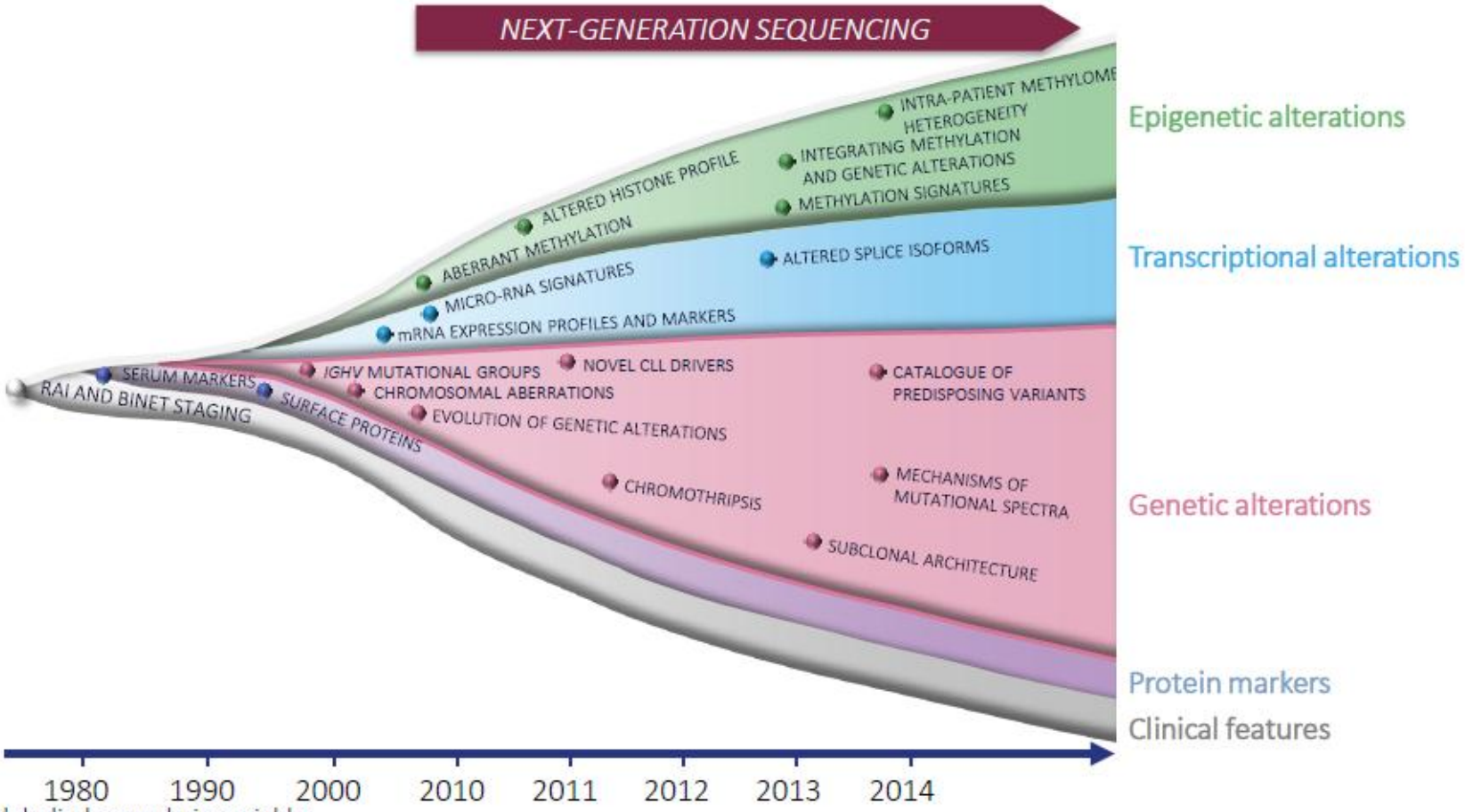
Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations and clinical impact.

Baliakas P, Jeromin S, Iskas M, Puiggros A, Plevova K, NguyenKhac F, Davis Z, Rigolin GM, Visentin A, Xochelli A, Delgado J, Baran-Marszak F, Stalika E, Abrisqueta P, Durechova K, Papaioannou G, Eclache V, Dimou M, Iliakis T, Collado R, Doubek M, Calasanz MJ, Ruiz-Xiville N, Moreno C, Jarosova M, Leeksma AC, Panayiotidis P, Podgornik H, Cymbalista F, Anagnostopoulos A, Trentin L, Stavroyianni N, Davi F, Ghia P, Kater AP, Cuneo A, Pospisilova S, Espinet B, Athanasiadou A, Oscier D, Haferlach C, Stamatopoulos K.

Blood. 2019 Jan 2

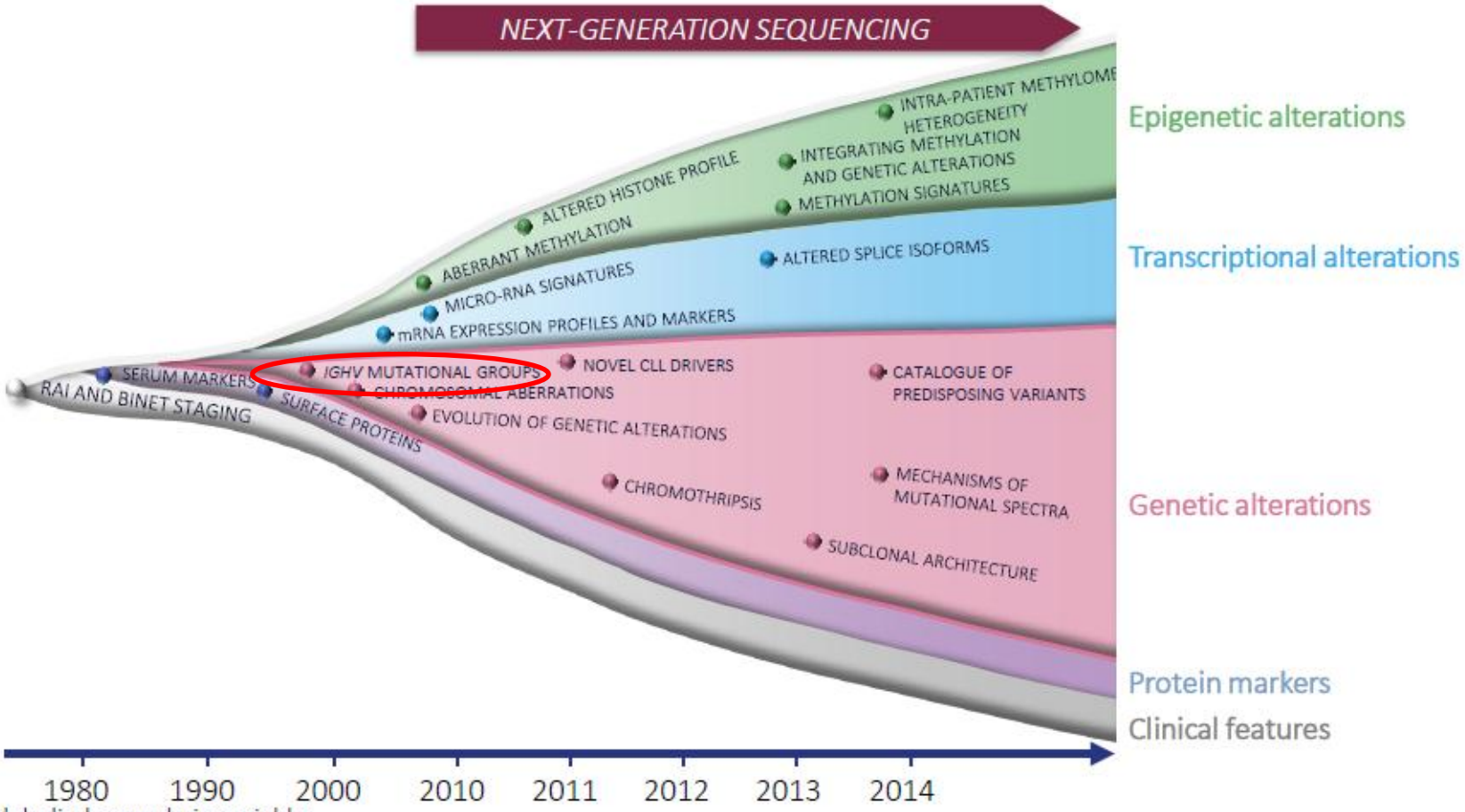
Rappels I



IGHV, immunoglobulin heavy chain variable.

Gruber M, Wu C. *Semin Hematol* 2014;**51**:177–87.

Rappels I



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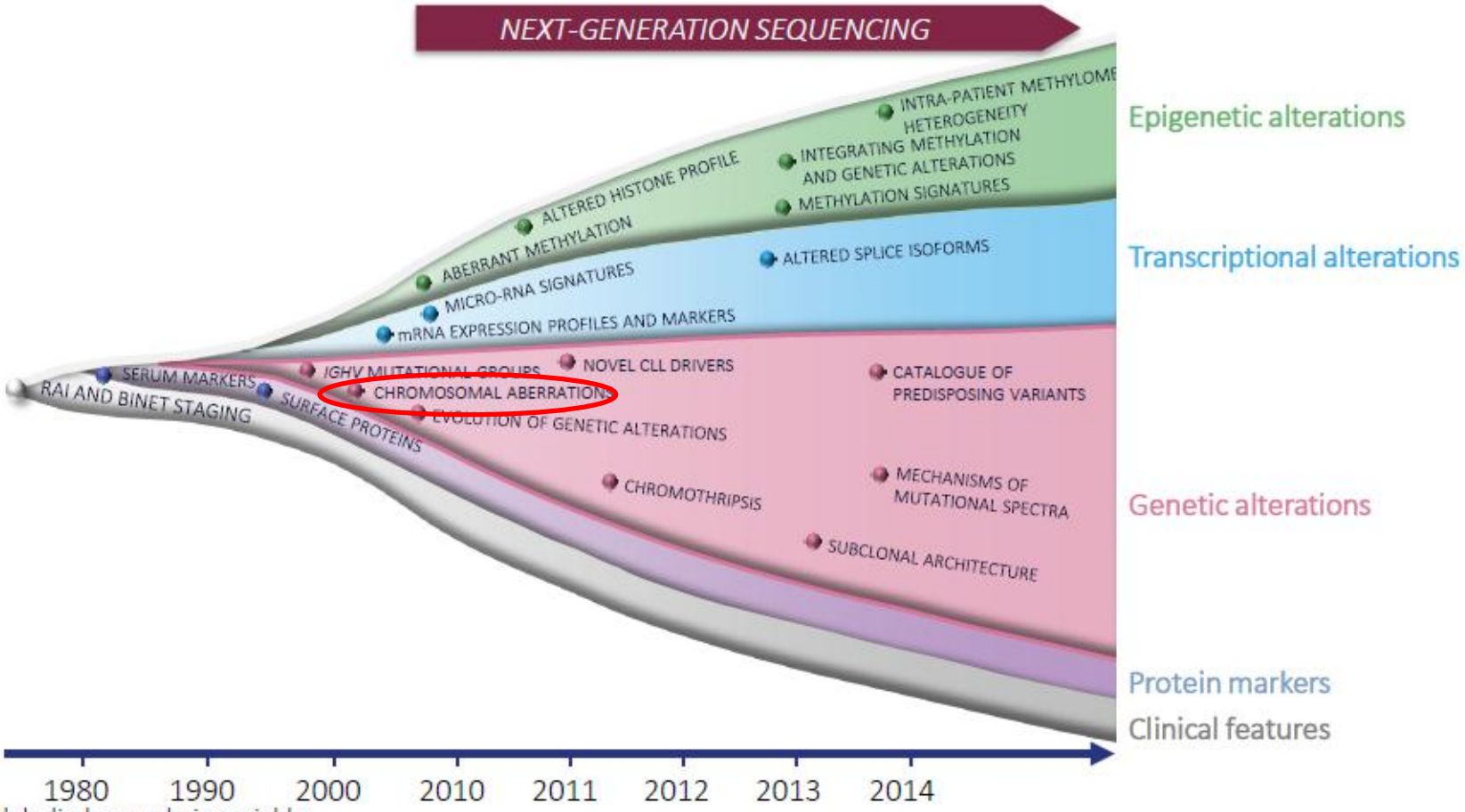
Hamblin, Blood 1999; Damle, Blood 1999

Rappels I



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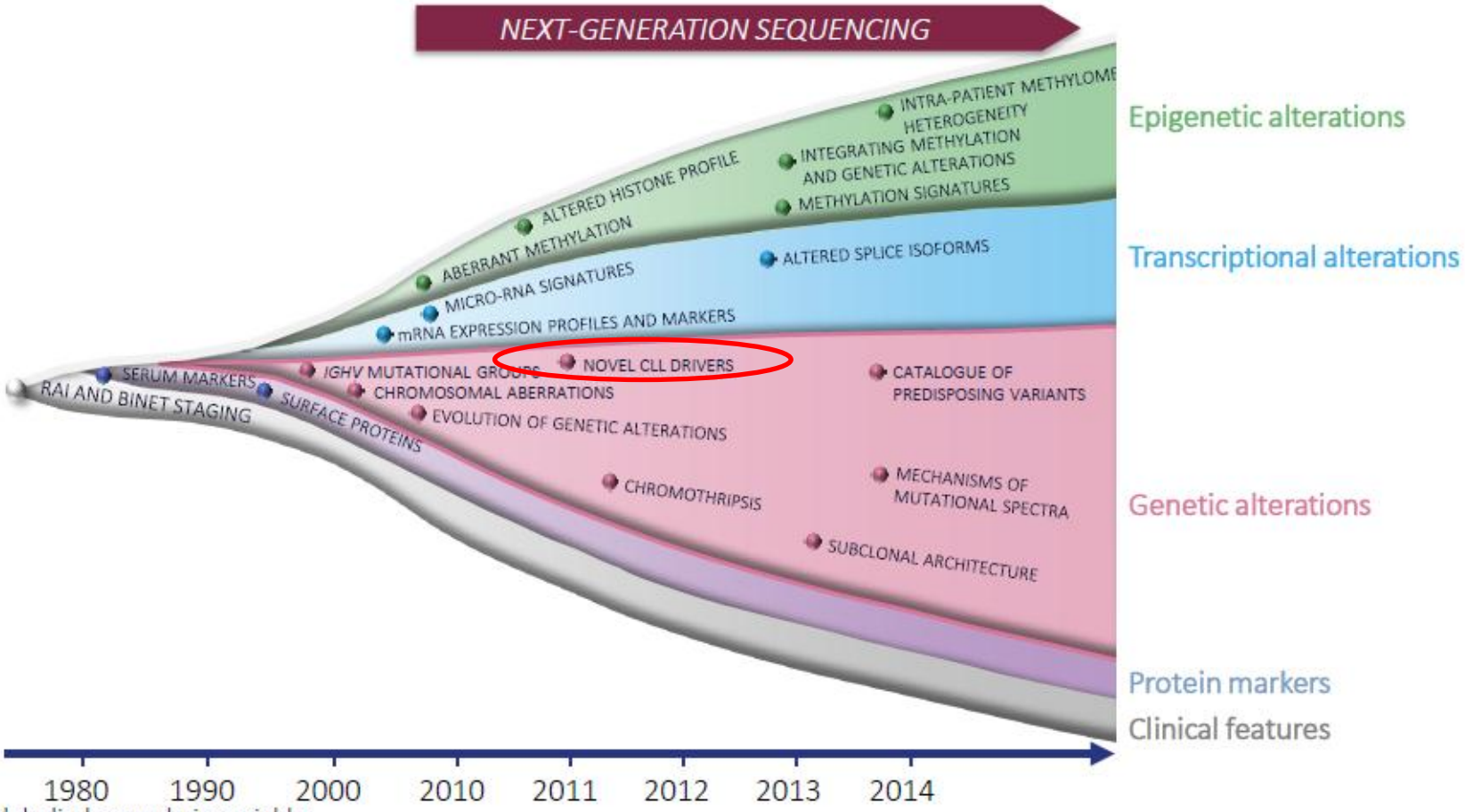
Döhner, NEJM, 2000

Rappels I



IGHV, immunoglobulin heavy chain variable.

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Puente, Nature, 2011

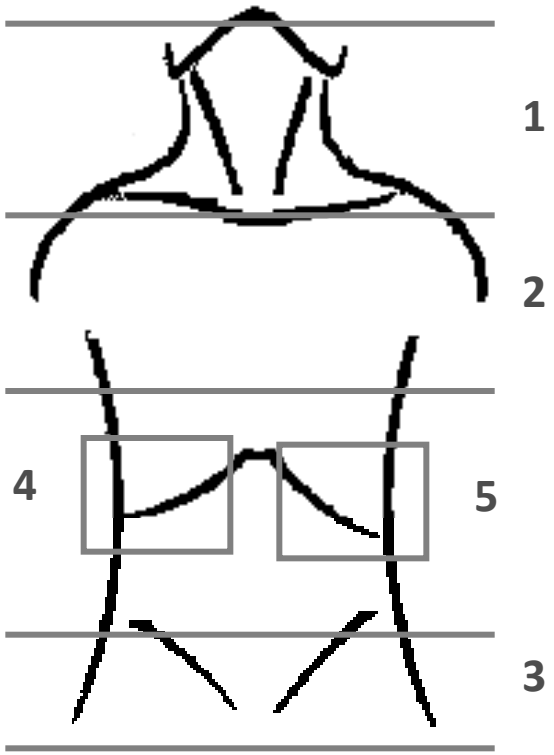
Leucémie lymphoïde chronique (LLC)

- plus fréquente des leucémies de l'adulte caucasien (incidence ≈ 3.5 nouveaux cas pour 100 000 hab/an)
- âge médian au diagnostic : 72 ans (75% > 65 ans et 50% > 75 ans)
- sex ratio H/F : 1,5-2/1
- diagnostic aisé (morphologie et immunophénotype : score de Matutes ≥ 4)
- lymphocytes B clonaux > 5 x 10^e9/L sinon diagnostic de MBL (« monoclonal B-cell lymphocytosis ») de type LLC
- lymphocytose B monoclonale : 3.5 -12% individus sains / « low count », « high count » / État pré-LLC ?
- stade A dans la majorité des cas mais évolutivité potentielle variable et prédictible avec paramètres biologiques simples
- décision de traitement sur les mêmes critères quel que soit l'âge : stade C ou A/B avec critère de maladie active

LLC □ classification de Binet

stade A	Hb ≥ 100 g/l et plaq ≥ 100 x 10^9/l < 3 aires lymphoïdes atteintes
stade B	Hb ≥ 100 g/l et plaq ≥ 100 x 10^9/l ≥ 3 aires lymphoïdes atteintes
stade C	Hb < 100 g/l et/ou plaq < 100 x 10^9/l quel que soit le nombre d'aires lymphoïdes atteintes

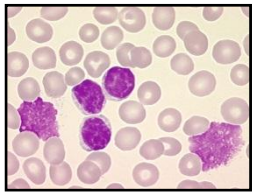
définition des aires lymphoïdes



70 à 80% de stades A au moment du diagnostic

Binet et al., Cancer 1981,

(Autre classification clinico-biologique : Rai *Rai et al., Blood 1975*)



CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
A heterogeneous disease

* Clinical and Biological **heterogeneity**

  - *IGHV* status mutated/ unmutated
  - Cytogenetic abnormalities
    - 13q14 deletion (*DLEU2/MIR15A-MIR16-1*) : 55%
    - Trisomy 12 : ~ 15%
    - 11q22 deletion (*ATM*, *BIRC3*) : 6% (Stages A) ; 20% (Stages B/C)
    - 17p13 deletion (*TP53*) : 5-8% (Diagnosis) ; 40% (Refractory CLL)
  - Mutations : *NOTCH1*, *SF3B1*, *TP53*….(<20%)

* **Molecular basis** of the disease heterogeneity still unclear

*** Drug resistance** associated in 40% of patients with *TP53* mutations/deletions (dysfunction)

Anomalies chromosomiques dans la LLC

Anomalies détectées dans plus de 80% des cas
Non spécifiques

Anomalies « classiques »

- **Délétion 13q : 55%**
- **Trisomie 12 : 10-15%**
- **Délétion 11q : 6% (Stades A) ; 20% (Stades B/C)**
- **Délétion 17p : 5-8% (Diagnostic) ; 40% (LLC réfractaires)**

Anomalies moins connues mais fréquentes

- **Délétion 6q : 6%**
- **Gain 2p : 7-26% (LLC réfractaires)**

Anomalies rares mais récurrentes (< 5%)

trisomie 18, trisomie 19, gain 8q24, t(14;18), t(14;19), t(8;14), délétion 14q, délétion 8p

(Pour revue, F Nguyen-Khac et al., Ann Biol Clin 2016)

Rappels III

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
Complete blood count and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment prior to treatment		
History and physical, performance status	Always	Always
Complete blood count and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests prior to treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum $ß_2$-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound**	Possible	NGI

NGI, not generally indicated

*, conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful prior to therapy, if established methodology is available.

IwCLL recommendations, Hallek et al., Blood 2018

Rappels III

Diagnostic test	General practice	Clinical trial
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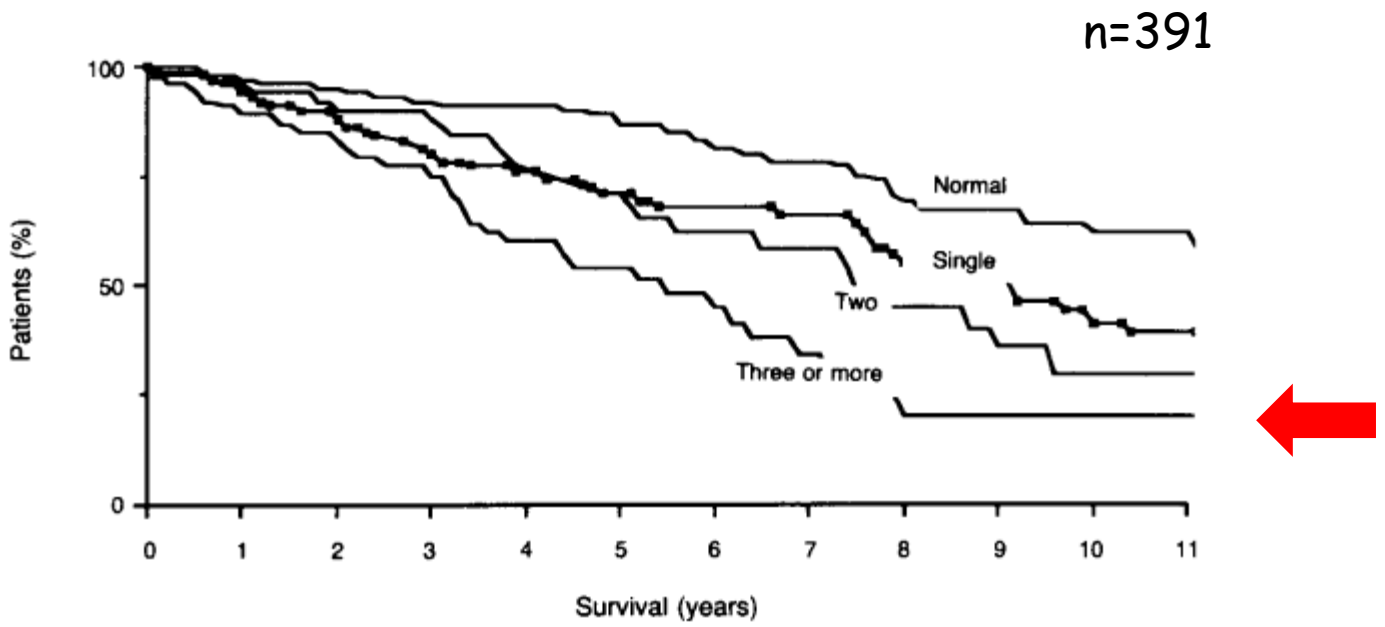
IwCLL recommendations, Hallek et al., Blood 2018

Rappels IV : caryotype complexe dans la LLC

CK (≥ 3 anomalies) est associé à une survie globale (OS) et un délai jusqu'au 1er traitement (TTFT) raccourcis



Caryotypes complexes : 53/391 (13%)
(non traités ; 276 (71%) Stade A, 115 (29%) Stades B/C)

Juliusson G et al., N Engl J Med 1990

Rappels IV

- Nombreuses études : caryotype complexe : marqueur indépendant
- FCR (chimio-immunothérapie)
- ibrutinib (inhibiteur btk)
- venetoclax (inhibiteur bcl2)

→But : place du caryotype complexe dans la prise en charge de la LLC sur une large série ?

5290 patients (CLL (5082)+ high count MBL (397)), 17 institutions
CK i.e. ≥3 structural and/or numerical aberrations : 794/5290 cases (15%)
cases with clinical MBL (n=30/383, 8%)

Table 1. Main clinicobiological features of the patients included in the study.

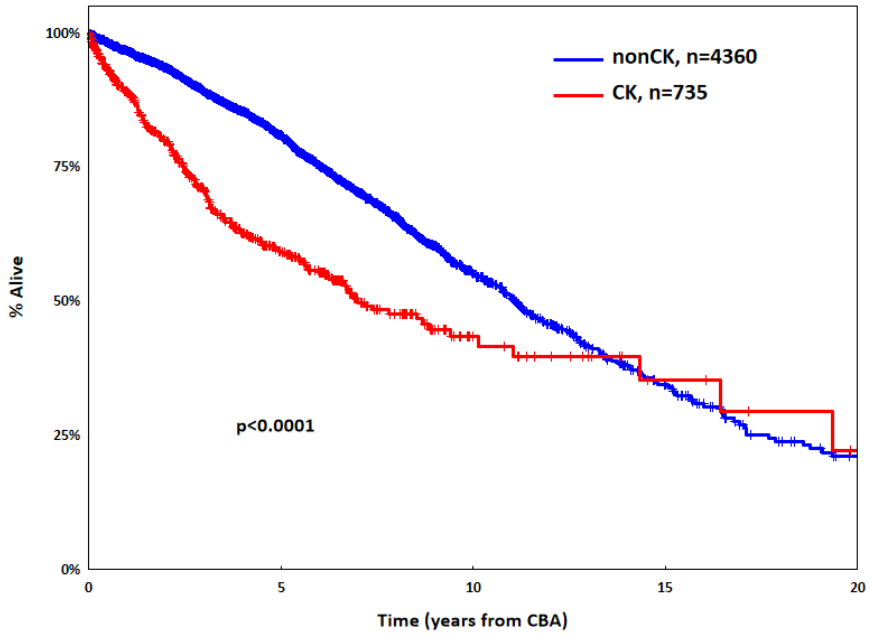
Feature	Entire cohort (n=5290)	Non CK (0-2 abs, n=4496)	CK ≥3 abs, n=794	Low-CK Intermediate-CK, 3-4abs n=523	High-CK ≥5 abs n=271	P-value nonCK vs CK	P-value Low-/intermediate-CK vs high-CK
Male	3302/5290, 62%	2790/4496, 62%	522/794, 66%	351/523, 67%	171/271, 63%	0.047	0.56
Median age (diagnosis)	64.6 years	64.3 years	64.7 years	64.2 years	66.1 years	0.58	0.02
MBL	383/4454, 9%	353/3813, 9%	30/641, 5%	27/412, 7%	3/229, 1%	0.0001	0.004
Binet A	3030/4454, 68%	2643/3813, 69%	387/641, 60%	263/412, 64%	124/229, 54%	<0.0001	0.017
Binet B/C	1041/4454, 23%	817/3813, 22%	224/641, 35%	122/412, 29%	102/229, 45%	<0.0001	0.0002
U-CLL	1514/3453, 44%	1187/2939, 40%	327/514, 64%	201/351, 57%	126/163, 77%	<0.0001	<0.0001
***TP53*abs**	657/4968, 13%	337/4204, 8%	320/764, 42%	151/501, 30%	169/263, 64%	<0.0001	<0.0001
del(11q)	487/4500, 11%	353/3714, 9%	165/622, 26%	119/413, 29%	46/209, 22%	<0.0001	0.07
Trisomy 12	685/4500, 15%	557/3714, 15%	150/622, 24%	117/413, 28%	33/209, 16%	<0.0001	0.0005
idel(13q)	1734/4500, 38%	1621/3714, 44%	113/622, 18%	86/413, 21%	27/209, 13%	<0.0001	<0.0001

CK: complex karyotype, ≥3 aberrations; low-CK: 3 aberrations; intermediate-CK: 4 aberrations; high-CK: ≥5 aberrations; MBL: Monoclonal B-cell lymphocytosis, U-CLL: Unmutated IGHV genes, *TP53*abs: deletion of chromosoe 17p and/or *TP53* mutation, del(11q): deletion of chromosome 11q, idel(13q) isolated deletion of chromosome 13q. Statistical significant level was defined as 0.008 following the Bonferroni correction for multiple testing.

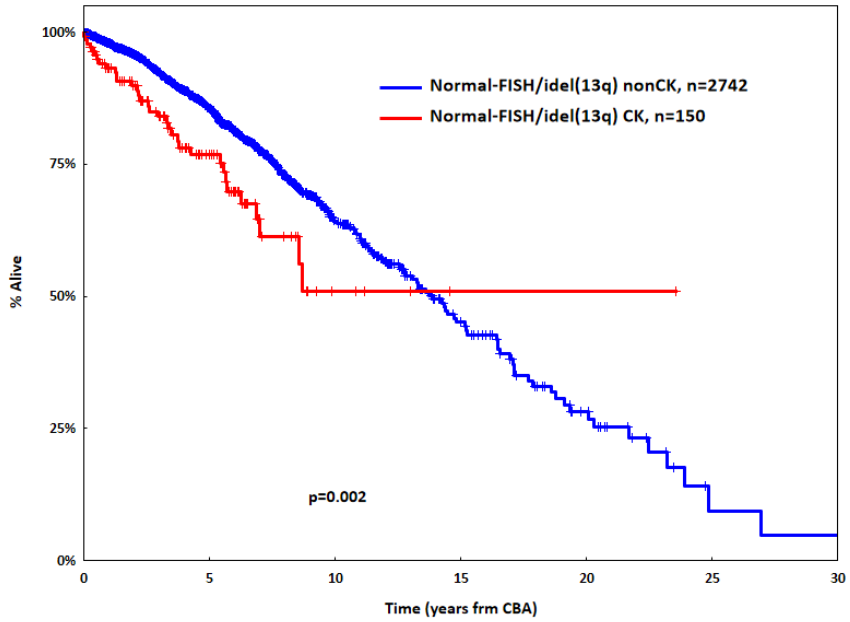
CK (≥ 3) : survie plus courte

Y compris dans le groupe FISH Normal/del13q isolée

1A



1B



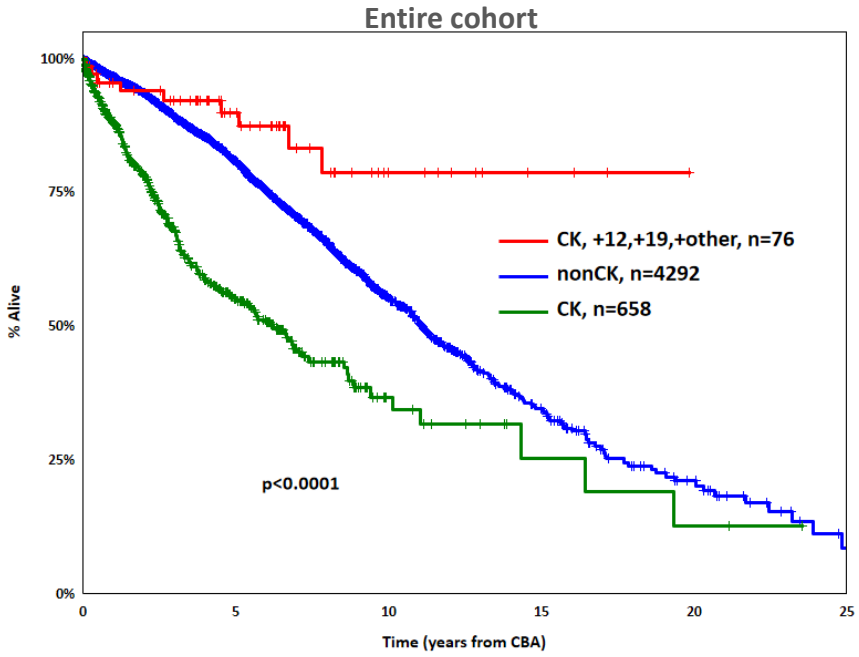
Supplemental Table 4. Univariable and multivariable analysis for Overall Survival (OS).

Parameter	Univariable analysis (n=5095)			Multivariable analysis (n=2376)		
	HR	95% CI	p-value	HR	95% CI	p-value
Male	1.202	1.070-1.350	0.001	1.123	0.946-1.338	0.18
CK (≥3abs)	2.059	1.789-2.370	<0.001	1.578	1.267-1.966	<0.0001
idel(13q)	0.894	0.792-1.010	0.07	-	-	-
Trisomy 12	1.310	1.125-1.525	<0.001	1.139	0.926-1.401	0.21
del(11q)	1.942	1.659-2.273	<0.001	1.109	0.883-1.393	0.37
***TP53*abs**	2.904	2.517-3.350	<0.001	2.183	1.761-2.707	<0.001
U-CLL	2.851	2.467-3.295	<0.001	2.371	1.973-2.850	<0.001
Binet B/C	2.036	1.793-2.312	<0.001	1.585	1.324-1.897	<0.001

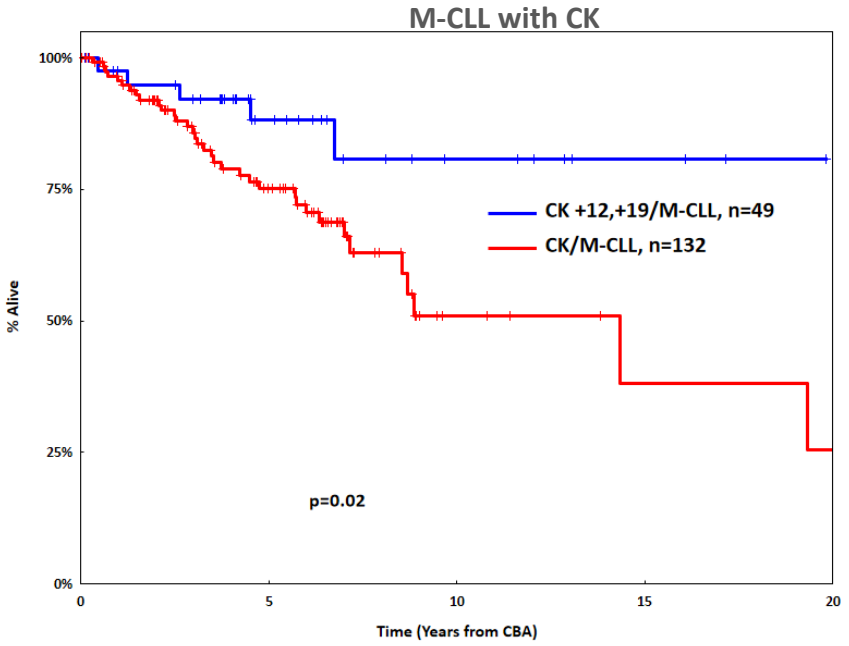
CK: complex karyotype; U-CLL: Unmutated IGHV genes; *TP53*abs: deletion of chromosome 17p detected by FISH and/or *TP53* mutation; del(11q): deletion of chromosome 11q determined by FISH; idel(13q): isolated deletion of chromosome 13q detected by FISH.

- CK +12+19+ other : survie plus longue
- Parmi les CK IGHV-M : +12+19+other : survie plus longue

1C



1D

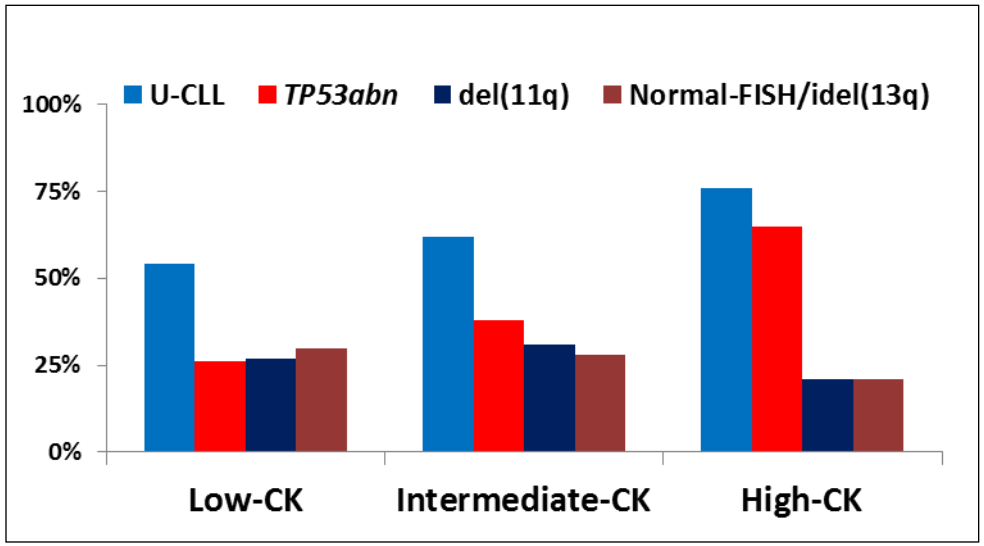


Supplemental Table 5. Main clinicobiological features of patients with complex karyotype (CK) carrying +12+19 plus another trisomy or structural abnormality.

	+12+19+other trisomy (n=43)	+12+19+structural (n=38)	P-value
Age at diagnosis (median)	64.6	56.6	0.7
Male	33/43, 77%	30/38, 79%	0.81
Binet B/C	8/39, 21%	6/24, 25%	0.68
M-CLL	19/21, 90%	32/34, 94%	0.61
del(13q)	39/43, 91%	30/35, 86%	0.49
del(11q)	0/39, 0%	1/36, 0.3%	0.29
*TP53*abs	2/41, 0.5%	1/37, 0.3%	0.61

CK: complex karyotype; M-CLL: Mutated IGHV genes; *TP53*abs: deletion of chromosome 17p detected by FISH and/or *TP53* mutation; del(11q): deletion of chromosome 11q detected by FISH; del(13q): deletion of chromosome 13q detected by FISH. Statistical significant level was defined as 0.008 following the Bonferroni correction for multiple testing.

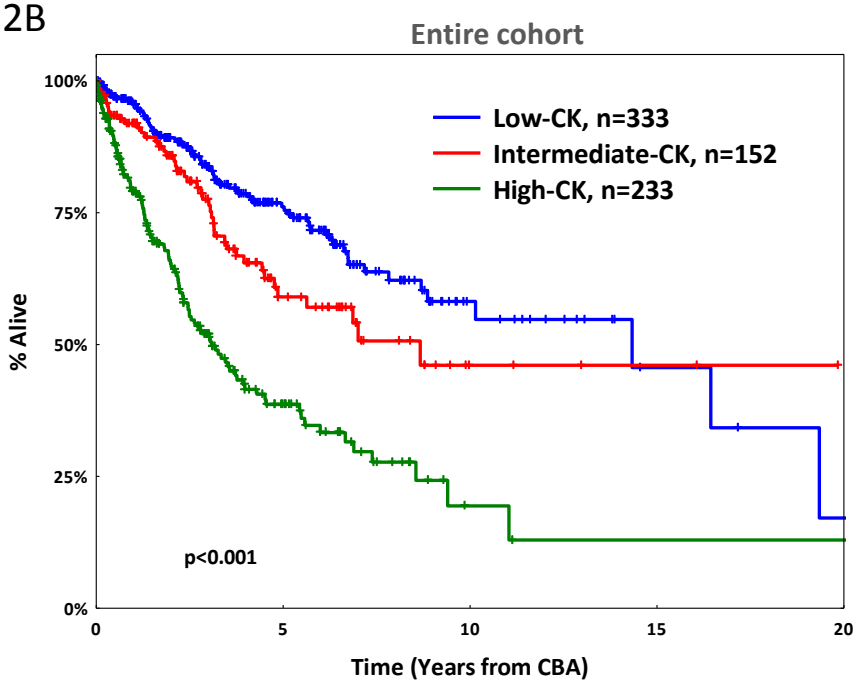
2A



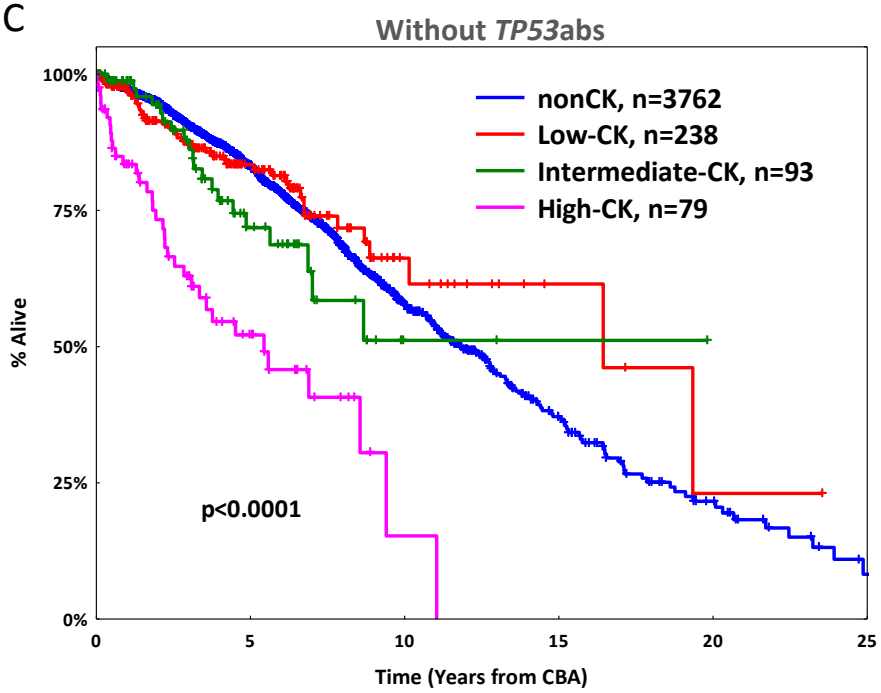
→HCK (≥5) : enrichis en *IGHV* non mutés et *TP53* anomalies

→ del13q isolée : même répartition

2B

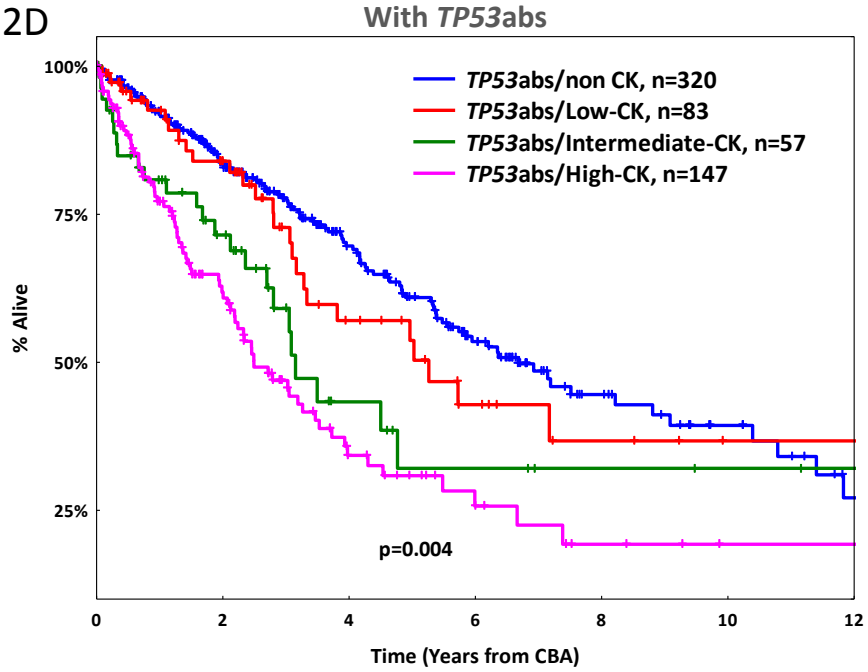

Entire cohort
100%
75%
50%
25%
0%
% Alive
Low-CK, n=333
Intermediate-CK, n=152
High-CK, n=233
p<0.001
0
5
10
15
20
Time (Years from CBA)

2C



→Sans anomalie *TP53*, seul HCK : survie plus courte

2D



→Avec anomalie *TP53* : le nombre d'anomalies aggrave le mauvais pronostic
HCK : survie la plus courte

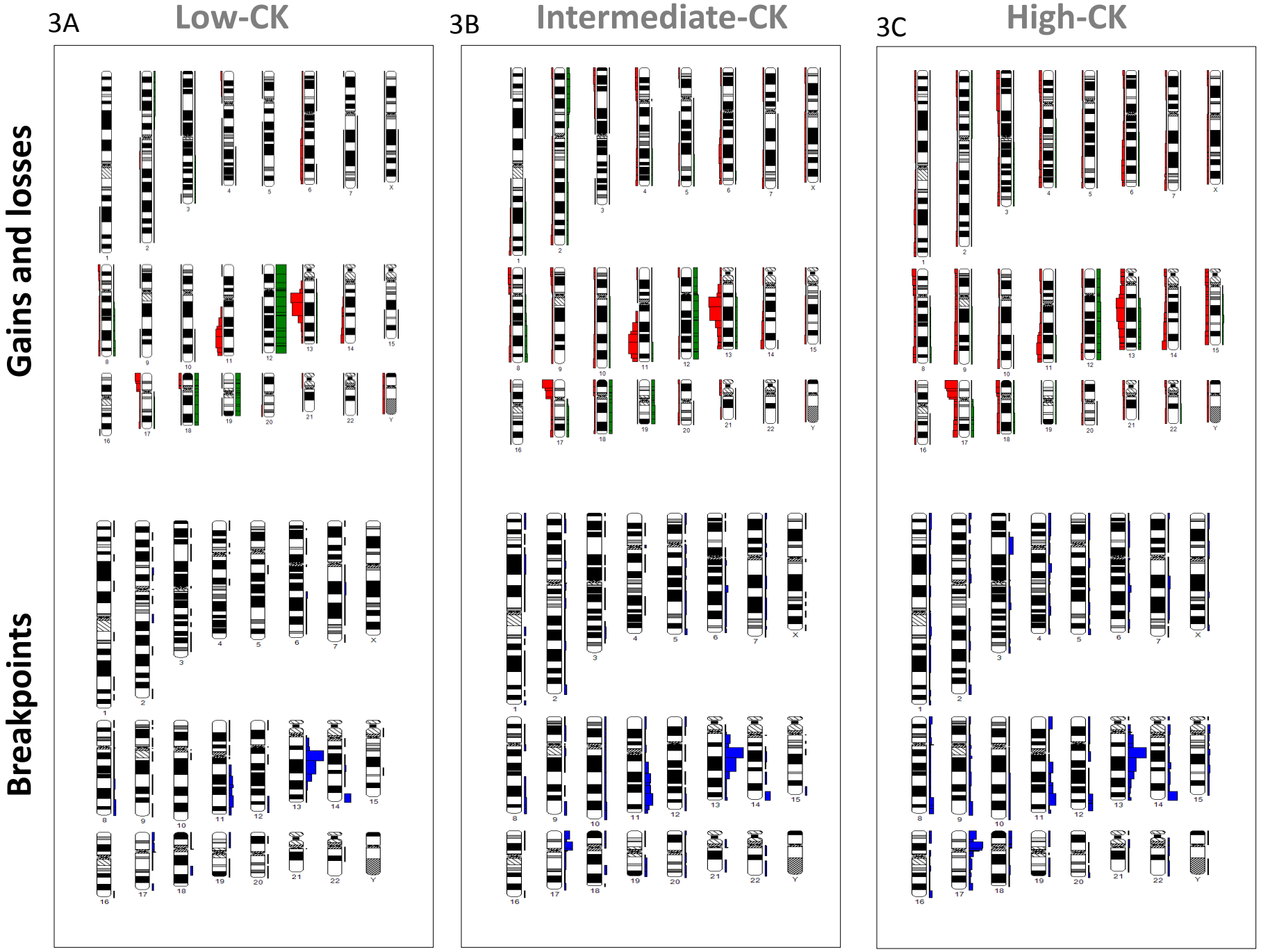
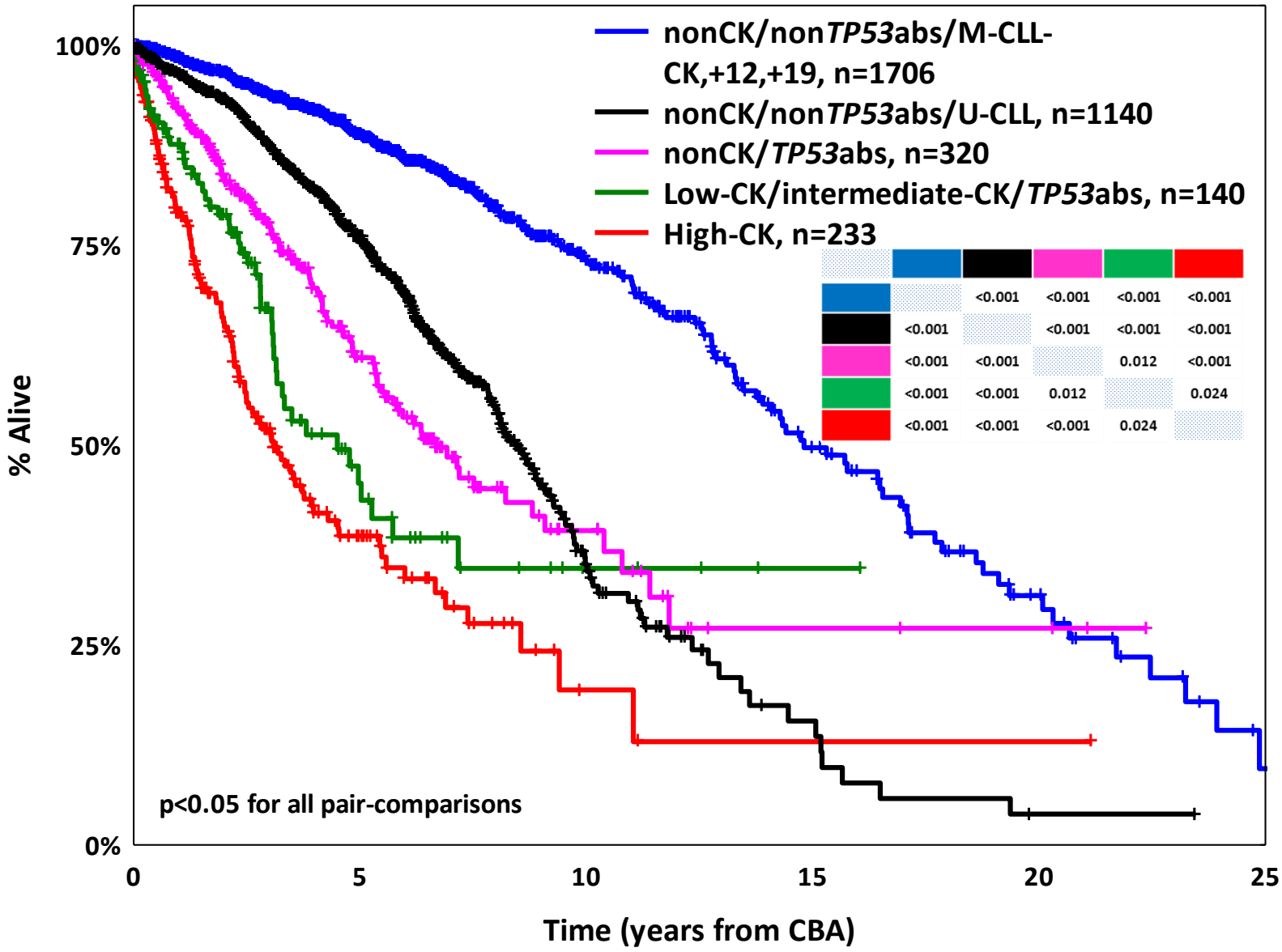

3A
Low-CK
3B
Intermediate-CK
3C
High-CK
Gains and losses
Breakpoints

Table 2. Univariable and multivariable analysis for Overall Survival (OS). High-CK (≥5 aberrations) is an independent predictor for shorter OS contrasting low-CK/intermediate-CK (3 and 4 aberrations respectively) which failed to retain significance in the multivariable analysis.

Parameter	Univariable analysis (n=5095)			Multivariable analysis (n=2376)		
	HR	95% CI	p-value	HR	95% CI	p-value
Male	1.202	1.070-1.350	0.001	1.159	0.974-1.379	0.09
Low-CK/ intermediate-CK	1.216	1.007-1.470	0.042	1.214	0.918-1.606	0.17
High-CK	2.059	1.789-2.370	<0.001	2.226	1.603-3.092	<0.001
idel(13q)	0.894	0.792-1.010	0.07	-	-	-
Trisomy 12	1.310	1.125-1.525	<0.001	1.206	0.979-1.487	0.08
del(11q)	1.942	1.659-2.273	<0.001	1.152	0.914-1.451	0.23
***TP53*abs**	2.904	2.517-3.350	<0.001	1.960	1.558-2.465	<0.001
U-CLL	2.851	2.467-3.295	<0.001	2.320	1.927-2.793	<0.001
Binet B/C	2.036	1.793-2.312	<0.001	1.575	1.313-1.888	<0.001

CK: complex karyotype; Low-CK: 3 aberrations; intermediate-CK: 4 aberrations; High-CK: ≥5 aberrations; U-CLL: Unmutated IGHV genes; *TP53*abs: deletion of chromosome 17p detected by FISH and/or *TP53* mutation; del(11q): deletion of chromosome 11q; idel(13q): isolated deletion of chromosome 13q detected by FISH.

Modèle hiérarchique



→: IGHV-M/no CK/no del17p/TP53mut ou CK+12,+19 : bon