Myélomes indolents et scores pronostiques

25 novembre 2021
Journée DES Hématologie

Olivier Decaux
Service d'Hématologie Clinique
CHU de Rennes

MGUS → SMM → MM

1- Définition des SMM (crirères IMWG 2014)?

2- Quels est le risque évolutif des SMM?

3- Critères de SMM à haut risque ?

4- Faut-il traiter les SMM ?

5- Comment améliorer l'identification des SMM à haut risque?

➔ Etude CARRISMM

Myélome multiple

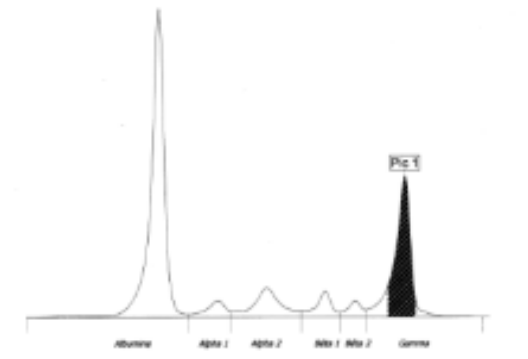
Critères diagnostiques de l'IMWG 2003

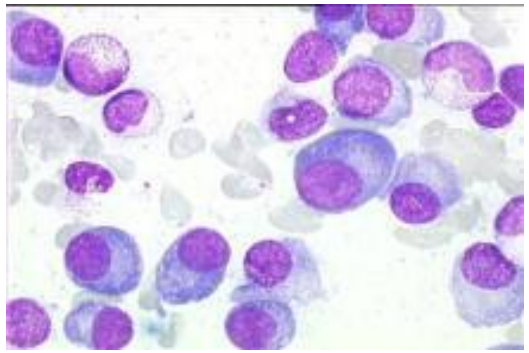
Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group.

International Myeloma Working Group 2003

International Myeloma Working Group. Br J Haematol. 2003 Jun;121(5):749-57.

International Myeloma Working Group
Critères diagnostiques 2003





	MGUS	Myélome indolent (SMM)	Myélome multiple
	< 30 g/l	> 30 g/l	Pas de valeur seuil
	et	ou	
	< 10%	> 10%	> 10%
C HyperCalcémie R Insuffisance Rénale A Anémie B Lésions Osseuses (Bones)	-	-	+

International Myeloma Working Group. Br J Haematol. 2003 Jun;121(5):749-57.

Evolution clinique et pronostic du MM indolent

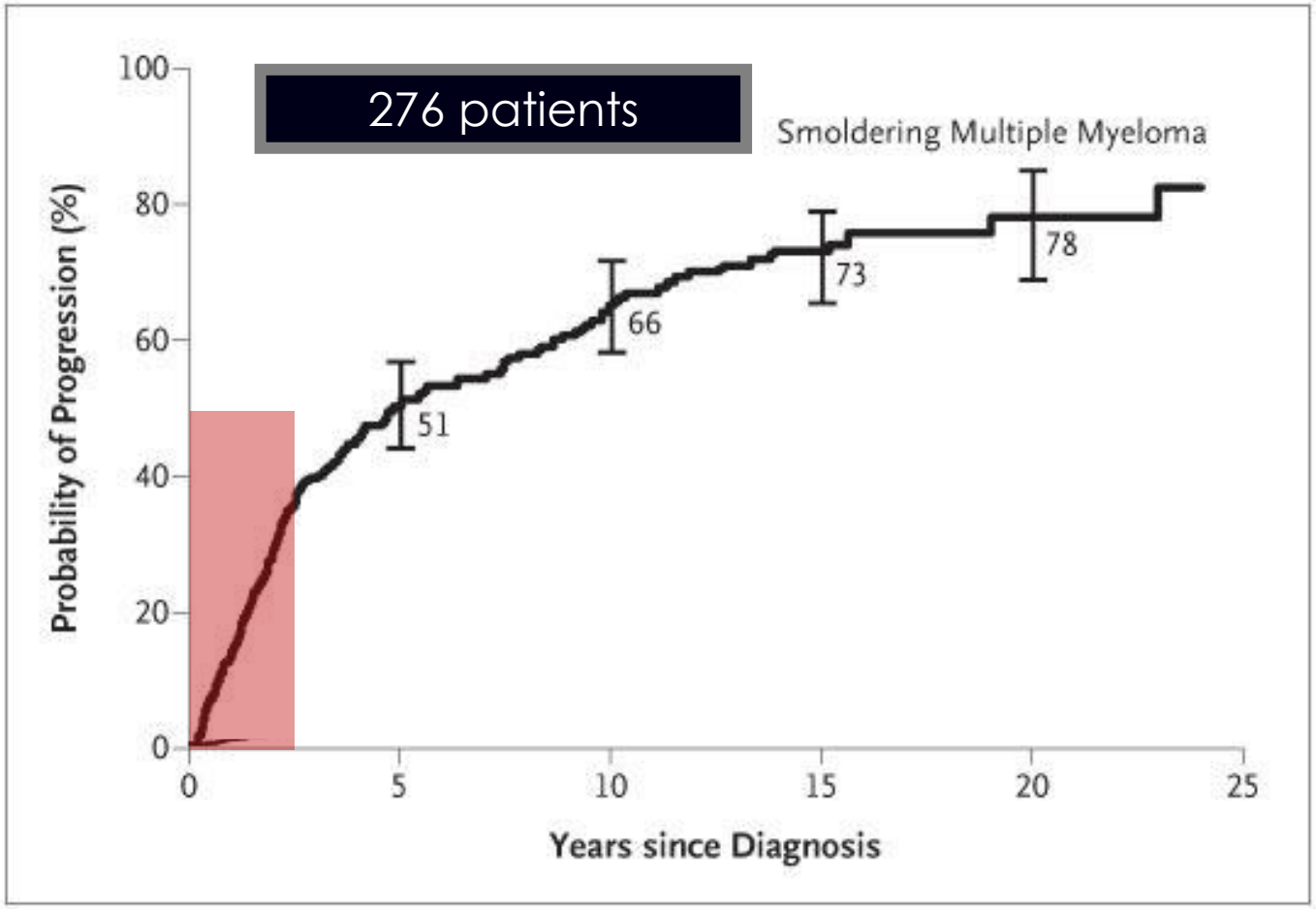
Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma

Robert A. Kyle, M.D., Ellen D. Remstein, M.D., Terry M. Therneau, Ph.D., Angela Dispenzieri, M.D., Paul J. Kurtin, M.D., Janice M. Hodnefield, M.S., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., Diane F. Jelinek, Ph.D., Rafael Fonseca, M.D., Lee Joseph Melton III, M.D., and S. Vincent Rajkumar, M.D.

SMM

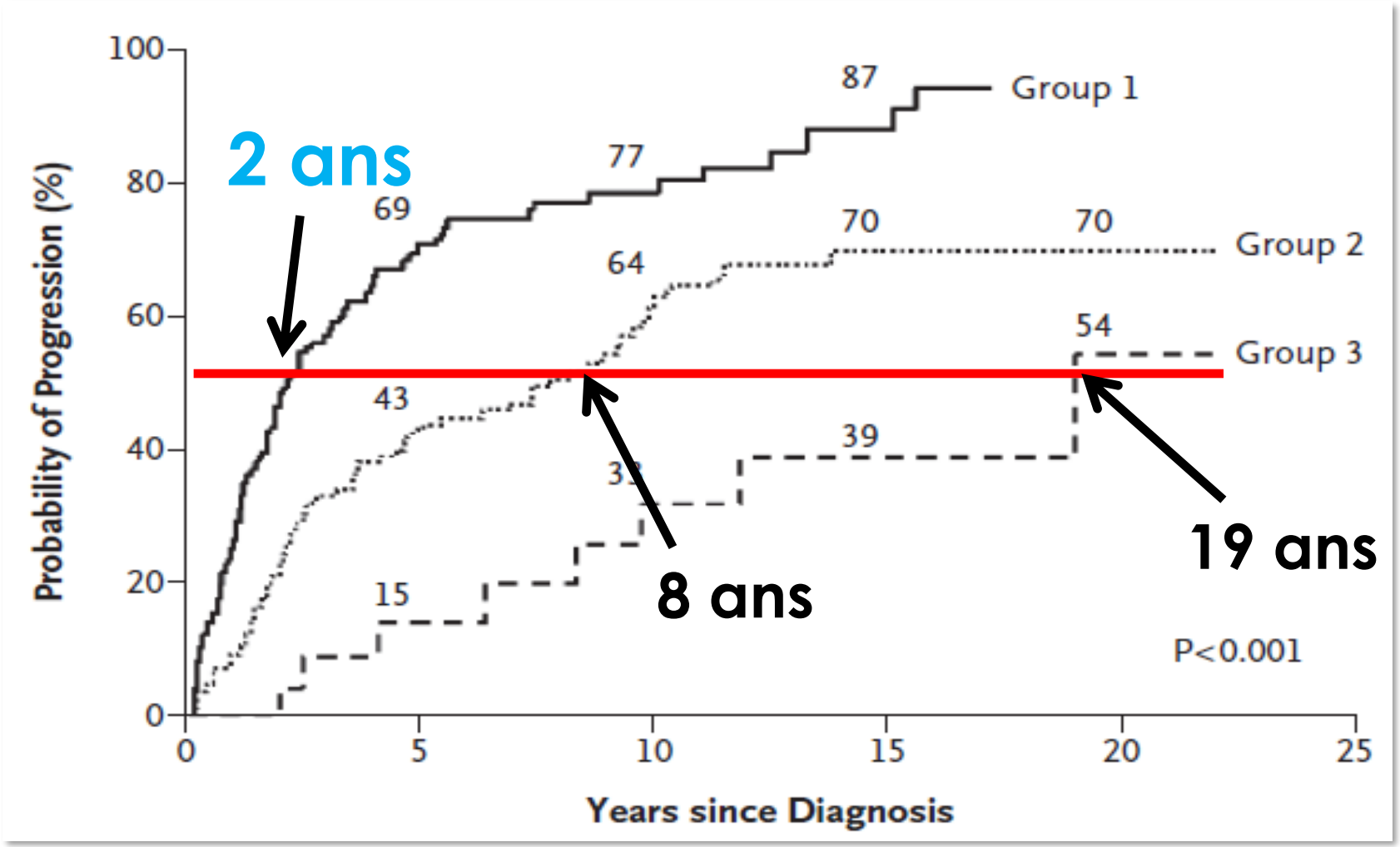
10 % par an

RR Myélome 522



Kyle RA et al, N Engl J Med. 2007;356:2582-90.

Hétérogénéité des MM indolents



Pic > 30 g/l et PM > 10%

Pic < 30 g/l et **PM > 10%**

Pic > 30 g/l et PM< 10%

Kyle RA et al, N Engl J Med. 2007;356:2582-90.

Facteurs prédictifs de progression des MM indolents

Risk group	Probability of progression to myeloma or related disorder in first 2 years from initial diagnosis of SMM (%)
Bone marrow clonal plasma cells ≥60%	90
Serum involved/uninvolved free light chain ratio ≥100	80
Abnormalities on MRI (>1 focal lesion)	70
Abnormal plasma cell immunophenotype ≥95%	50
Evolving type of SMM*	65
t(4;14) or del 17p	50
M protein ≥30 g/l and bone marrow clonal plasma cells ≥10%	50
Serum involved/uninvolved free light chain ratio ≥8 and <100	40
No high-risk factors	10–20

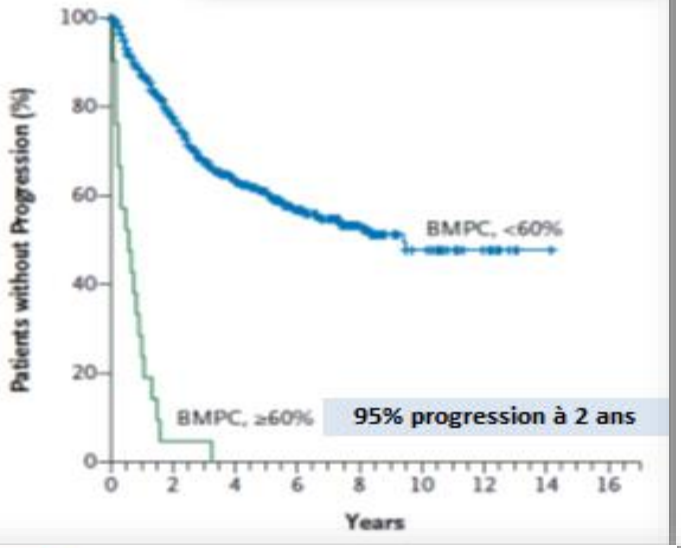
Diagnosis of Smoldering Multiple Myeloma

S. Vincent Rajkumar, M.D.
Dirk Larson, M.S.
Robert A. Kyle, M.D.

N ENGL J MED 365;5 NEJM.ORG AUGUST 4, 2011

655 patients

Plasmocytose médullaire ≥ 60%
21 patients (3,2%)



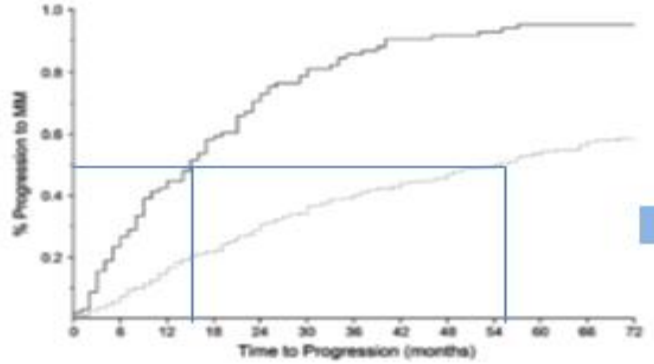
95% progression à 2 ans

ORIGINAL ARTICLE

Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma

586 patients

RKL > 100 - 90 patients (15%)

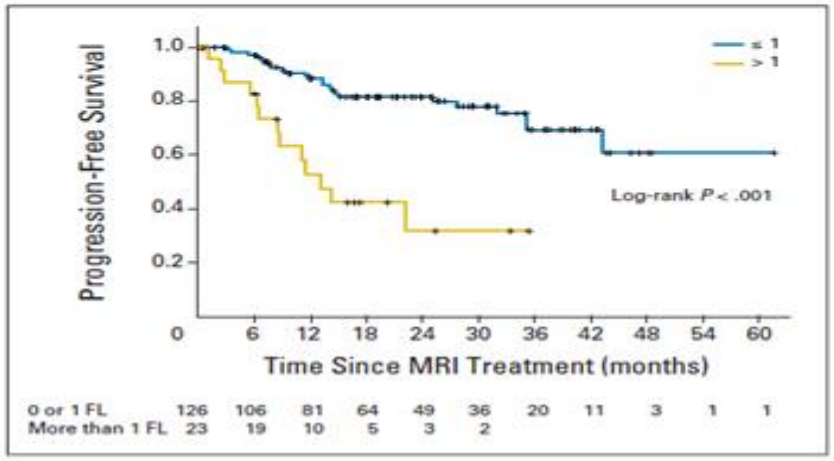


TTP 15 vs 55 mois

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Significance of Focal Lesions in Whole-Body Magnetic Resonance Imaging in Patients With Asymptomatic Multiple Myeloma

149 patients - IRM corps entier
23 patients (15%) > 1 lésion focale



Lenalidomide et dexamethasone pour des MM indolents à haut risque

HAMM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

N ENGL J MED 369;5 NEJM.ORG AUGUST 1, 2013

Résultats - Temps jusqu'à progression vers un myélome multiple

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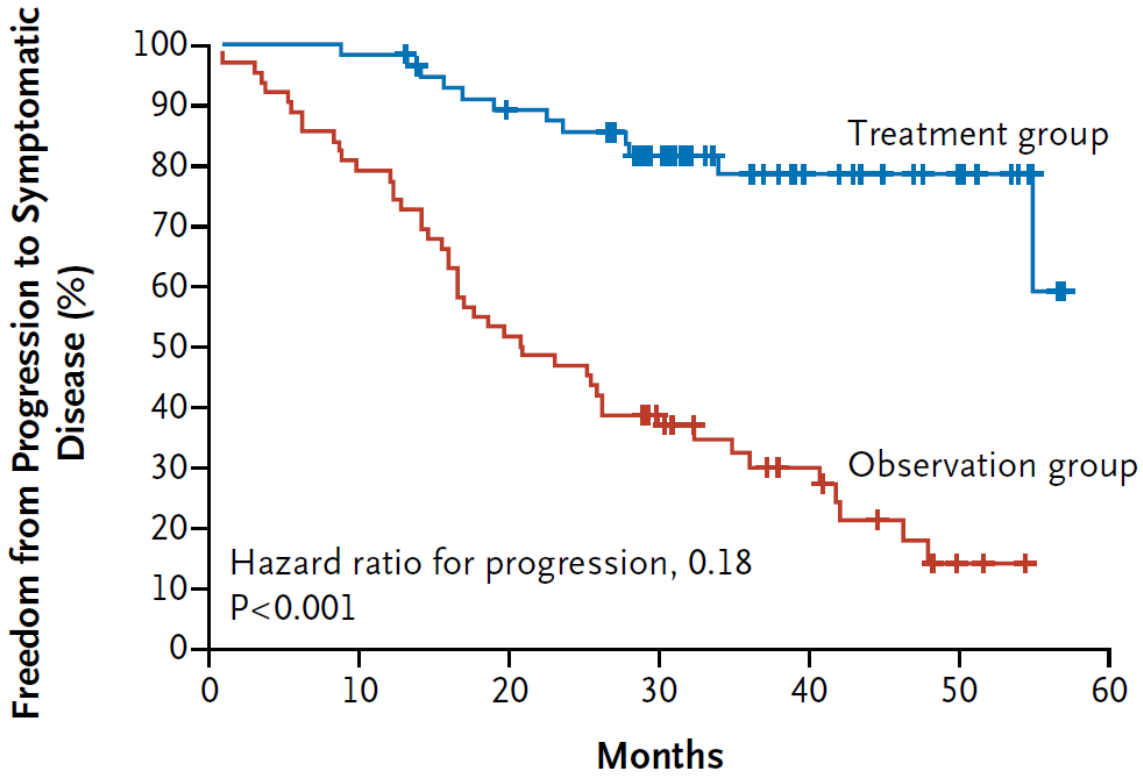

No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

NR	**13 pts (23 %)**
21 mois	**47 pts (76 %)**

Mateos MV et al, N Engl J Med. 2013;369(5):438-47.

Résultats - Survie globale

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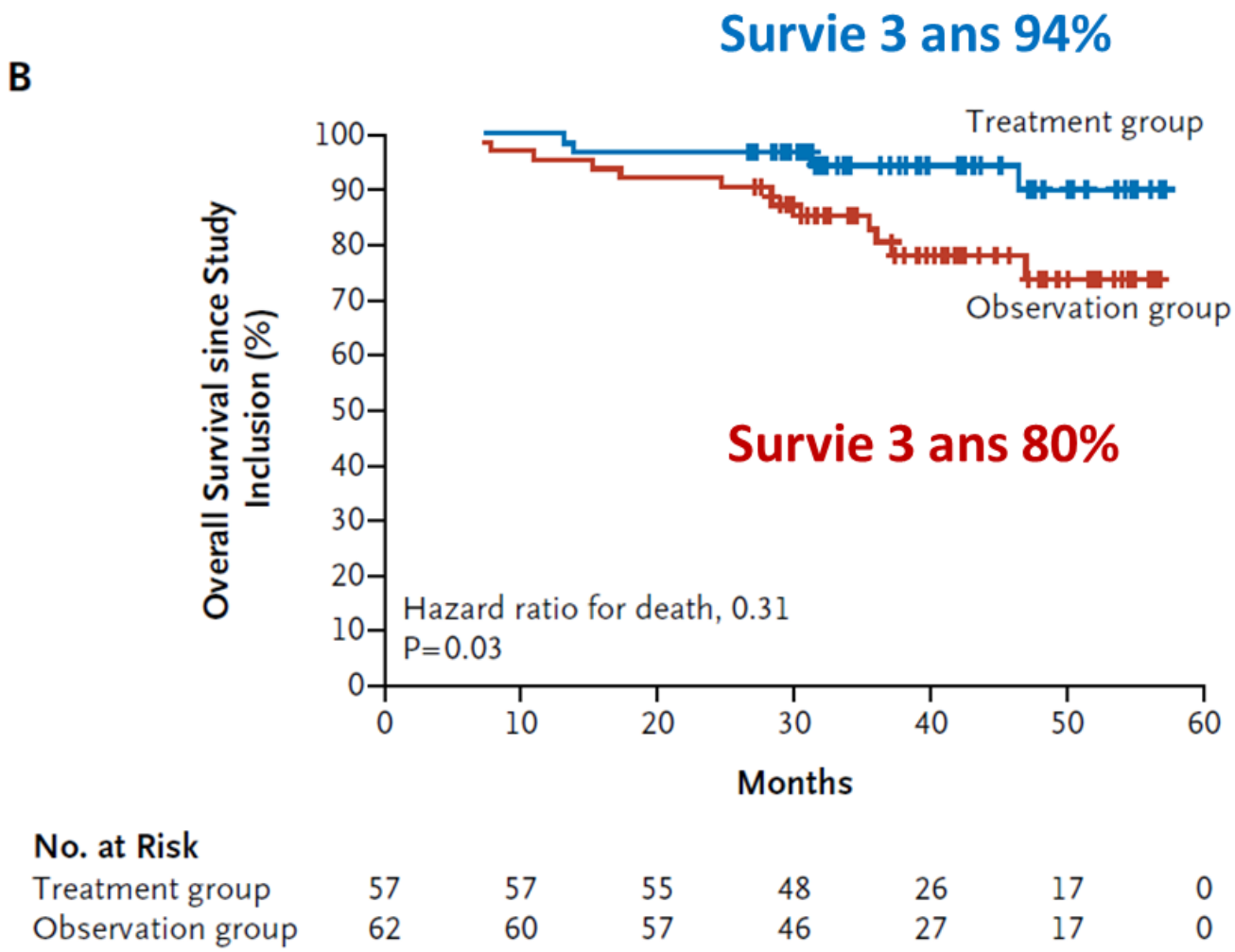
Depuis l'inclusion



Mateos MV et al, N Engl J Med. 2013;369(5):438-47.

Les nouveaux critères diagnostiques du myélome multiple – IMWG 2014

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Les nouveaux critères diagnostiques du myélome multiple – IMWG 2014

Plasmocytose médullaire clonale > 10%

ou plasmocytome prouvé histologiquement

Présence d'au moins un des critères suivants

CRAB

- **hypercalcémie** (> 0,25 mmol/L /N ou > 2,75 mmol/L)
- **insuffisance rénale** (créat. > 177 mmol/L ou Cl créat < 40 ml/min)
- **anémie** (Hb < 2 g/dL / N ou < 10g/dL)
- **≥ 1 lésion ostéolytique** – radiographies, TDM, TEP

NOUVEAUX CRITERES

- **Plasmocytose médullaire clonale ≥ 60%**
- **Rapport κ/λ ou λ/κ > 100 (et concentrati**
- **> 1 lésions focales IRM (≥ 5 mm)**

Radio
TDM faible dose
TEP

Rajkumar SV et al, Lancet Oncol. 2014;15(12):e538-48.

Imagerie

- ≥ 1 lésion ostéolytique (≥ 5 mm) TDM ou TEP suffit à poser le diagnostic de myélome
- une lésion hypermétabolique TEP sans ostéolyse sous-jacente ne suffit pas
- si lésion focale IRM < 5 mm il est recommandé de compléter par TDM ou TEP

Les nouveaux critères diagnostiques du MM indolent – IMWG 2014

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

IgG ou IgA monoclonale ≥ 30 g/l

ou protéine monoclonale urinaire ≥ 500 mg/24h

ou plasmocytose médullaire clonale 10-60 %

Absence de critères de myélome multiple (CRAB / nouveaux critères)

Quels changements pour la pratique?

MGUS

SMM

SMM à haut potentiel

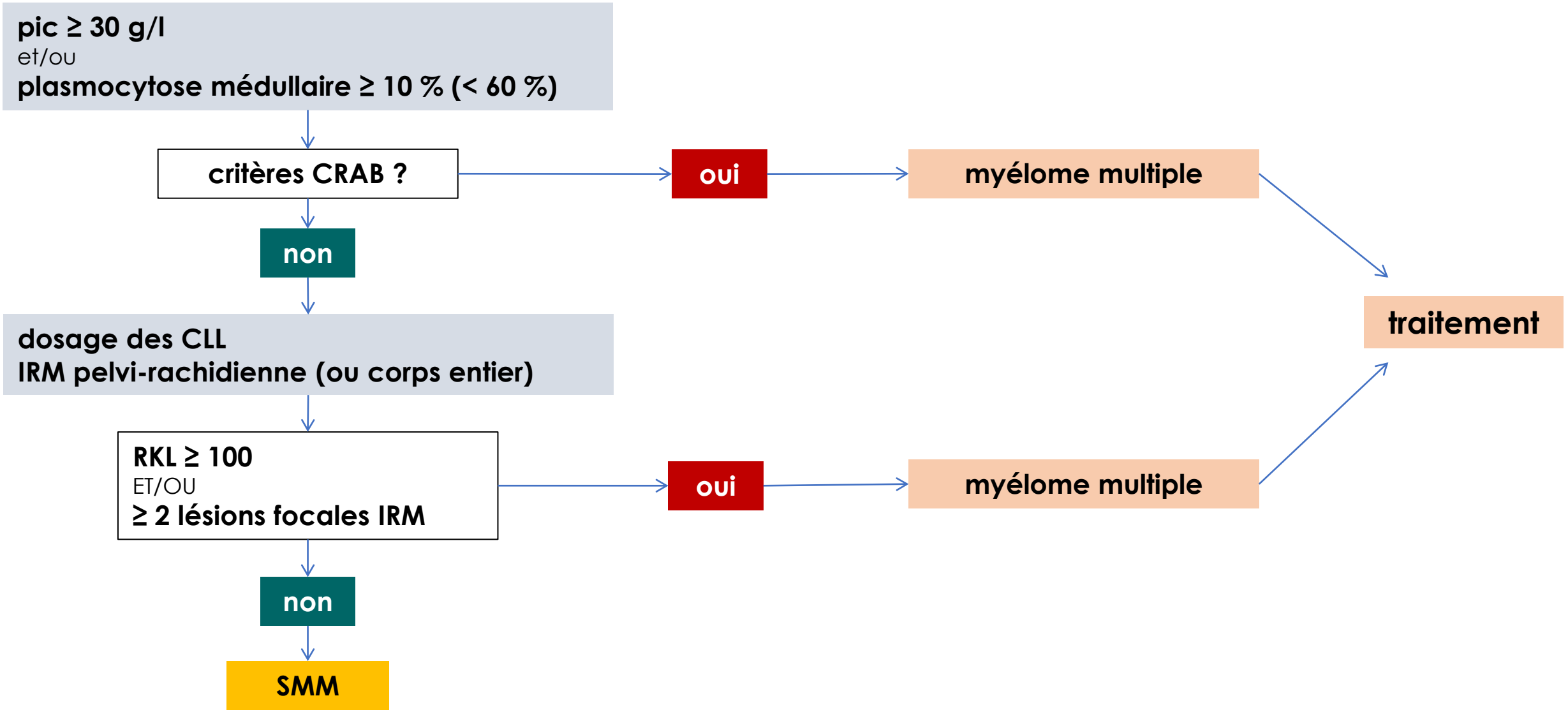
Myélome multiple

Quelles explorations au diagnostic de MM indolent ?

Myélome multiple

➔ traitement

Quelles explorations au diagnostic de MM indolent ?



Quels changements pour la pratique?

MGUS

SMM

SMM a haut potent

Myélome multiple

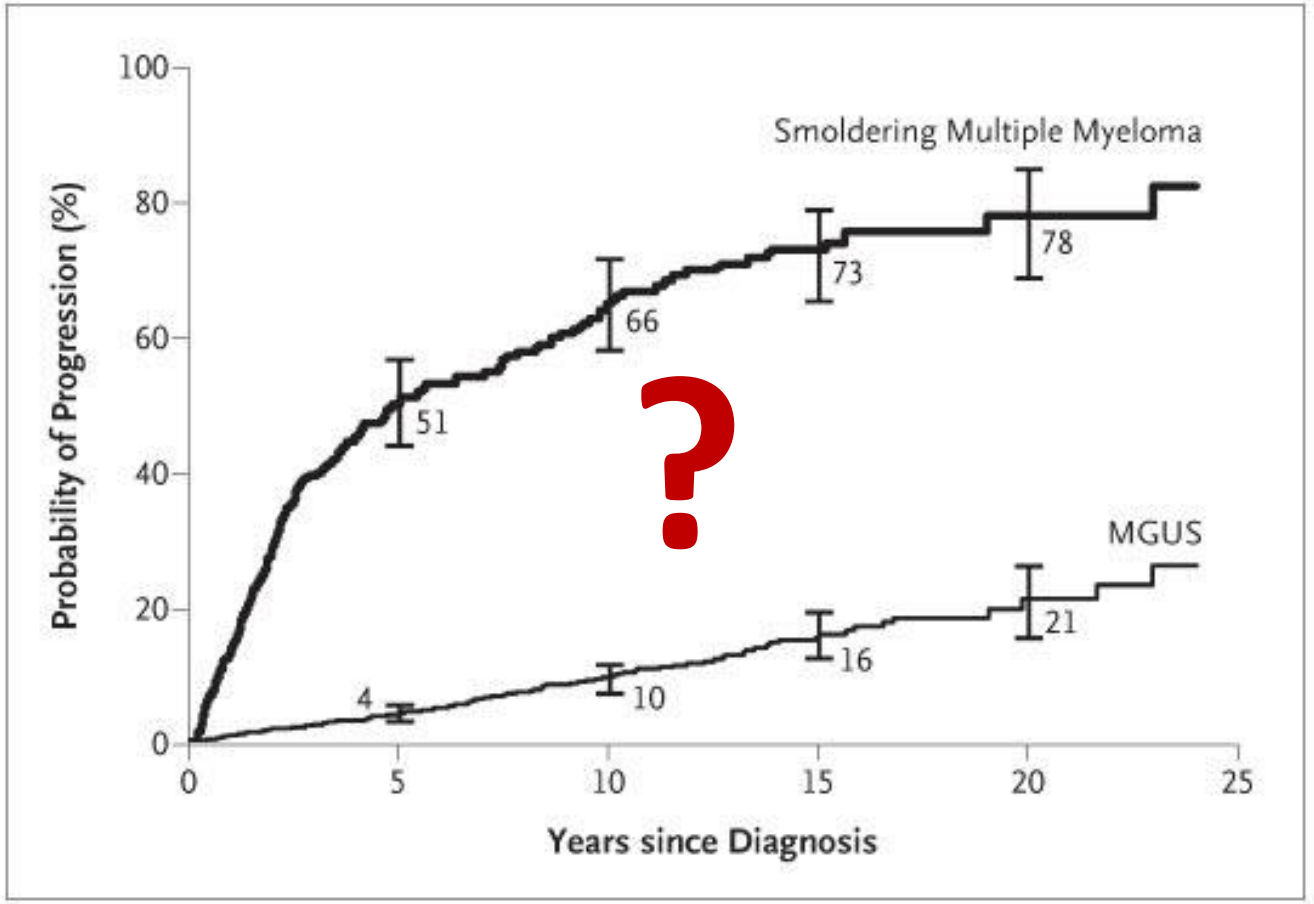
Prise en charge des MM indolents (critères 2014) ?

Myélome multiple

➔ traitement

Prise en charge des MM indolents (critères 2014) ?

- Que devient le risque évolutif des MM indolents (critères 2014)?



Prise en charge des MM indolents (critères 2014) ?

- Que devient le risque évolutif des MM indolents (critères 2014)?
- Quels facteurs pronostiques ?

Facteurs de risque de progression des MM indolents ?

Table 2. Definition of high-risk SMM

Temps jusqu'à progression

médiane = 2 ans

25 % par an

Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or 1q gain
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

mais SMM critères IMWG 2003

Rajkumar et al, Blood 2015

Lakshman et al. *Blood Cancer Journal* (2018)8:59
DOI 10.1038/s41408-018-0077-4

Blood Cancer Journal

ARTICLE Open Access

Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria

Arjun Lakshman[1], S. Vincent Rajkumar[1], Francis K. Buadi[1], Moritz Binder[1], Morie A. Gertz[1], Martha Q. Lacy[1], Angela Dispenzieri[1], David Dingli[1], Amie L. Fonder[1], Suzanne R. Hayman[1], Miriam A. Hobbs[1], Wilson I. Gonsalves[1], Yi Lisa Hwa[1], Prashant Kapoor[1], Nelson Leung[1], Ronald S. Go[1], Yi Lin[1], Taxiarchis V. Kourelis[1], Rahma Warsame[1], John A. Lust[1], Stephen J. Russell[1], Steven R. Zeldenrust[1], Robert A. Kyle[1] and Shaji K. Kumar[1]

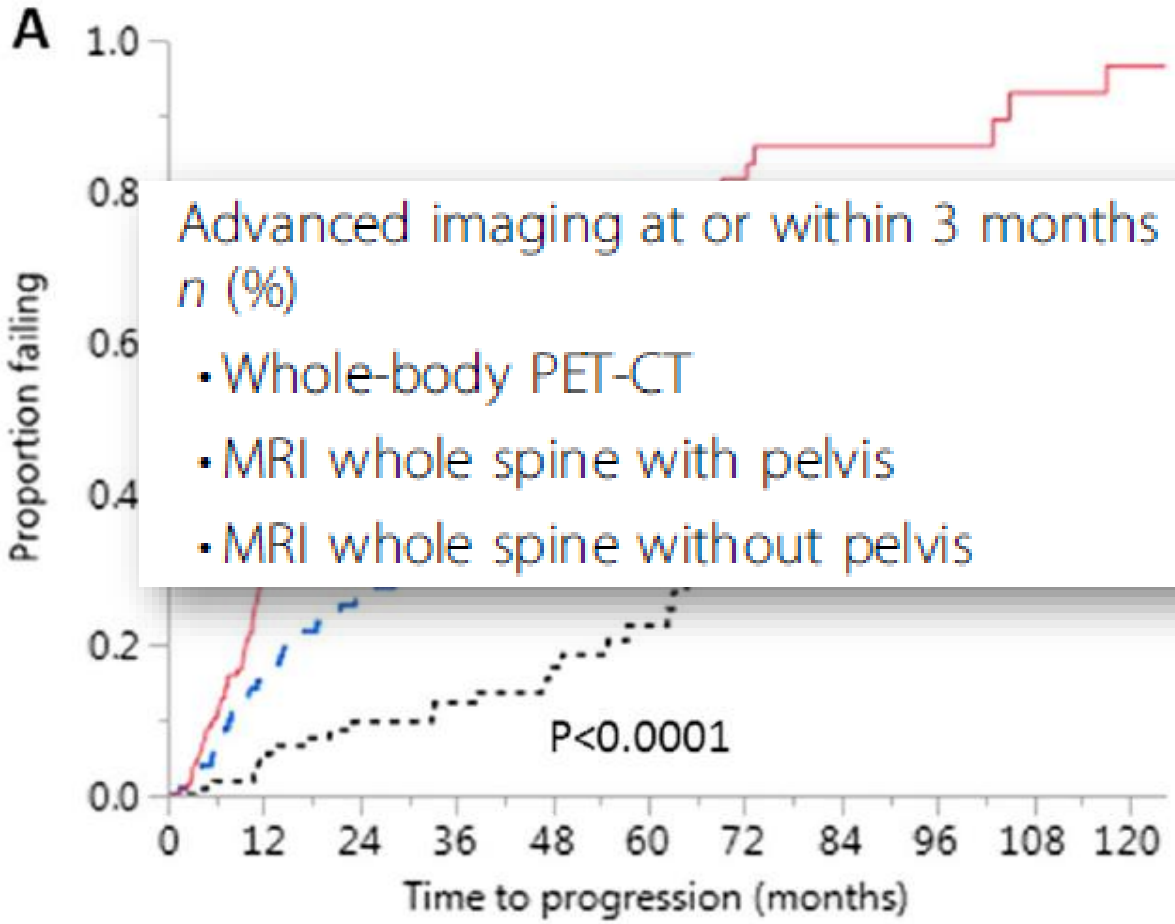
421 patients SMM (2014 IMWG criteria)

3 factors score

- BMPC > 20%
- M protein > 20 g/L
- FLC ratio > 20

median TTP

≥ 2 risk factors 29,2 months



Advanced imaging at or within 3 months from diagnosis, *n* (%)	124 (29.5)
• Whole-body PET-CT	110 (88.7)
• MRI whole spine with pelvis	8 (6.5)
• MRI whole spine without pelvis	6 (4.8)

Mateos et al. *Blood Cancer Journal* (2020)10:102
https://doi.org/10.1038/s41408-020-00366-3

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CONFIRMATION DU SCORE 20/20/20
→ score IMWG 2018

International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM)

1996 patients
SMM (critères 2014)

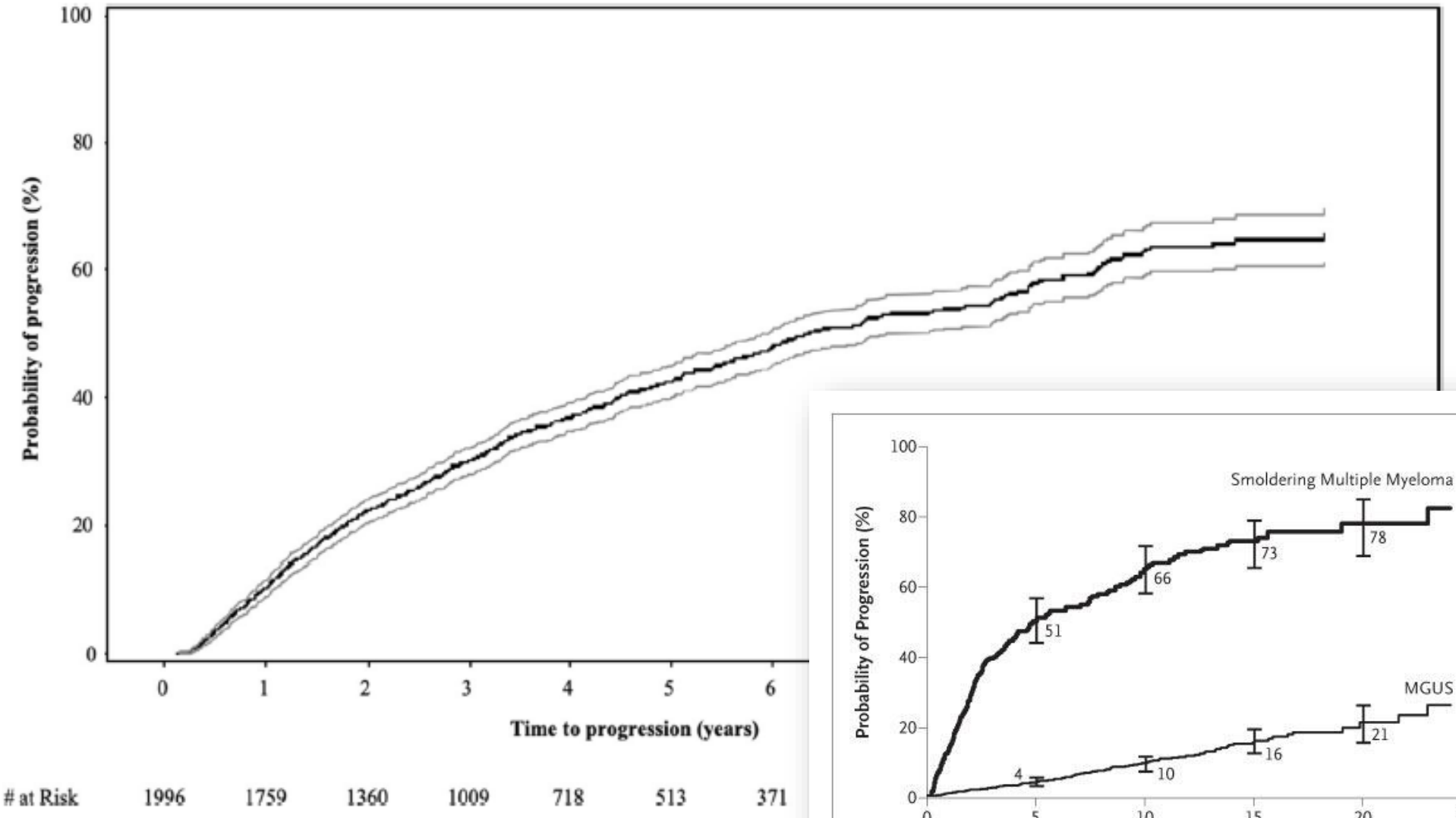

Fig. 1 Probability of progression over time in the full study cohort (*n* = 199
years (95% CI 6.0–7.2); the 2-, 5-, and 10-year risk of progression were 22, 42, and

Mateos et al. *Blood Cancer Journal* (2020)10:102
https://doi.org/10.1038/s41408-020-00366-3

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International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM)

CONFIRMATION DU SCORE 20/20/20
→ score IMWG 2018

1996 patients

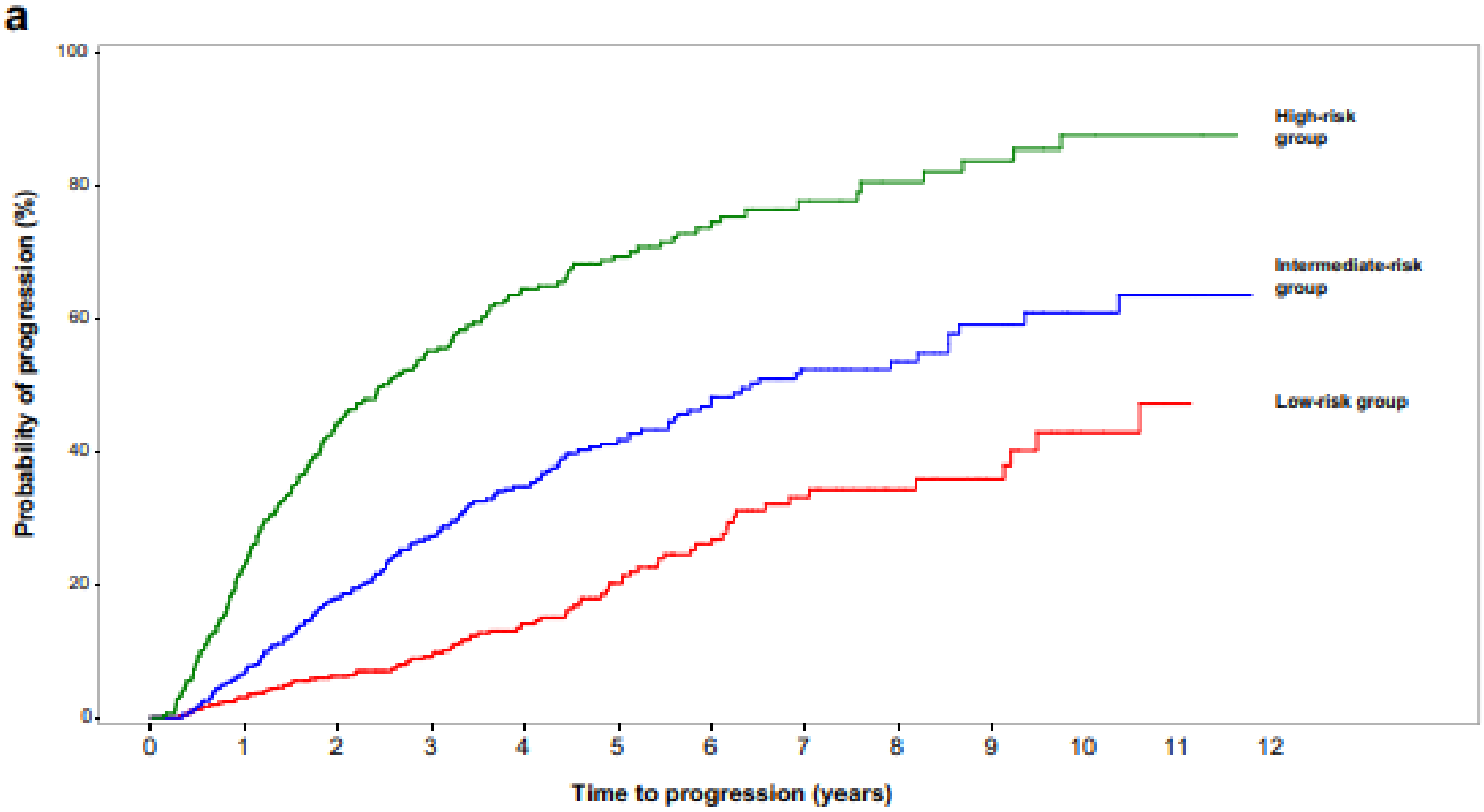
SMM (critères 2014)

BM MM cells > 20%

M-protein > 20 g/L

FLCr > 20

MAIS PAS D'INFO SUR IRM



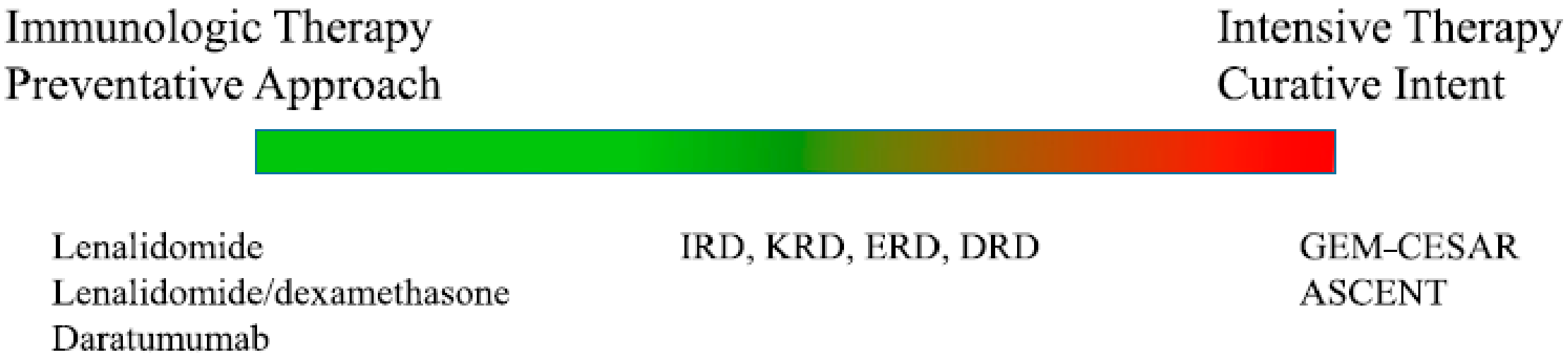
Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)

FAUT-IL TRAITER LES SMM ?

Traitement des MM indolents à haut risque ?

2 stratégies :

- **Retarder la progression** **-Guérir**



Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

HAMM

Sagar Lonial, MD[1]; Susanna Jacobus, MSc[2]; Rafael Fonseca, MD[3]; Matthias Weiss, MD[4]; Shaji Kumar, MD[5]; Robert Z. Orlowski, MD, PhD[6]; Jonathan L. Kaufman, MD[1]; Abdulraheem M. Yacoub, MD[7]; Francis K. Buadi, MD[5]; Timothy O'Brien, MD[8]; Jeffrey V. Matous, MD[9]; Daniel M. Anderson, MD[10]; Robert V. Emmons, MD[11]; Anuj Mahindra, MD[12]; Lynne I. Wagner, PhD[13]; Madhav V. Dhodapkar, MBBS[1]; and S. Vincent Rajkumar, MD[5]

J Clin Oncol 37.

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Characteristic	Lenalidomide (n = 90)	Observation (n = 92)	Total (N = 182)
Percent BMPC, No. (%)			
< 10	2 (2.2)	4 (4.4)	6 (3.3)
≥ 10†	88 (97.8)	88 (95.6)	176 (96.7)
> 20‡	31 (34.4)	41 (44.6	72 (39.6)
≥ 60	3 (3.3)	3 (3.3)	6 (3.3)
FLC ratio, No. (%)			
< 0.125 or > 8.0†	65 (72.2)	67 (72.8)	132 (72.5)
Normal	25 (27.8)	25 (27.2)	50 (27.5)
< 0.26 or > 1.65	87 (96.7)	89 (96.7)	176 (96.7)
> 20‡	26 (28.9)	22 (23.9)	48 (26.4)
> 100 (involved > 10 mg/dL)	6 (6.7)	9 (9.8)	15 (8.2)
MRI abnormality, No. (%)			
Absent	48 (53.9)	47 (51.7)	95 (52.8)
Present	41 (46.1)	44 (48.4)	85 (47.2)
Missing	1	1	2

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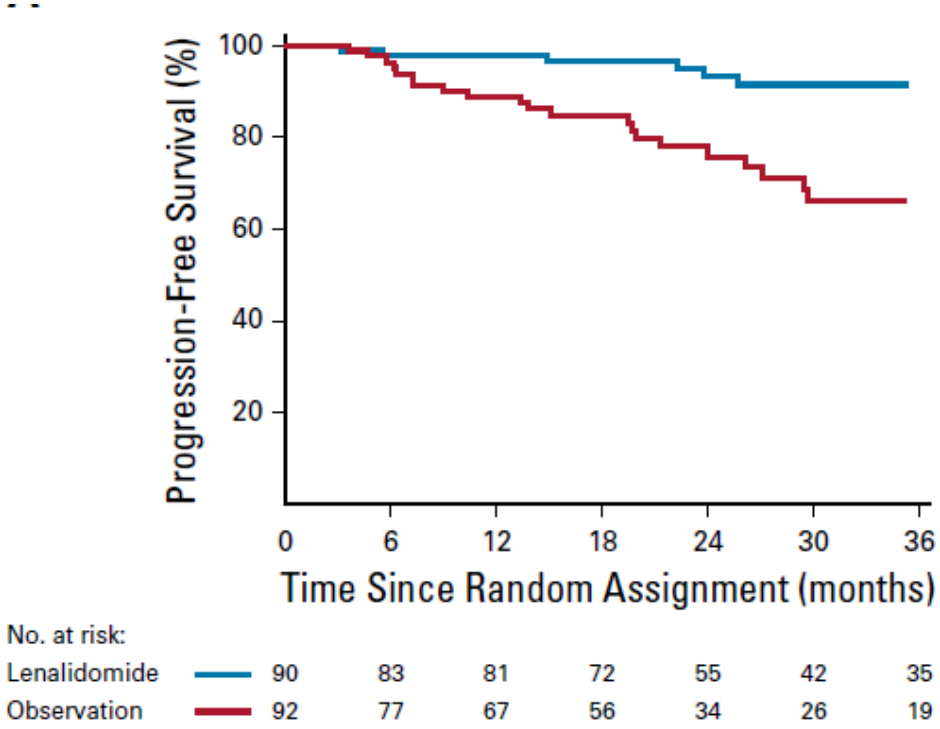
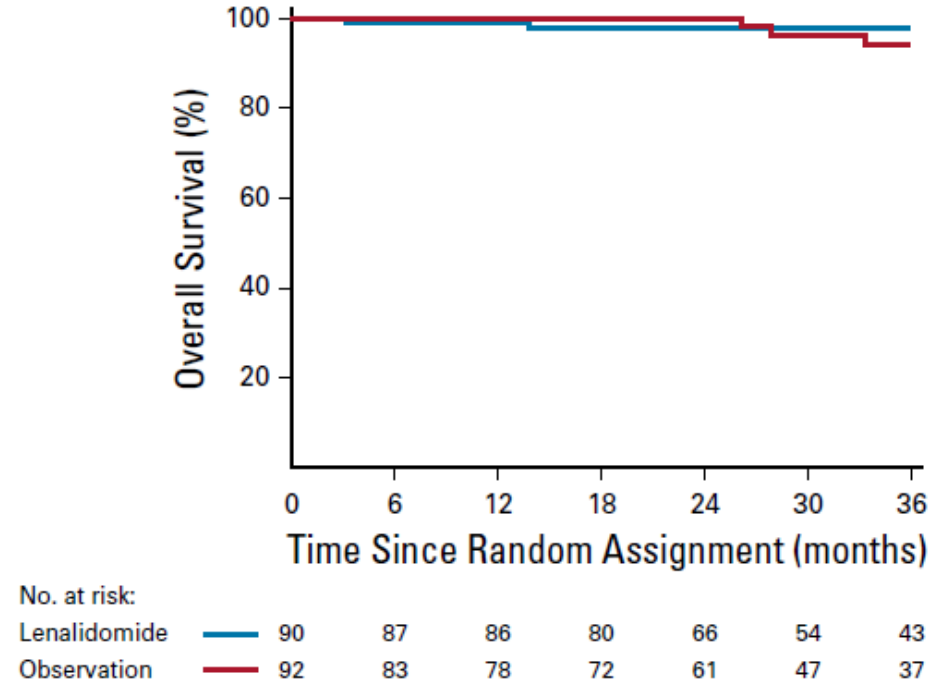
PFS


Progression-Free Survival (%)
100
80
60
40
20
0
6
12
18
24
30
36
Time Since Random Assignment (months)
No. at risk:
Lenalidomide 90 83 81 72 55 42 35
Observation 92 77 67 56 34 26 19

OS


Overall Survival (%)
100
80
60
40
20
0
6
12
18
24
30
36
Time Since Random Assignment (months)
No. at risk:
Lenalidomide 90 87 86 80 66 54 43
Observation 92 83 78 72 61 47 37

PFS en fonction score IMWG 2018

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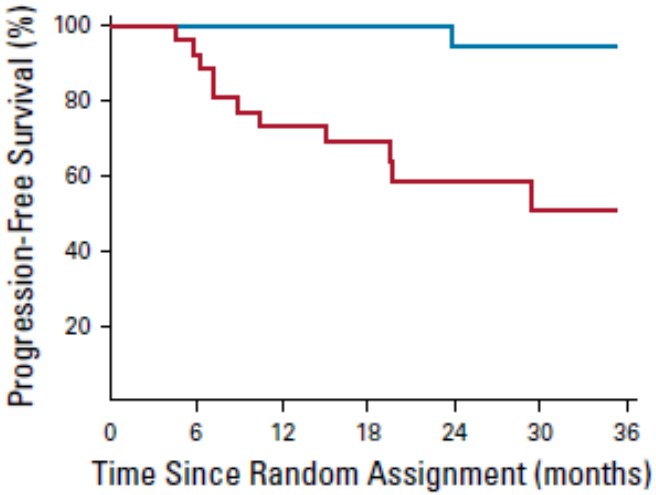
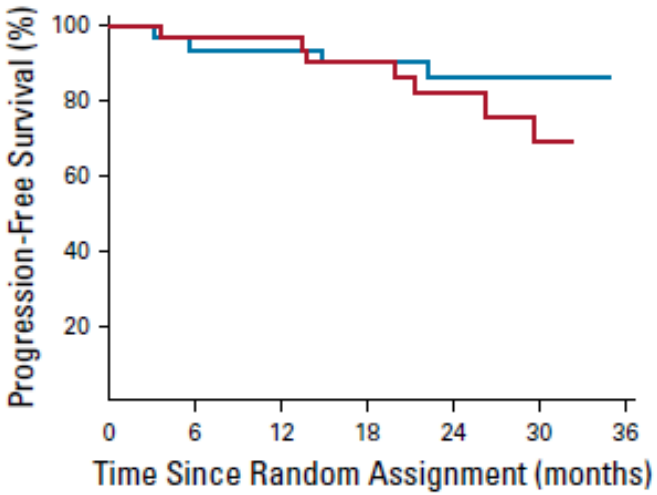
Haut risque



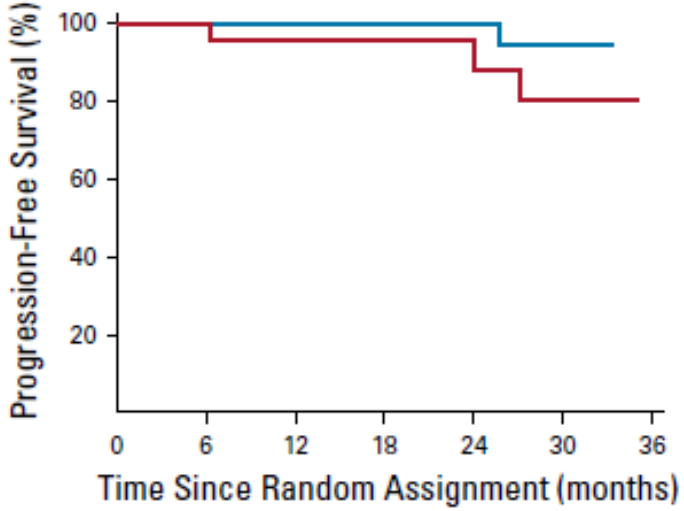
No. at risk:								
Lenalidomide	25	25	23	22	18	15	13
Observation	31	24	19	14	8	7	5

Risque intermédiaire



No. at risk:								
Lenalidomide	34	29	29	24	18	14	11
Observation	34	30	29	25	14	10	8

Faible risque



No. at risk:								
Lenalidomide	31	29	29	25	19	13	11
Observation	27	23	19	17	12	9	6

IMPORTANCE DE BIEN IDENTIFIER LES PATIENTS A HAUT RISQUE AVANT D'ENVISAGER UNE STRATEGIE DE TRAITEMENT PRECOCE

COMMENT AMELIORER L'IDENTIFICATION DES SMM A HAUT RISQUE DE PROGRESSION ?

*génétique

Mateos et al. *Blood Cancer Journal* (2020)10:102
https://doi.org/10.1038/s41408-020-00366-3

Blood Cancer Journal

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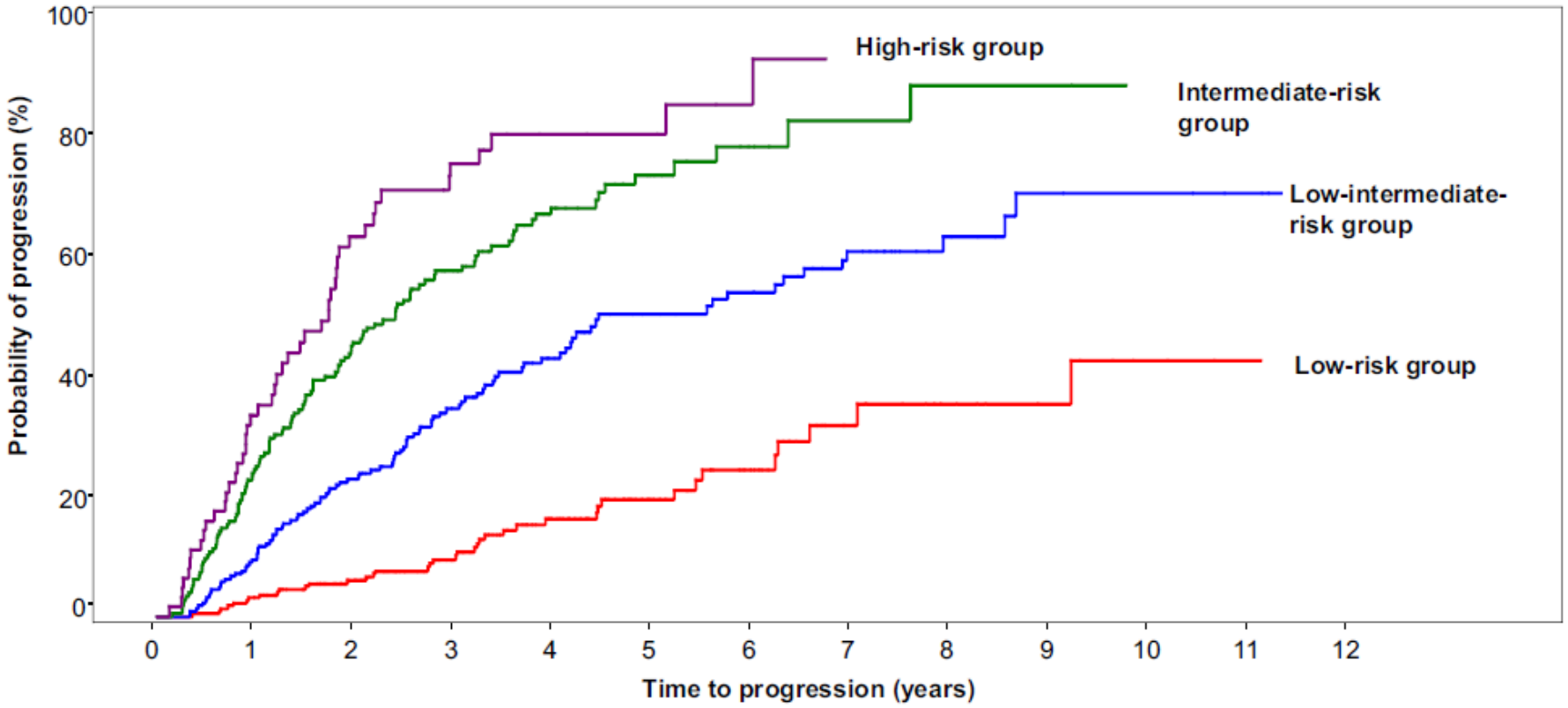
International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM)

Score 20/20/20 + cytogénétique

(t(4;14), t(14;16), +1q, and/or del13q/monosomy 13).



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0	Reference	6.0%	225 (32.7%)
Low-intermediate	1	4.16 (2.26 – 7.67)	22.8%	224 (32.5%)
Intermediate	2	9.82 (5.46 – 17.7)	45.5%	177 (25.7%)
High	3-4	15.5 (8.23 – 29.0)	63.1%	63 (9.1%)

Mateos et al. *Blood Cancer Journal* (2020)10:102
https://doi.org/10.1038/s41408-020-00366-3

Blood Cancer Journal

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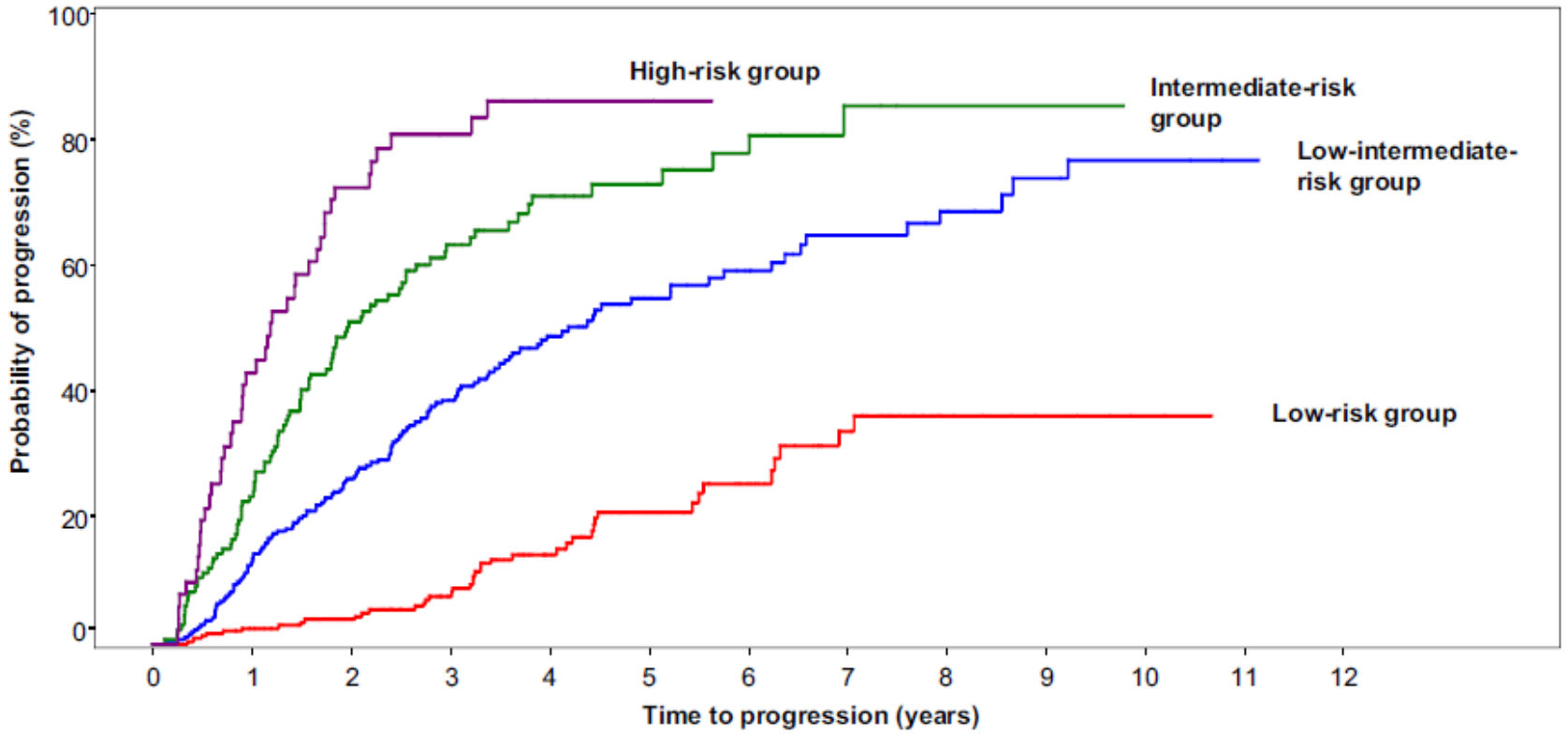
International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM)

Risk factor	Coefficient	Odds ratio (95% CI)	*p* value	Score
FLC IU				
0–10 (reference)	–	–	–	0
>10–25	0.69	1.99 (1.15, 3.45)	0.014	2
>25–40	0.96	2.61 (1.36, 4.99)	0.004	3
>40	1.56	4.73 (2.88, 7.77)	<0.0001	5
M-protein				
0–1.5 (reference)	–	–	–	0
>1.5–3	0.95	2.59 (1.56, 4.31)	0.0002	3
>3	1.3	3.65 (2.02, 6.61)	<0.0001	4
BMPC				
0–15 (reference)	–	–	–	0
>15–20	0.57	1.77 (1.03, 3.06)	0.04	2
>20–30	1.01	2.74 (1.6, 4.68)	0.0002	3
>30–40	1.57	4.82 (2.5, 9.28)	<0.0001	5
>40	2	7.42 (3.23, 17.02)	<0.0001	6
FISH abnormality	0.83	2.28 (1.53, 3.42)	<0.0001	2

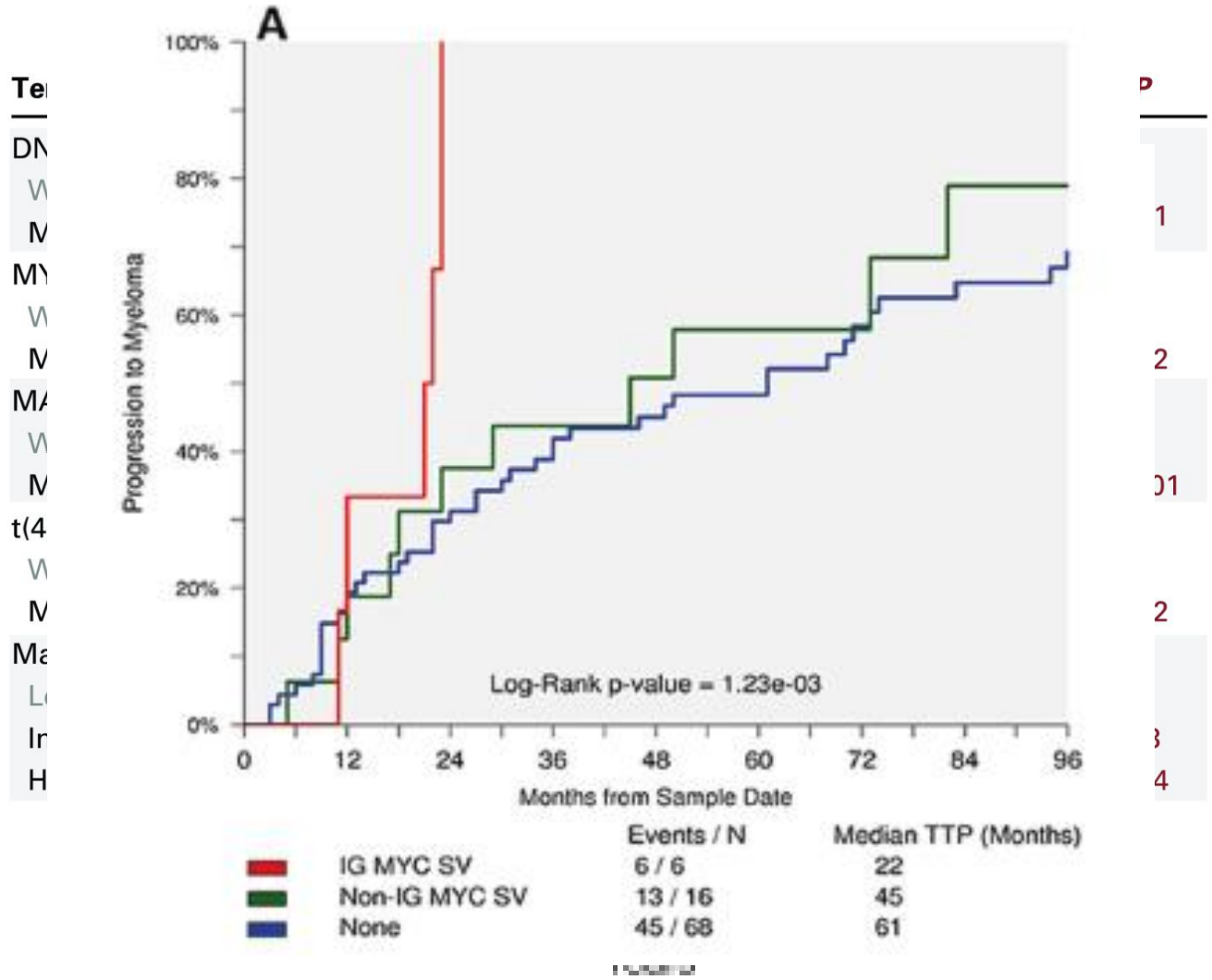
FLC IU involved to uninvolved serum-free light chain ratio.



Risk Stratification groups	Total risk score	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0-4	Reference	3.8%	241 (35.0%)
Low-intermediate	5-8	7.56 (3.77 – 15.2)	26.2%	264 (38.3%)
Intermediate	9-12	17.3 (8.63 – 34.8)	51.1%	133 (19.3%)
High	>12	31.9 (15.4 – 66.3)	72.5%	51 (7.4%)

COMMENT AMELIORER L'IDENTIFICATION DES SMM A HAUT RISQUE DE PROGRESSION ?

- t(4;14) and del17p (Rajkumar et al. Leukemia 2013)
- 1q gain (Neben et al. JCO 2013)
- MYC translocations (Misund et al. Leukemia 2019)
- Alterations in the DNA repair pathway, MYC and MAPK pathway (Bustoros et al. JCO2020)
- KRAS mutations (Boyle et al. Nat Comm 2021)



- ↘ T effecteurs mémoires et cytotoxiques, ↗ des Tγδ et cellules NK (Termini et al. ASH 2020)

COMMENT AMELIORER L'IDENTIFICATION DES SMM A HAUT RISQUE DE PROGRESSION ?

*génétique

*critères dynamiques

OPEN

Citation: Blood Cancer Journal (2016) 6, e454; doi:10.1038/bcj.2016.65

www.nature.com/bcj

ORIGINAL ARTICLE

Evolving changes in disease biomarkers and risk of early progression in smoldering multiple myeloma

P Ravi[1], S Kumar[2], JT Larsen[2], W Gonsalves[2], F Buadi[2], MQ Lacy[2], R Go[2], A Dispenzieri[2], P Kapoor[2], JA Lust[2], D Dingli[2], Y Lin[2], SJ Russell[2], N Leung[2], MA Gertz[2], RA Kyle[2], PL Bergsagel[3] and SV Rajkumar[2]

Biological evolving patern

- 190 SMM (2014 IMW criteria)
- Evolving patern
  - Monoclonal protein (e MP)
    - ≥ 10% within first 6 months (if M-prot ≥ 30 g/l)
    - ≥ 25% within first 6 months (if M-prot < 30 g/l)
    - And ≥ 5 g/l
  - Hemoglobin (e Hb)
    - ≥ 0,5 g/dl within first 12 months

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3 factors score

- BMPC ≥ 20%
- e MP
- e Hb

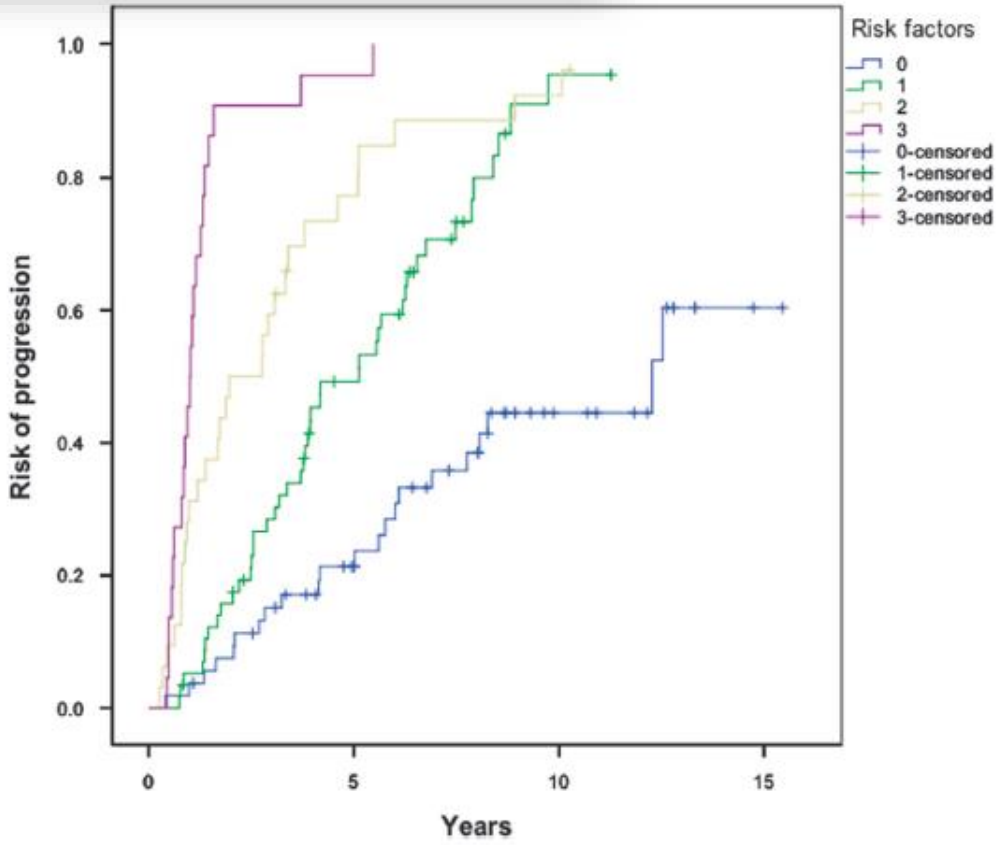


Figure 1. Risk of progression in SMM patients, stratified by the number of risk factors (eMP, eHb and BMPC ⩾20%) at diagnosis. $P < 0.001$.

MRI evolving patern

Leukemia (2014), 1–7

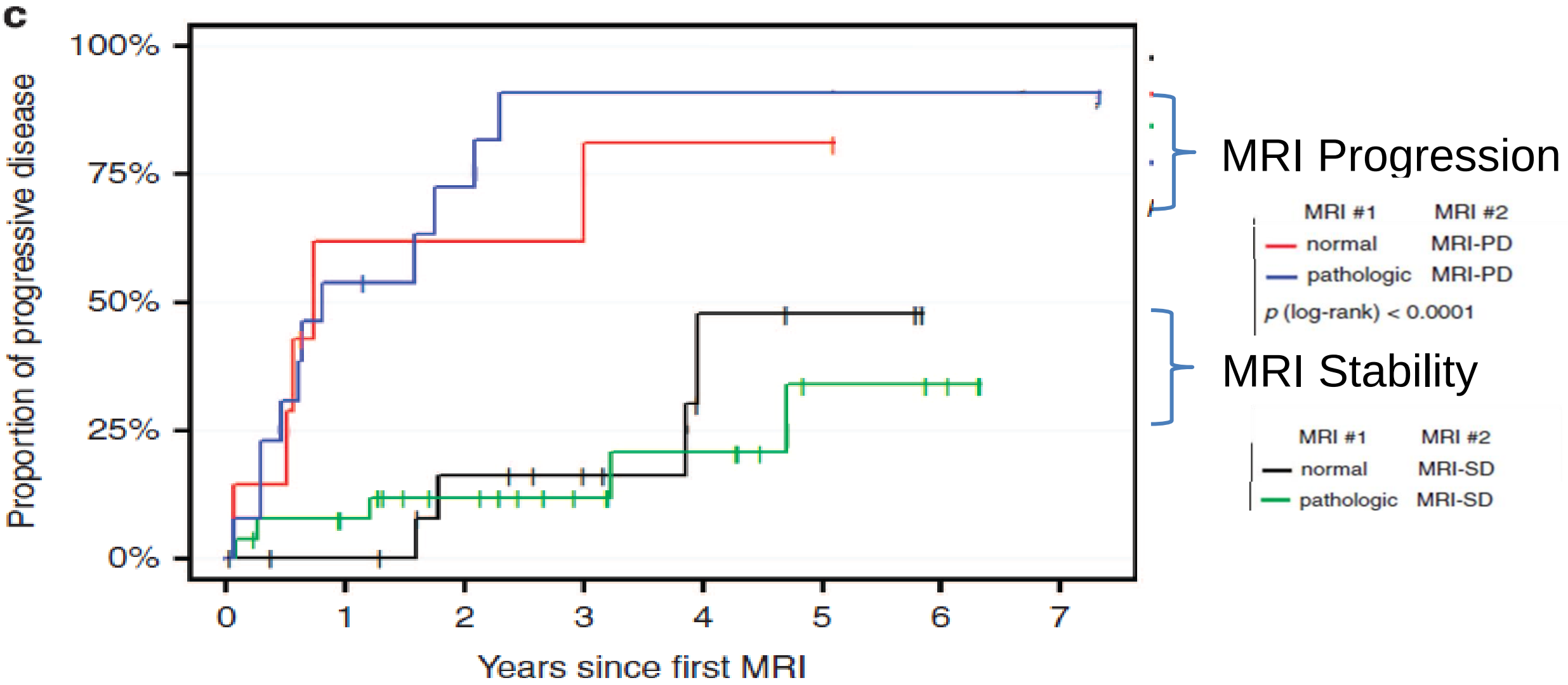
www.nature.com/leu

ORIGINAL ARTICLE

Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma

M Merz[1,2], T Hielscher[3], B Wagner[2], S Sauer[1], S Shah[1], MS Raab[1], A Jauch[4], K Neben[1], D Hose[1], G Egerer[1], M-A Weber[5], S Delorme[2], H Goldschmidt[1,6] and J Hillengass[1,2]

- 63 SMM
- ≥ 2 MRI during follow-up


c
100%
75%
50%
25%
0%
Proportion of progressive disease
0
1
2
3
4
5
6
7
Years since first MRI
MRI Progression
MRI #1 MRI #2
normal MRI-PD
pathologic MRI-PD
p (log-rank) < 0.0001
MRI Stability
MRI #1 MRI #2
normal MRI-SD
pathologic MRI-SD

FAUT-IL RENOUVELER AU COURS DU SUIVI

- Dosage des CLL?
- IRM ?
- Myélogramme?

COMMENT AMELIORER LA PRISE EN CHARGE DES MYELOMES INDOLENTS ?

- Traitement précoce? Guérir vs retarder la progression

-IFM ➔ étude observationnelle CARRISMM

IFM 2017-04

CARRISMM

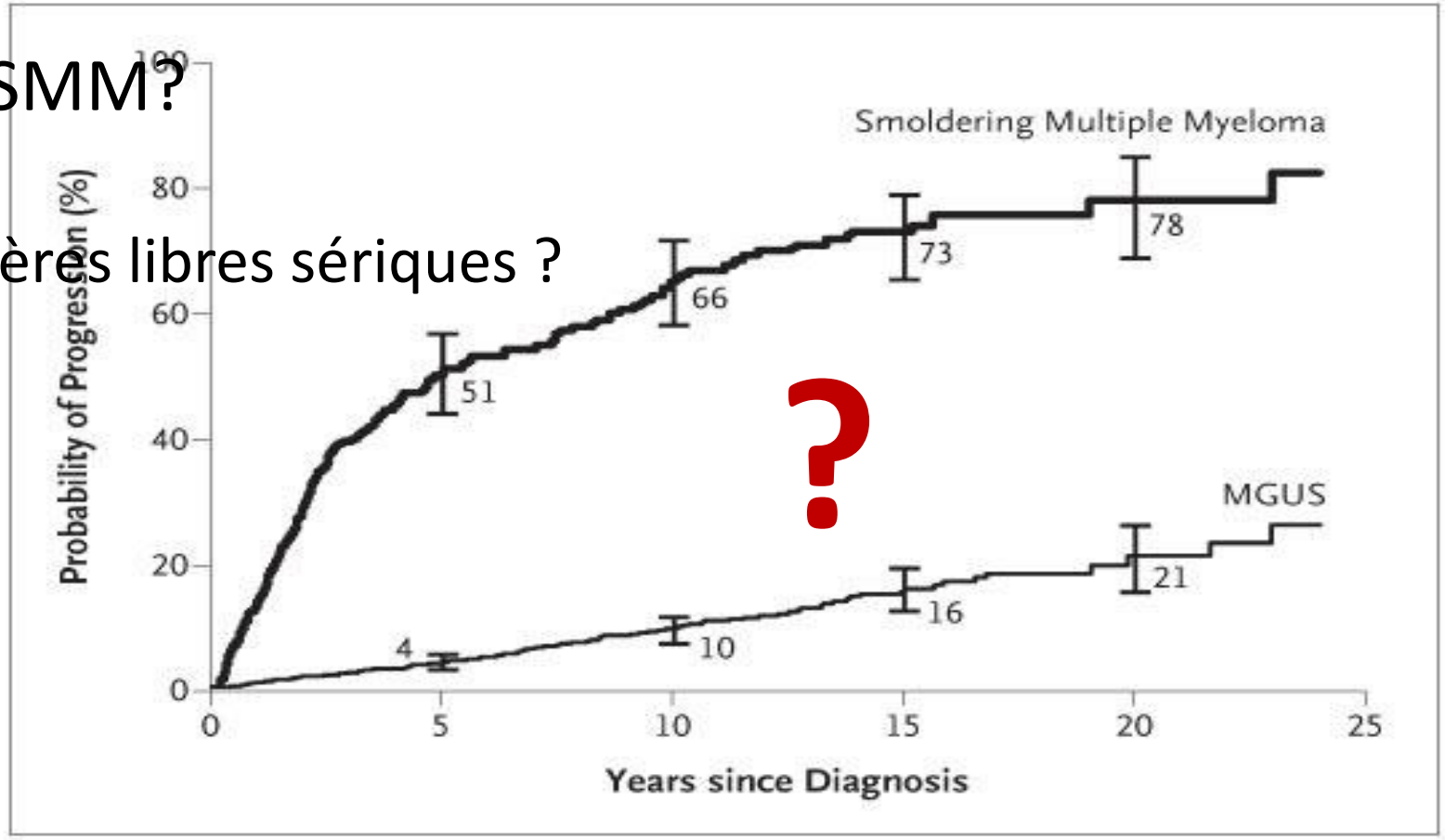
(Optimisation of CARe and RISk stratification of SMoldering Myeloma)

Evaluation of the impact of the update multiple myeloma criteria on the natural history of smoldering myeloma in order to establish new recommendations about follow-up and prognostic evaluation of Smoldering Myeloma.

Prise en charge des SMM nouvelle définition?

- Que devient le risque évolutif des SMM nouvelle définition?

- Modalités de suivi des SMM?
  - myélogramme ?
  - dosage des chaînes légères libres sériques ?
  - IRM ?



Cohorte prospective

- Critères inclusion
  - SMM selon critères IMWG 2014
  - Diagnostic < 1 an

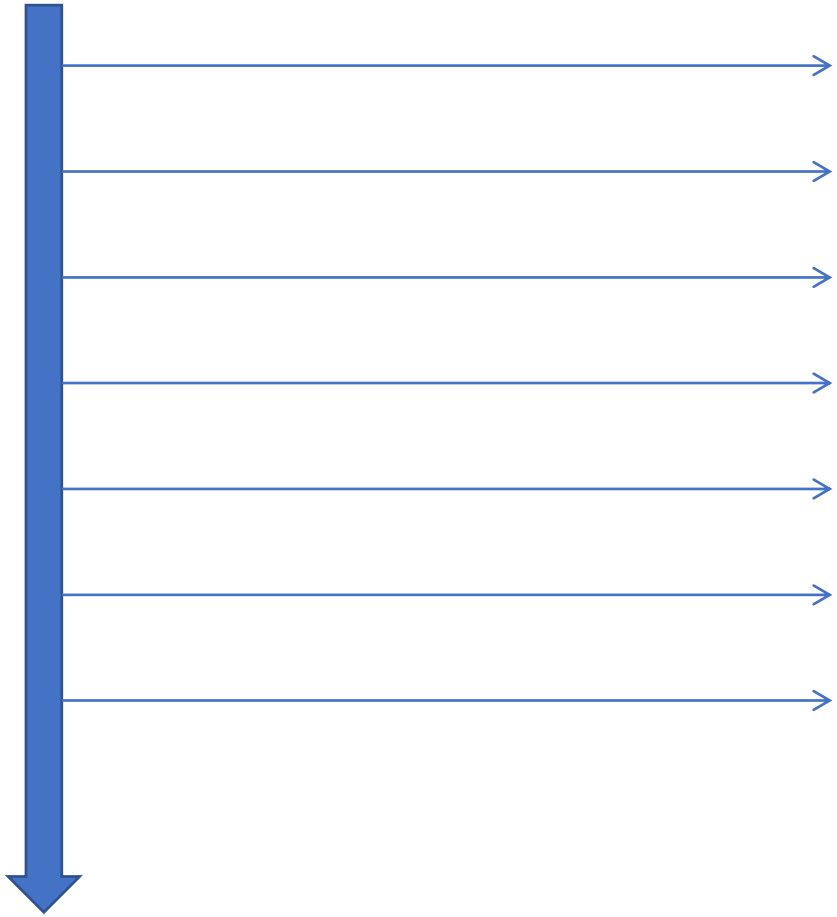
Cohorte prospective

- IRM (+/- TEP) à l'inclusion
- Suivi standardisé pendant 2 ans
  - Contrôle biologique tous les 3 mois
  - Dosage des CLL tous les 6 mois
  - Prélèvement médullaire annuel

    →analyse en CMF (% plasmo monoclonaux/polyclonaux)

    →purification plasmocytes pour analyses génétiques
  - IRM annuelle
- Suivi biologique semestriel pendant 3 ans

Cohorte prospective



Évolution vers un MM

- **Critères CRAB**
- **Early MM**

Objectifs ?

Inclusion 450 patients

➔Evaluer le risque évolutif des SMM (nouveaux critères)

➔Intérêt du suivi systématique par FLC, IRM, myélogramme?

➔Etablir de nouvelles recommandations pour le suivi des SMM

➔Valider les facteurs prédictifs déjà décrits

➔Identifier de nouveaux facteurs prédictifs notamment génétiques

➔Etudier impact pronostiques des critères dynamiques - progression biologique/IRM

➔Etudier prospectivement et simultanément plasmocytes ET environnement immunitaire

POUR CONCLURE

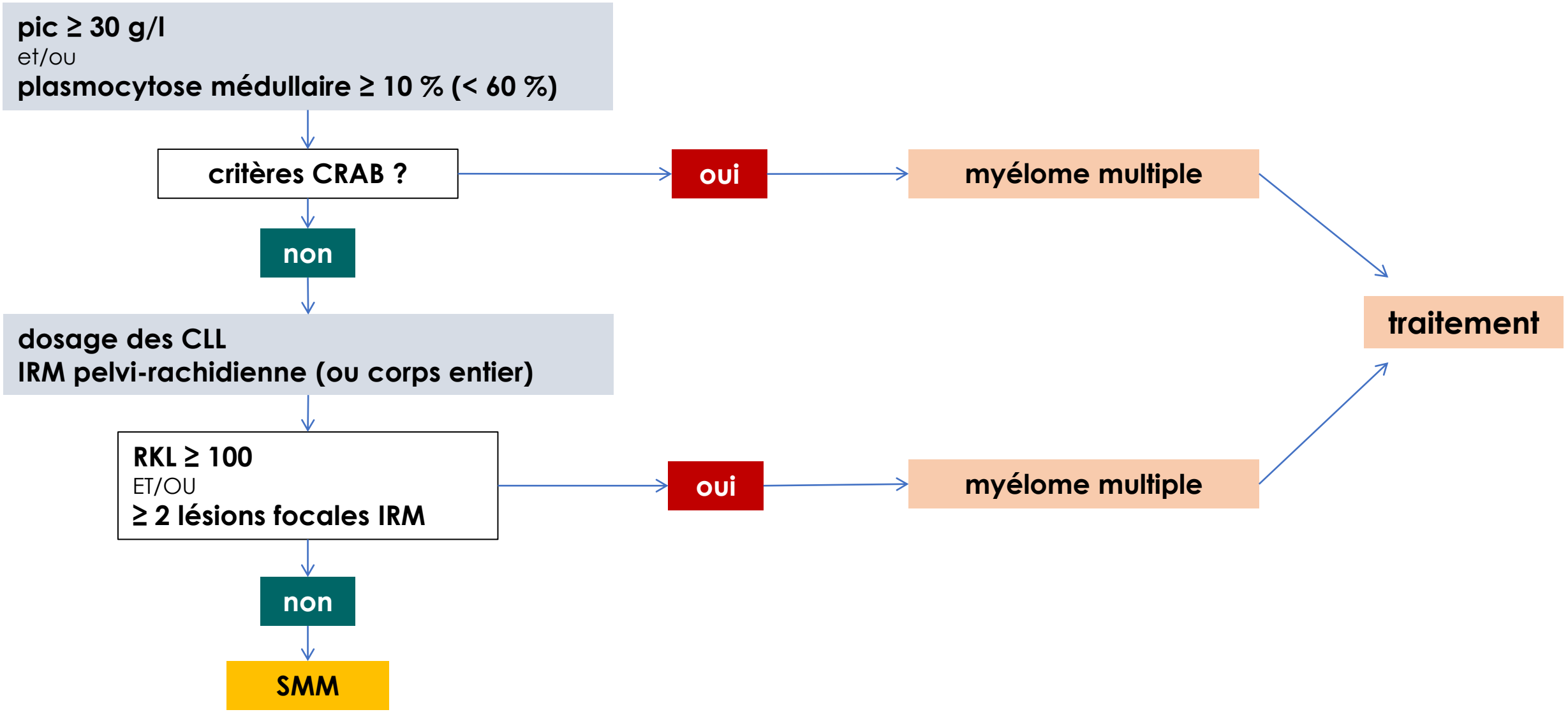
1. L'IRM et le dosage des chaînes libres sériques sont indispensables pour poser le diagnostic de myélome indolent (IMWG 2014).

2. Le pronostic reste hétérogène ;
   il persiste des patients à haut risque nécessitant une surveillance plus rapprochée.

3. L'abstention reste la règle avec surveillance adaptée au risque individuel

4. L'étude observationnelle de l'IFM, CARRISMM, permettra d'identifier de nouveaux marqueurs pronostiques et de définir les modalités de surveillance optimale

Quelles explorations au diagnostic de MM indolent ?



Sur quels critères adapter le suivi ?