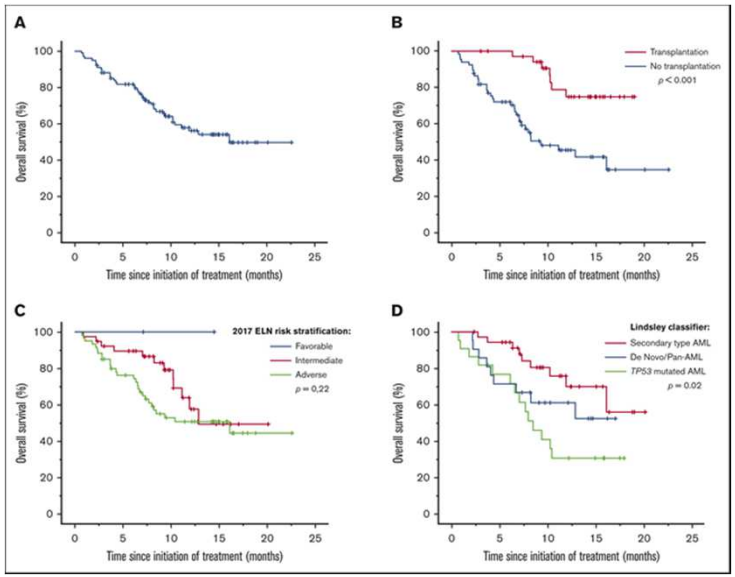
LMC



Millot et al, Cancer, 2017

La notion de CK peut être une aide dans la décision thérapeutique

- Allogreffe (LAM, SMD, MP)
- Nouvelles thérapies



CPX-351 / LAM

Chiche et al., 2021

BTKi/ relapsed, refractory, or treatment-naïve CLL

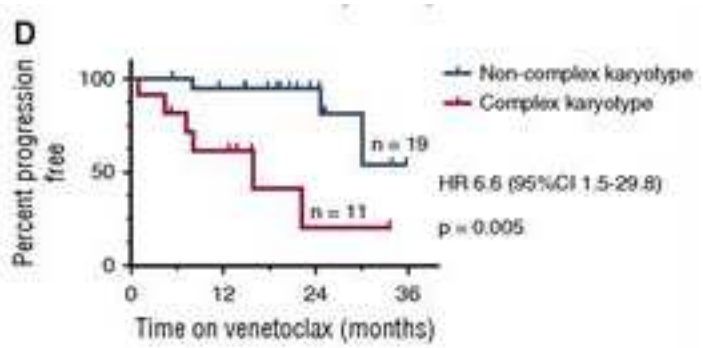
Table 2. Multivariable Models for Cumulative Incidence of Ibrutinib Discontinuation According to Reason for Discontinuation

Variable	Transformation		Progressive CLL*		Other Event	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Complex karyotype (yes *v* no)	5.00 (1.51 to 16.52)	.008	2.81 (1.34 to 5.88)	.006	—	—
MYC abnormality (yes *v* no)	2.15 (1.00 to 4.65)	.051	—	—	—	—
Del(17)(p13.1) present on FISH (yes *v* no)	—	—	2.14 (1.15 to 3.96)	.016	—	—
Age (≥ *v* < 65 years)	—	—	0.49 (0.27 to 0.91)	.023	2.02 (1.25 to 3.28)	.004
Prior therapies > 3 (yes *v* no)	—	—	—	—	1.99 (1.23 to 3.23)	.005

NOTE. All models were adjusted for treatment with ibrutinib monotherapy versus combination therapy with ibrutinib and ofatumumab.
Abbreviations: CLL, chronic lymphocytic leukemia; FISH, fluorescent in situ hybridization; HR, hazard ratio.
*Landmark analysis at 1 year.

Woyach et al., JCO, 2017

Venetoclax / R/R LLC



Anderson et al., Blood, 2017

De la difficulté de compter les anomalies …..

Table 2
IWGMC consensus guidelines for counting aberrations in MDS karyotypes.

General rule: count 1 aberration for each item between commas in the nomenclature string.

More specifically:
(1) count 1 aberration for each numerical change (including -Y), balanced translocation and simple structural change;
(2) count 1 aberration for each complex structural change;
(3) count 0 for a constitutional aberration, but if in doubt, count 1 aberration;
(4) when multiple clones are present, add all independent aberrations, but count a single (specific) change only once;
(5) count 1 aberration for tetraploidy; and
(6) for the IPSS cytogenetic risk, until it is revised, all chromosome 7 abnormalities are considered "poor" [1].

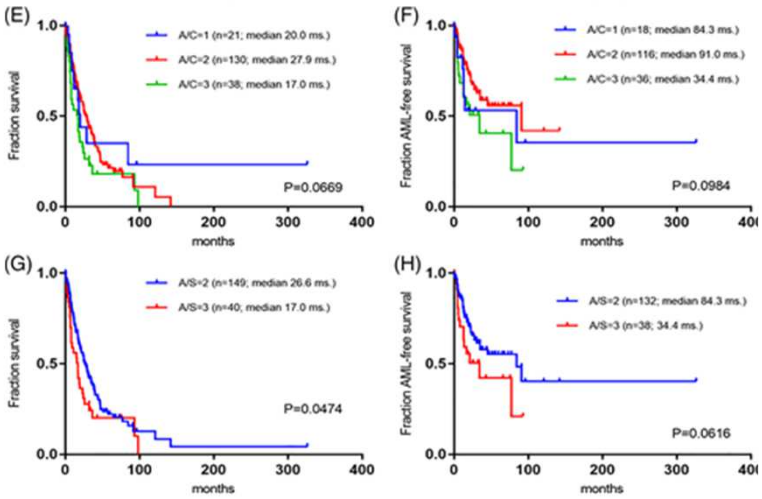
Chun et al., Leukemia Research, 2010

Abnormality type	Examples	Number of chromosome abnormalities
Numerical gain	Trisomy Duplication of a derivative chromosome	1
Numerical loss	Monosomy, includes –Y	1
Balanced structural abnormality *(no gain, no loss of chromosomal material)*	Simple balanced translocation Complex balanced translocation (involving 3 or more chromosomes) Inversion Balanced insertion	1
Unbalanced aberrations involving one chromosome (leading to gain or loss of chromosomal material)	Isochromosome Deletion* Duplication* Simple ring chromosome Isodicentric chromosome Homogeneously staining region Double minutes Unidentified marker chromosome	1
	Tetrasomy of same chromosome Triplication or quadruplication Isoderivative chromosome	2
Unbalanced aberrations involving two or more chromosomes	Unbalanced translocation Unbalanced insertion Derivative chromosome Complex ring chromosome Isoderivative chromosome	2
Ploidy abnormalities	Multiplication of complete chromosome set (normal or aberrant)	1
Multiple clones (subclones or independent clones)	Count chromosome abnormalities in each clone/subclone separately Number of chromosome abnormalities is defined by the clone with highest number of abnormalities *For composite karyotype* Count clonal chromosomal aberrations in metaphase with highest number of abnormalities	
Constitutional abnormalities	Do not include in the count; if unknown then include	0

* Includes multiple of one chromosome.

ISCN 2020

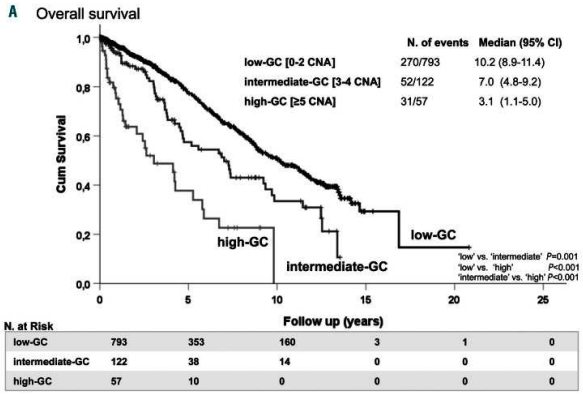
Il est important pour définir le nombre d'anomalies de compter TOUTES les anomalies de l'échantillon et pas seulement celles présentes dans le clone le plus complexe



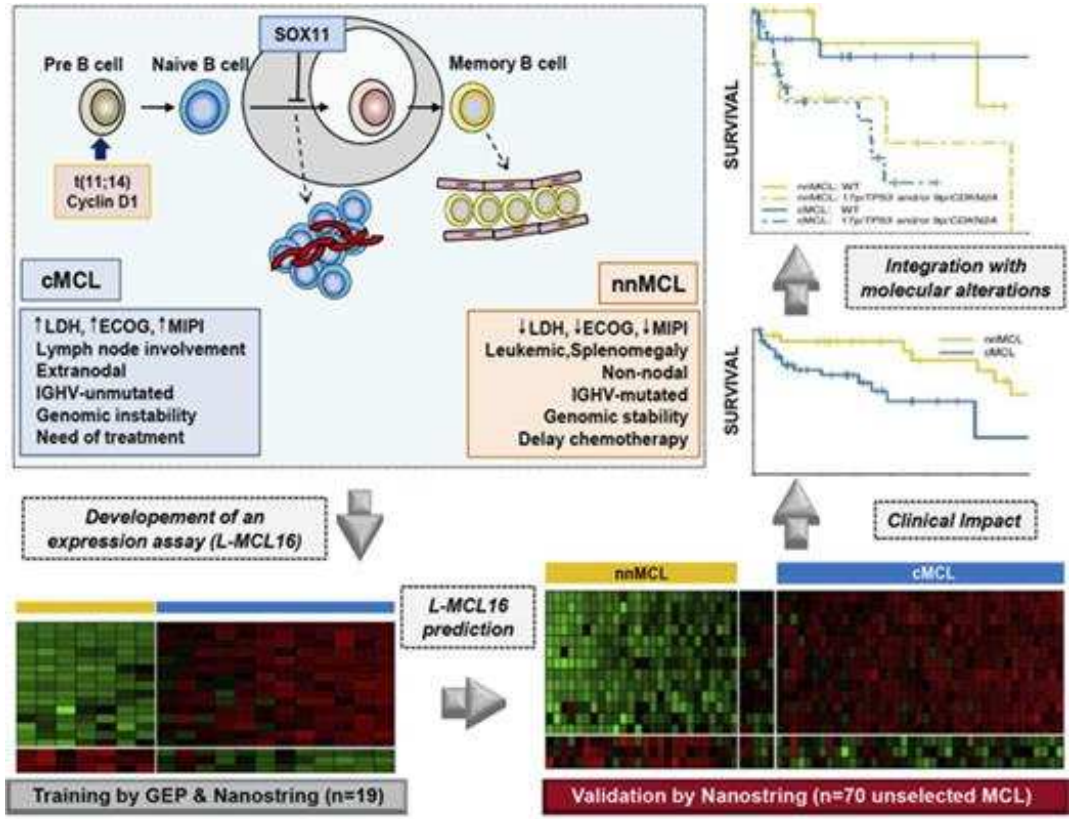
Schanz, Genes, Chromosomes and Cancer, 2018

Diagnosis	Karyotype	Cytogenetic consequences	Number of CA according to the literature	Complexity according to the literature	Number of CA with the ISCN 2020 system	Complexity with the ISCN 2020 system
MDS	**45,X,-Y[3]/45,sl,del(20)(q11)[10]/46,sl,+8[4]/45,sl,+8,-21[4]**	loss of Y loss 20q +8 -21	4	CK>3	3	CK=3
CLL	**46,XY,del(11)(q14q24)[13]/47,XY,t(2;17)(p21;q21),+12[7]**	loss 11q t(2;17) +12	3	CK	2	Not CK

FISH, SNPa, CGHa, séquençage du génome entier …. Les autres techniques génomiques sont complémentaires plutôt que substituables à la CG conventionnelle



Leeksma et al., Hematologica , 2021



Clot et al., Blood , 2018

Cartographie optique de l'ADN / OGM

Merci pour votre attention

Merci à Florence Nguyen-Khac pour son énorme travail de coordination

Merci aux « experts »

Merci au GFCH Groupe Francophone de Cytogénétique Hématologique