MYELOME MULTIPLE
MGUS - SMM

GFCH
13/10/21
Dominique Penther

MGUS

Epidémiologie MGUS

- Prévalence : 2.4%
- Age médian du diagnostic 70 ans
- 2% des MGUS < 40 ans

3 critères

- Protéine monoclonale (non IgM) < 3g/dL
- Plasmocytose médullaire < 10%
- Absence de critères CRAB

MGCS : monoclonal gammapathy of clinical significance

- Lésions cliniques liées à la paraprotéine
- Dépôts de chaines légères ou chaines lourdes (amylose AL, cryo type I)
- Activité auto AC de la paraprotéine (cryo mixte, agglutinines froides, déficit en inhibiteurs de C1 angioedeme, neuropathie IgM
- Activation de la voie du complément
- POEMS syndrome
- Anomalie d'adsorption des protéines (FW,
- Syndrome de Schnitzer, sclérodermie, syndrome TEMPI

=> traitement à instaurer

MGRS : gammapathie de signification rénale

Gammapathie néphrotoxique :

- MGUS
- SMM
- Waldenström
- lymphocytose B monoclonale
- LNH bas grade

=> dépôts de chaines légères ou de chaines lourdes

SMOLDERING MYELOMA

Définition IMWG 2003

- M proteine ≥ 3g/dL ou protéine U ≥ 500 mg/24h
- Ou 10 à 60 % de plasmocytes
- sans critères MDE (myeloma defining events) ou amylose

=> Risque de progression vers MM supérieur/MGUS

IMWG 2014 : ultra high risk SMM => risque de progression majeur de 80%

- Ratio free light chain sFLC > ou = 100
- Plus de 60% de plasmocytes médullaires
- Plus de 2 lésions osseuses

=> à traiter comme MM

MYELOME MULTIPLE

Epidémiologie

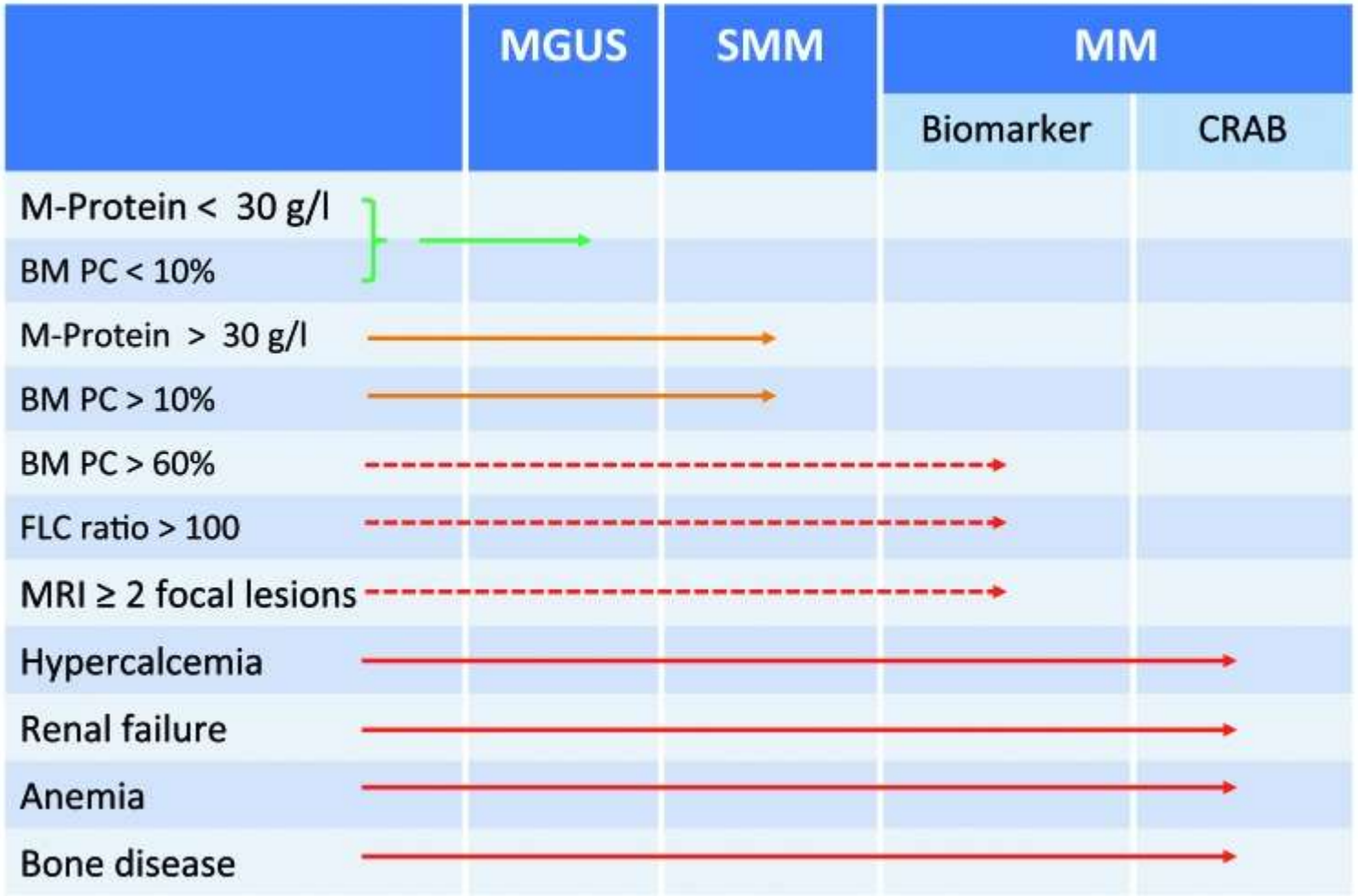
- 1% des cancers
- 10% des hémopathies malignes
- Plus fréquent chez les hommes/femmes
- Age médian au diagnostic : 65 ans

2 critères suivants

- Plasmocytose clonale médullaire ≥ 10% ou plasmocytome extra médullaire prouvé par biopsie
- Au moins 1 des critères MDE
    - hypercalcemie
    - insuffisance rénale : clearance < 40 mL/min ou creatinine >177 µmol/L (> 2mg/dL)
    - anemie
    - au moins 1 lésions osseuses osteolytique (Radio, TDM, PET)
    - plasmocytose médullaire ≥ 60%
    - ratio FLC ≥ 100
    - > 1 lésion en IRM d'au moins 5 mm

Diagnostic différentiel MGUS/SMM/MM

Infiltration médullaire
Signes cliniques
Biomarqueurs pour traitement

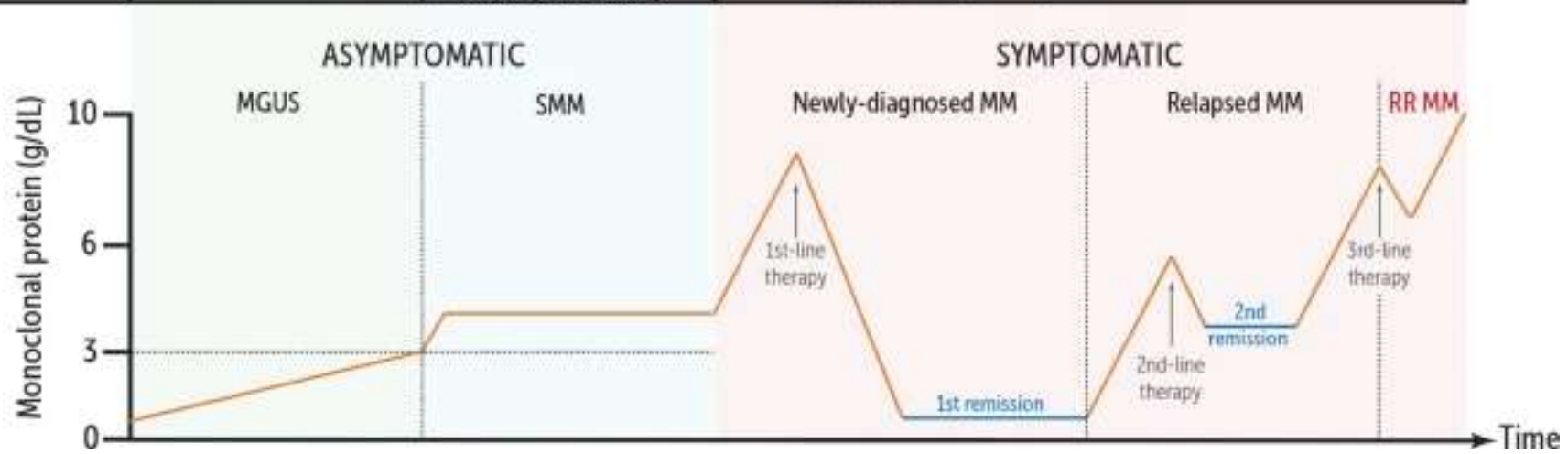


Critères CRAB
hyperCalcémia
Renal failure
Anemia
Lytic Bone lésion

Caers, Haematologica,2018

Modèle clinique de progression critères IMWG

Disease stage	MGUS	SMM	Active MM
Serum M-protein	<3 g/dL	≥3 g/dL	≥1 **myeloma defining events** + (1) or (2): End-organ damage (CRAB): any one of • Hypercalcemia, renal insufficiency, anemia, bone lesions Biomarkers of malignancy: • ≥60% clonal BM plasma cells, • Serum involved/uninvolved free light chain ratio ≥100 • >1 focal lesion on MRI ≥5mm in size (1) Clonal bone marrow plasma cells ≥10% or (2) Biopsy proven plasmacytoma
Urine M-protein	N/A	≥500 mg/day	
% BM plasma cells	<10%	10-60%	
Myeloma defining events	Absence of myeloma defining events or amyloidosis		
Progression risk	1% per year	10% per year (1st 5y) 3% per year (next 5y)	



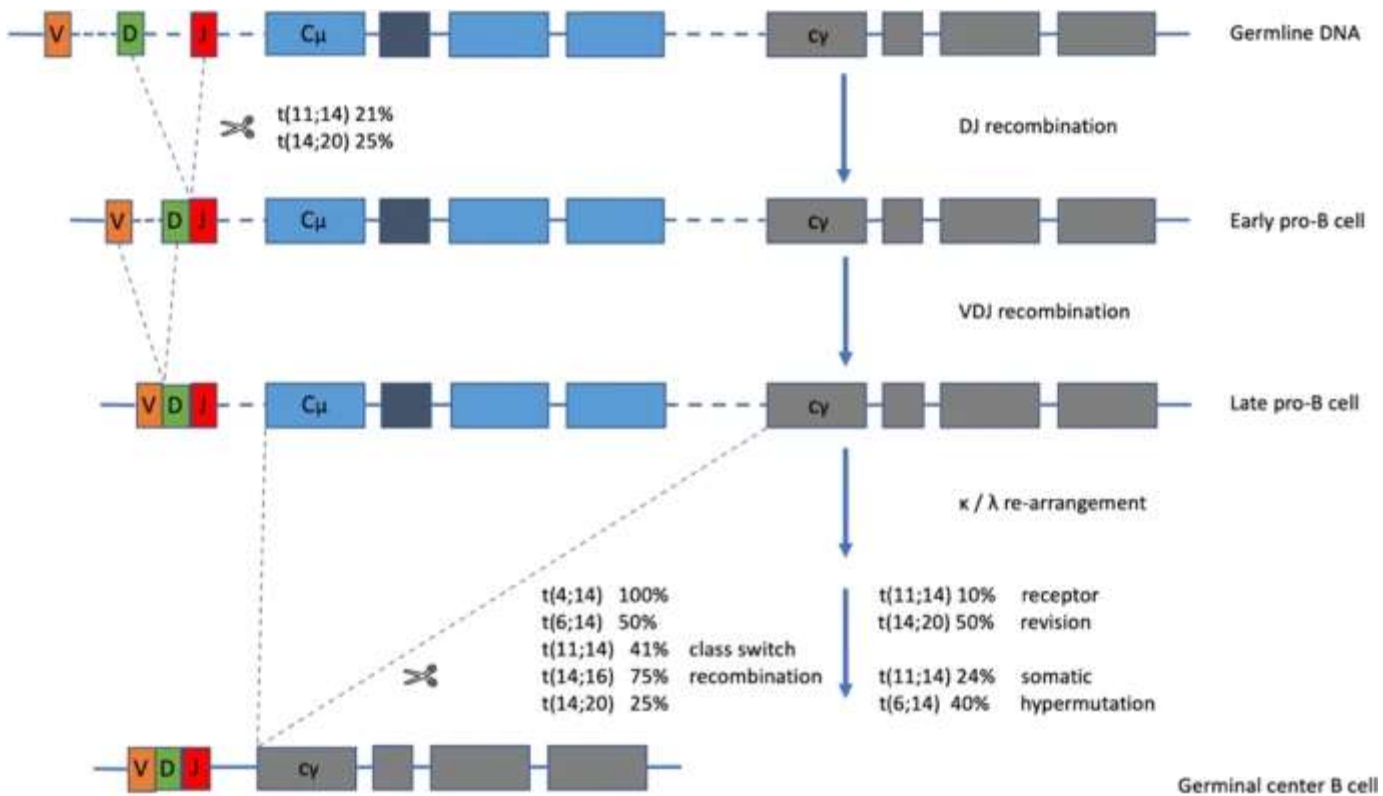
Ho,Leukemia,2020

Evènements moléculaires primaires et MM

Subtype	Gene(s)/chromosomes affected [a]	Percentage of myeloma patients
Trisomic multiple myeloma	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21	42
IgH translocated multiple myeloma		30
t(11;14) (q13;q32)	*CCND1* (cyclin D1)	15
t(4;14) (p16;q32)	*FGFR-3* and MMSET	6
t(14;16) (q32;q23)	*C-MAF*	4
t(14;20) (q32;q11)	*MAFB*	<1
Other IgH translocations [a]	*CCND3* (cyclin D3) in t(6;14) multiple myeloma	5
Combined IgH translocated/trisomic multiple myeloma	Presence of trisomies and any one of the recurrent IgH translocations in the same patient	15
Isolated Monosomy 14	Few cases may represent 14q32 translocations involving unknown partner chromosomes	4.5
Other cytogenetic abnormalities in absence of IgH translocations or trisomy or monosomy 14		5.5
Normal		3

Rajkumar, Am J Hematol, 2018

Points de cassure en IGH



Neuse, Leukemia, 2020

Abnormality	Gene(s)/chromosomes affected	Frequency (%)		Implications in SMM	
		In MGUS	In MM	Progression risk	Median TTP
Hyperdiploidy: Trisomy(ies) without IgH abnormality	Trisomy of odd-numbered chromosomes (but not chromosomes 1, 13, 21)	50[a]	55[a]	Intermediate	3 years
IgH-translocations					
• t(11;14)	*CCND1*	12[a]	19[a]	Standard	5 years
• t(4;14)	*FGFR-3* and *MMSET*	9[a]	13[a]	High	2 years
• t(14;16)	*C-MAF*	3[a]	4[a]	Standard	5 years
• t(14;20)	*MAFB*	3[a]	1[a]	Standard	5 years
• t(6;14)	*CCND3*	0[a]	1[a]	Standard	5 years
IgH translocations with trisomy(ies)			15[b]	Standard	5 years
Isolated monosomy 14			4.5[b]	Standard	5 years
Other cytogenetic abnormalities in absence of			5.5[b]		

Abnormality	Gene(s) affected	Frequency (%)	
		In MGUS	In MM
Gains			
• 1q	*CKS1B* and *ANP32E*	25[a]	50[a]
• 12p	*LTBR*		
• 17q	*NIK*		
Deletions			
• 1p	*CDKN2C, FAF1, and FAM46C*	6[a]	40[a]
• 6q			33[b]
• 8p			25[b]
• 11q	*BIRC2* and *BIRC3*	7[a]	7[a]
• 13	*RB1* and *DIS3*	30[a]	70[a]
• 14q	*TRAF3*		38[b]
• 16q	*CYLD* and *WWOX*		35[b]
• 17p	*TP53*	1[a]	12[a]
t(8;14) MYC		3–4[a]	20[a]
MYC dysregulation	*MYC*	<1[a]	67[a]
• Constitutive NFKB activation	*TRAF6, CYLD*	<1[a]	20[a]

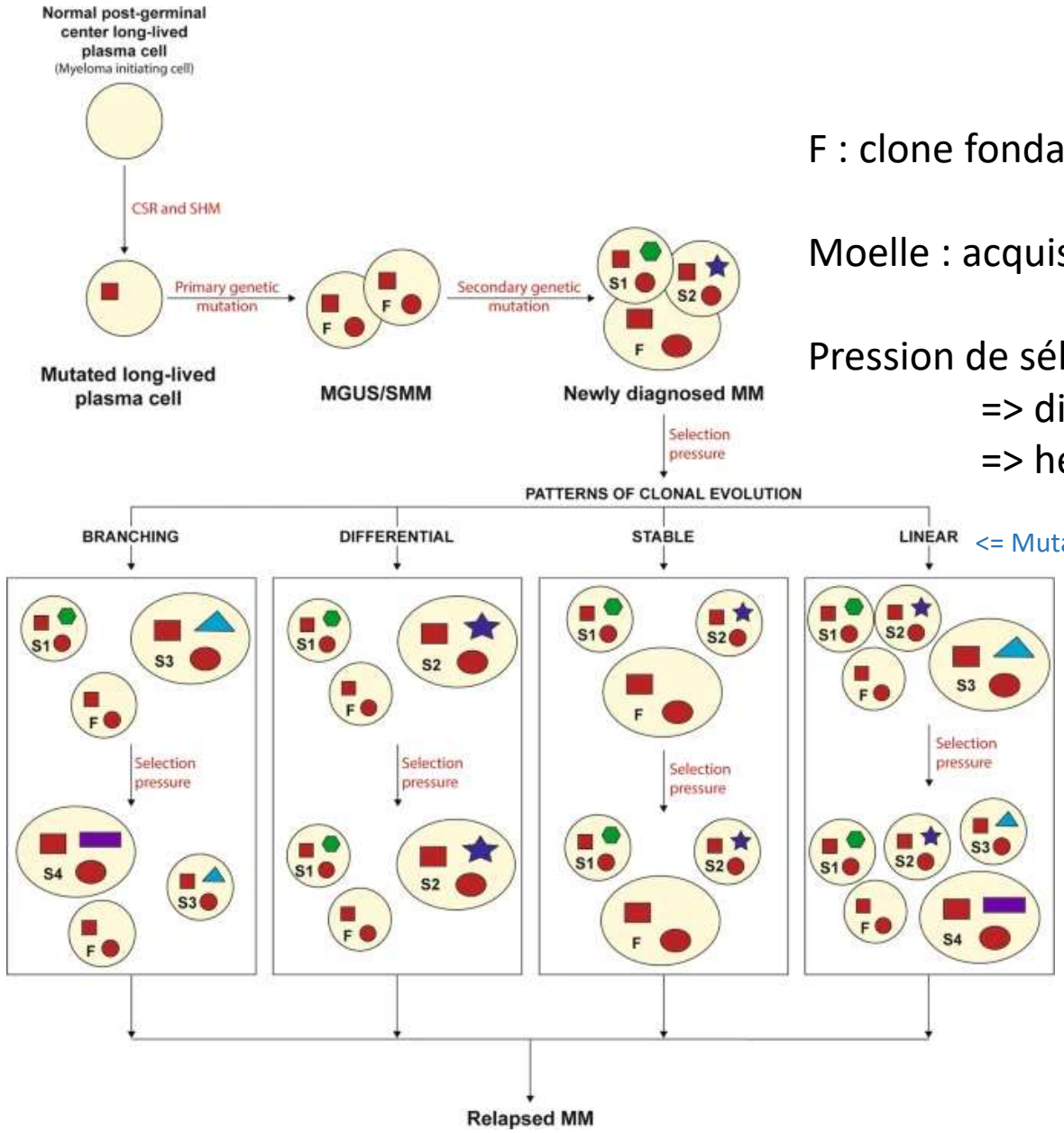
Anomalies cytogénétiques	Smoldering MM	Multiple myeloma
Trisomies	Intermediate-risk of progression, median TTP of 3 y	Good prognosis, standard-risk MM, median OS 7-10 y Most have myeloma bone disease at diagnosis Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard-risk of progression, median TTP of 5 y	Good prognosis, standard-risk MM, median OS 7-10 y
t(6;14) (p21;q32)	Standard-risk of progression, median TTP of 5 y	Good prognosis, standard-risk MM, median OS 7-10 y
t(4;14) (p16;q32)	High-risk of progression, median TTP of 2 y	High-risk MM, median OS 5 y Needs early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
t(14;16) (q32;q23)	Standard-risk of progression, median TTP of 5 y	High-risk MM, median OS 5 y Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard-risk of progression, median TTP of 5 y	High-risk MM, median OS 5 y; Needs early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance

Rajkumar, Am J Hematol, 2020

Anomalies cytogénétiques		
	Smoldering MM	Multiple myeloma
Gain(1q21)	High-risk of progression, median TTP of 2 y	High-risk MM, median OS 5 y; Needs early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
Del(17p)	High-risk of progression, median TTP of 2 y	High-risk MM, median OS 5 y; Needs early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
Trisomies plus any one of the IgH translocations	Standard-risk of progression, median TTP of 5 y	May ameliorate adverse prognosis conferred by high risk IgH translocations, and del 17p
Isolated monosomy 13, or isolated monosomy 14	Standard-risk of progression, median TTP of 5 y	Effect on prognosis is not clear
Normal	Low-risk of progression, median TTP of 7–10 y	Good prognosis, probably reflecting low tumor burden, median OS >7-10 y

Rajkumar, Am J Hematol, 2020

Modèle de progression clonale dans le MM



F : clone fondateur : switch, SHM, ano cytoG primaire

Moelle : acquisition d'anomalies supplémentaires => MM

Pression de sélection

=> différents profils d'évolution

=> hétérogénéité clonale

Mutations driver =>

<= Mutations driver

Mutations driver
Hétérogénéité
Sous clone dominant

Cibler mutation initiale

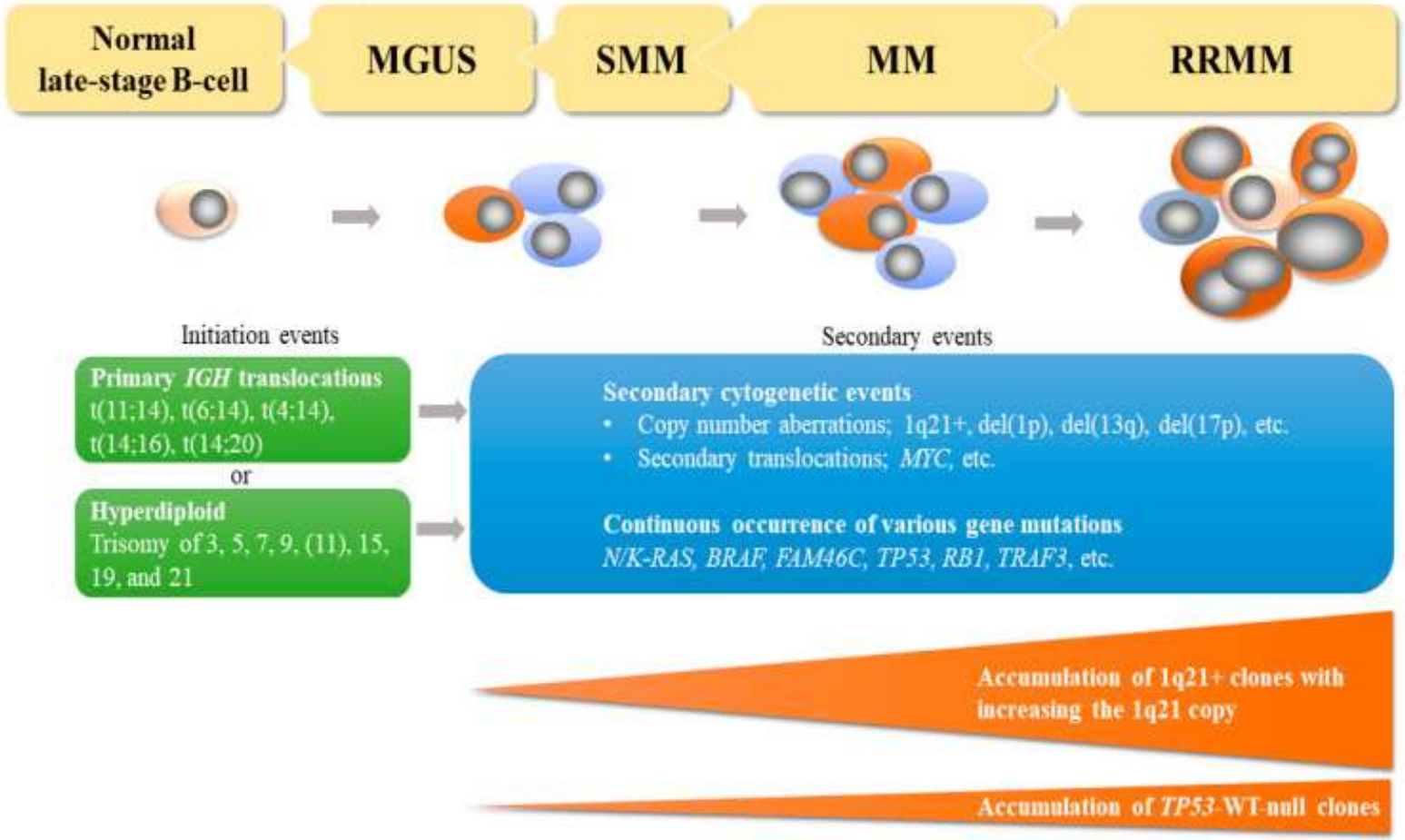
Cibler la mutation commune

Ho, Leukemia, 2020

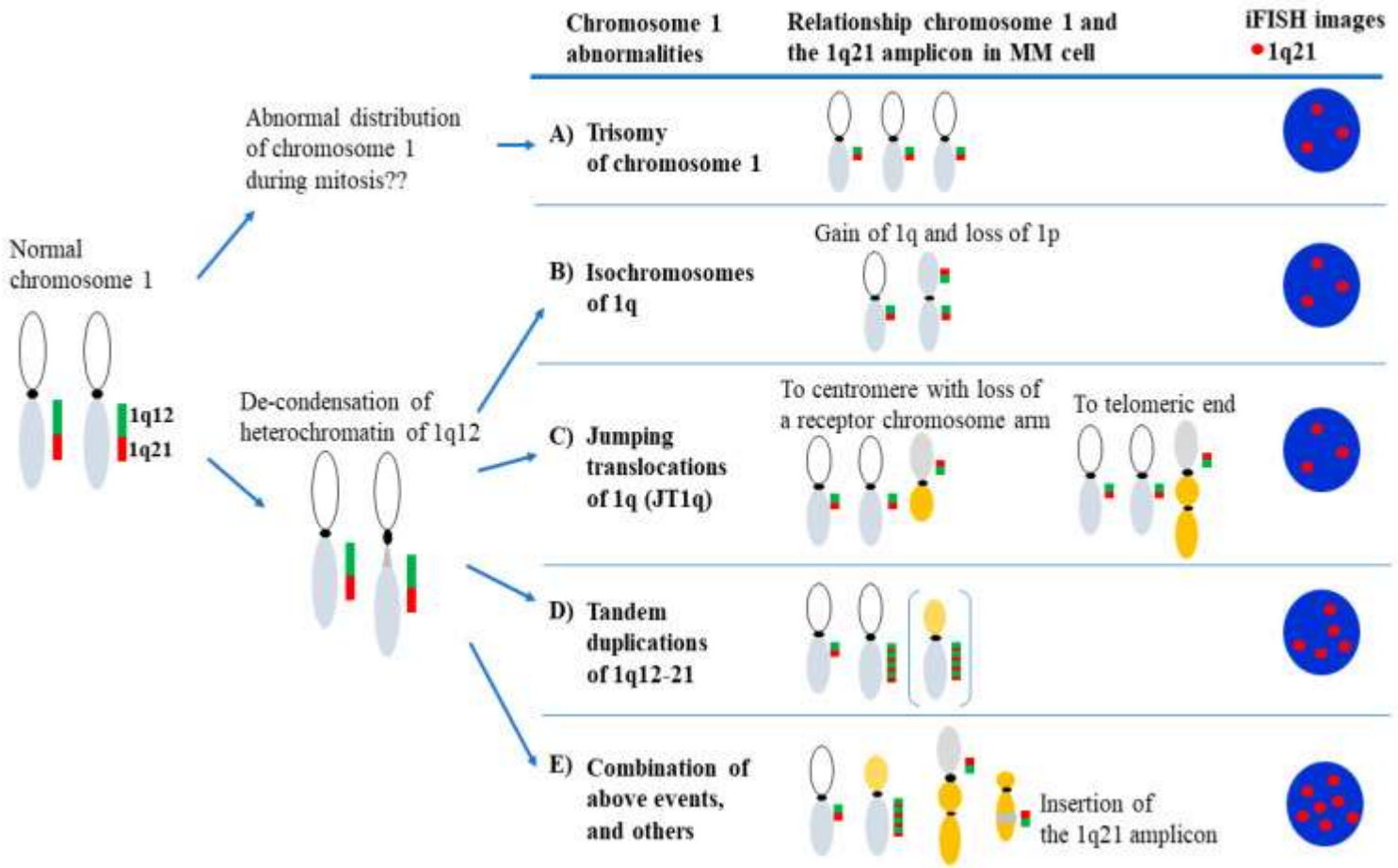
Genomic abnormalities in development of multiple myeloma

1q21+ augmente 20% MGUS => 70% MM

Biallelic inactivation TP53 augmente à rechute



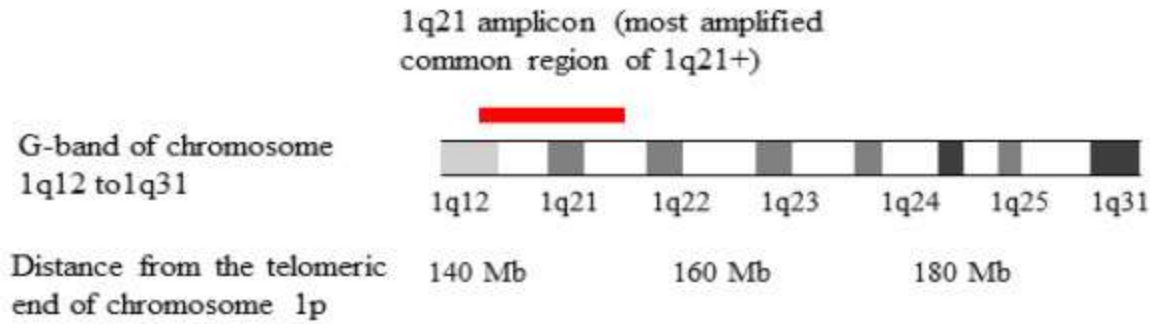
Ichiro Hanamura, Cancers 2021,13, 256.



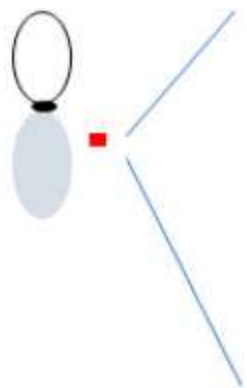
Schematic images of chromosome 1 aberrations and the 1q21 amplicon in multiple myeloma patients with 1q21+. Gain/amplification of 1q21 (1q21+) is
resulting from trisomy of chromosome 1 (**A**), and structural changes of chromosome 1
due to chromosomal instability of 1q12

Ichiro Hanamura, Cancers 2021,13, 256.

A)



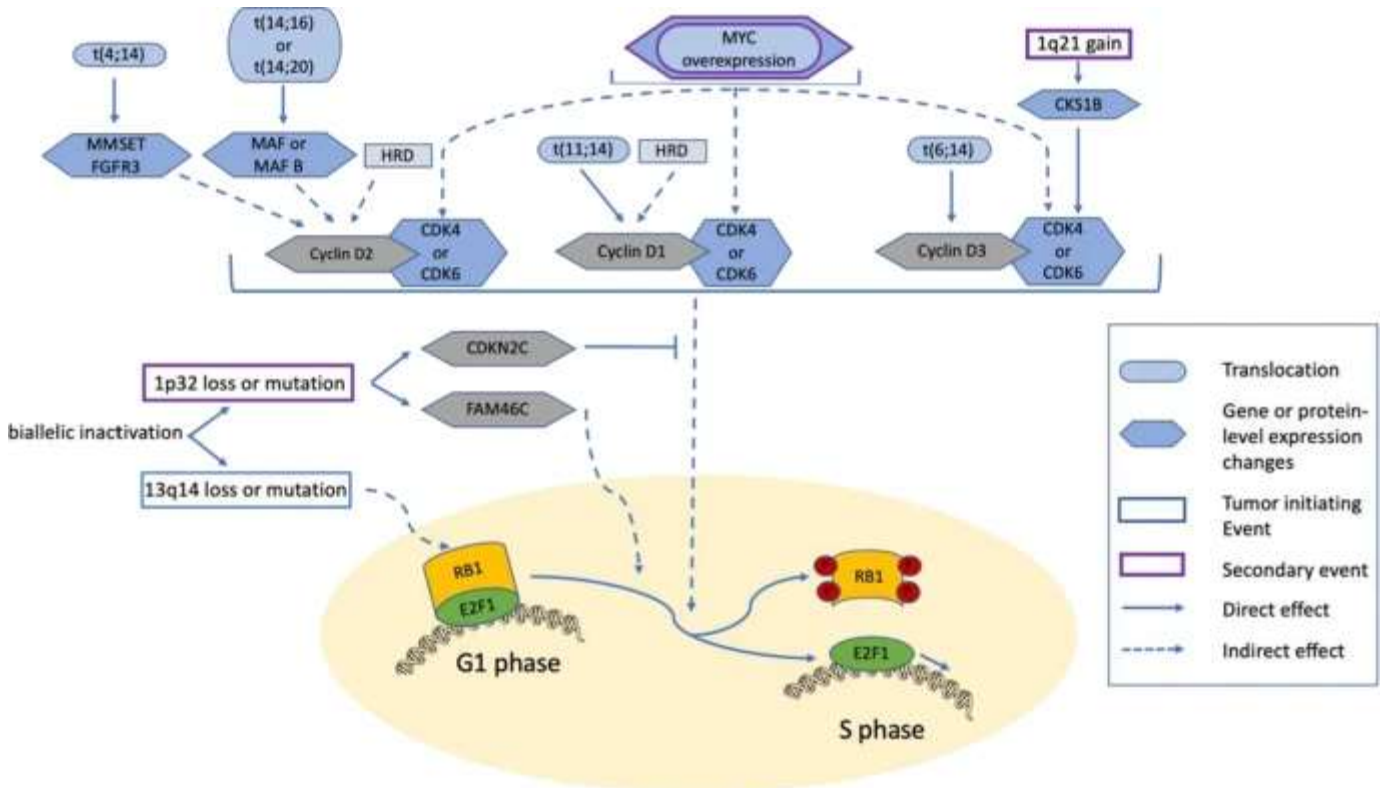
B)



Candidate genes	Distance from the telomeric end of chromosome 1p (Mb)	Putative function in MM cells with 1q21+
BCL9	147.5	Cell growth?
ANP32E	150.2	Epigenetic dysregulation
MCL1	150.5	Anti-apoptosis
PSMD4	151.2	Anti-PIs
ILF2	153.6	RNA metabolism
IL6R	154.4	Enhancement of IL6 effects
ADAR	154.8	RNA metabolism
CKS1B	154.9	Proteolysis of p27

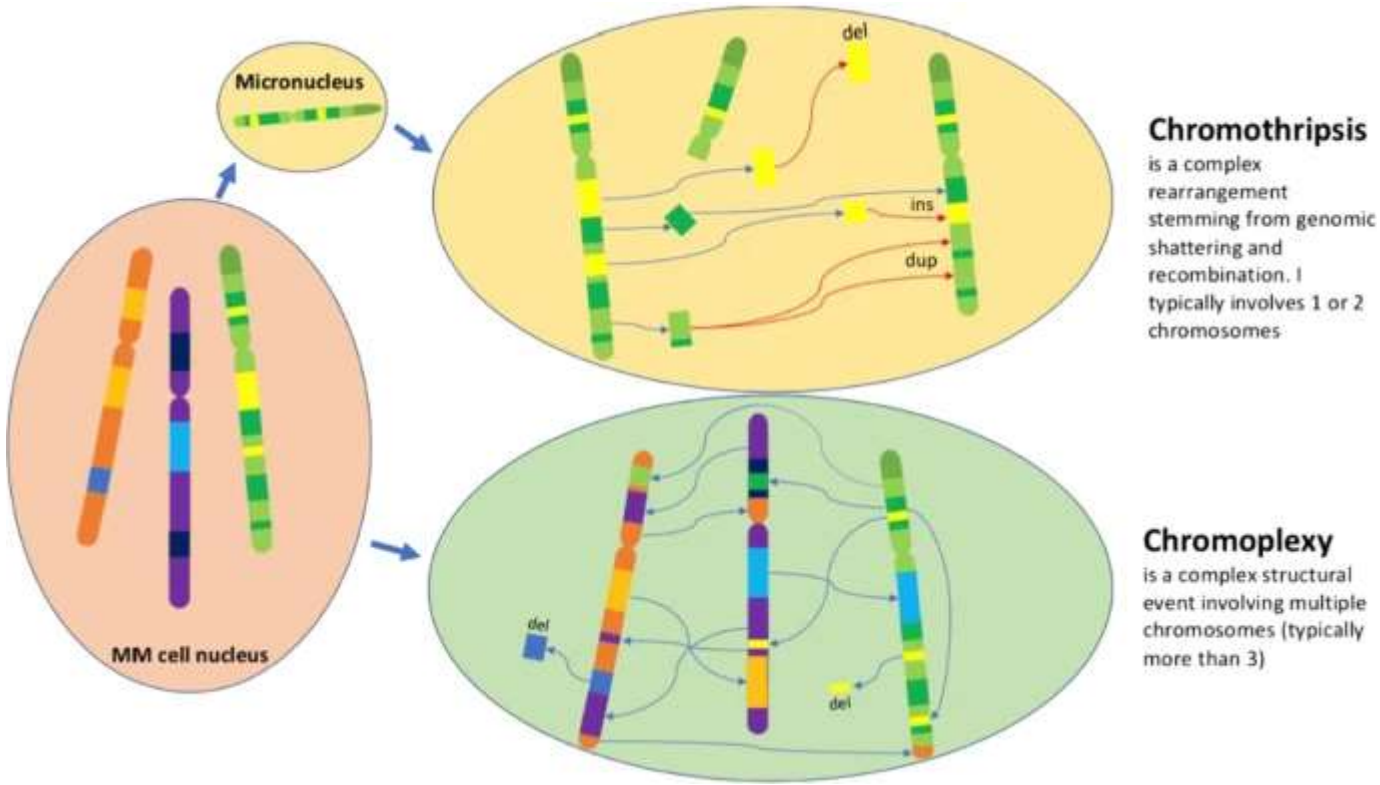
Ichiro Hanamura, Cancers 2021,13, 256.

Neuse, leukemia, 2020, 34,2887-2897



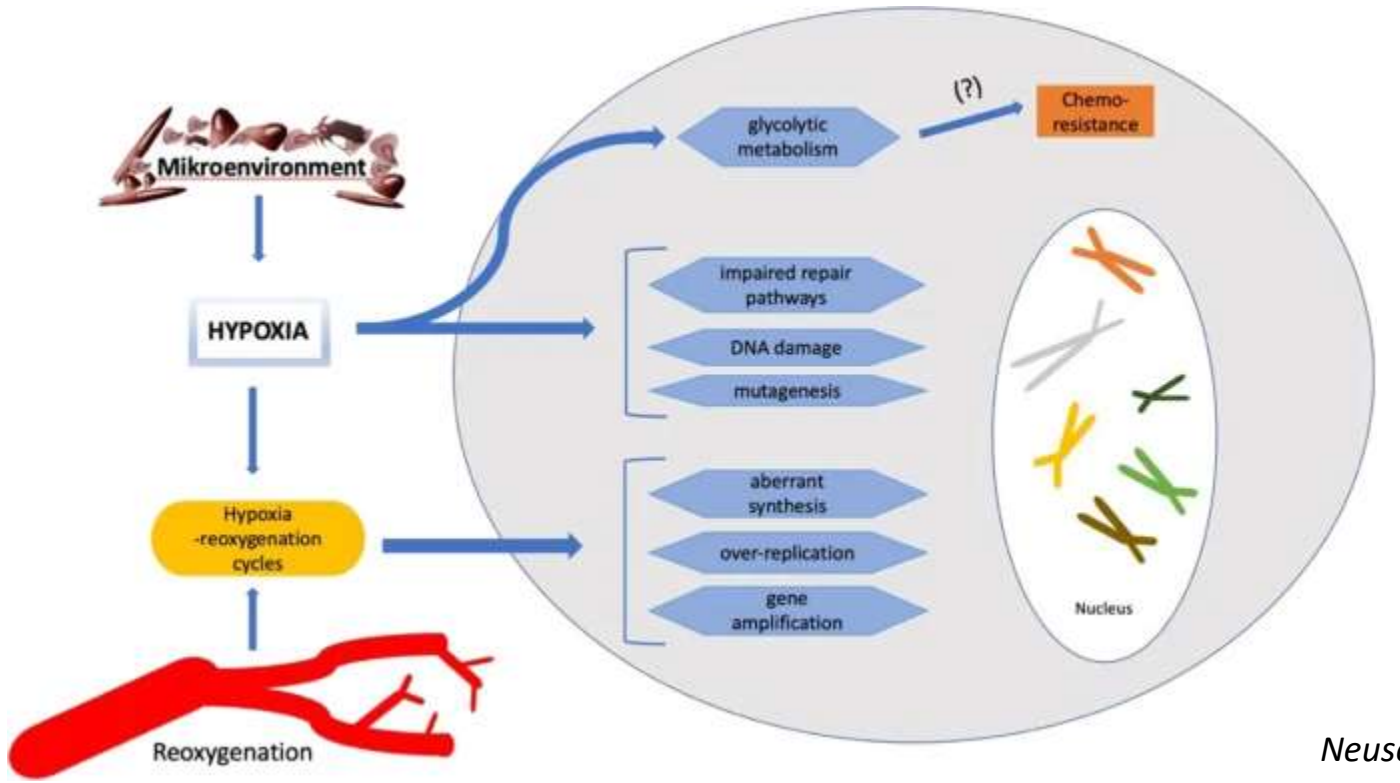
Neuse, leukemia, 2020, 34,2887-2897

Chromothripsis and chromoplexy involve random breakage and fusion of genomic segments. Chromothripsis can be associated with micronucleus formation and typically involves hundreds of locally clustered rearrangements while mostly affecting no more than two chromosomes. Chromoplexy is characterized by unclustered, chained rearrangem catastrophic event incident, whereas chromoplexy can involve sequential events.



Neuse, leukemia, 2020, 34,2887-2897

Conditions within the tumor microenvironment can induce significant instability in a cancer cell's genomic structure. Hypoxia has been associated with impaired repair events, DNA damage and mutagenesis. Hypoxia-reoxygenation cycles can lead to aberrant DNA synthesis, DNA overreplication, and gene amplification. The connection
between a glycolytic state of cell metabolism and chemoresistance demands further exploration.



Neuse, leukemia, 2020, 34,2887-2897

Table 1 An overview of genomic instability in MM highlighting its two major forms: chromosomal instability or hypermutatio

From: Genome instability in multiple myeloma

1.We outline mechanisms underlying these events, their outcomes, and their associated genomic changes.

Genomic instability	Mechanisms	Outcomes	Subtypes
Chromosomal instability	–Chromosomal mis-segregation –Aberrant centrosome duplication –Defects in microtubules and mitotic spindle –Defective DNA repair machinery –Cell-cycle dysregulation –Hypoxic tumor microenvironment	Copy number alterations (aneuploidy)	–Whole chromosome amplifications/deletions –WGD –Arm-level CNAs –Focal CNAs
		Structural variants	–*IgH* translocations –*MYC* translocations –Chromothripsis –Chromoplexy –Inversions
Hypermutation	–*TP53*, *Rb1* mutations –APOBEC activity –*t*(14;16) –*MYC* overexpression	Hypermutations kataegis	

Neuse, leukemia, 2020, 34,2887-2897

MRD et MM

- En accord avec IMWG, présenté au 61 eme congrès de l'ASH
- Techniques, exigences, seuil

CMF utilisation de 10 marqueurs, rapide, proche de 10^{-6}

NGS réarrangement VDJ DJ + compliqué

ASO PCR patient spécifique, long, non validé dans grosses études

But sensibilité 10^{-6} en pratique 10^{-5}

Applicable à plus de 90% des patients

Moelle si non diluée bcp mieux que sang (trop de faux neg)

Imagerie PET CT mais non complètement évalué

A faire pour tous les patients inclus dans des études, mrd à faire à chaque moelle d'évaluation post traitement. Préciser technique et seuil et valeur du résultat

Luciano J, Leukemia, 2021