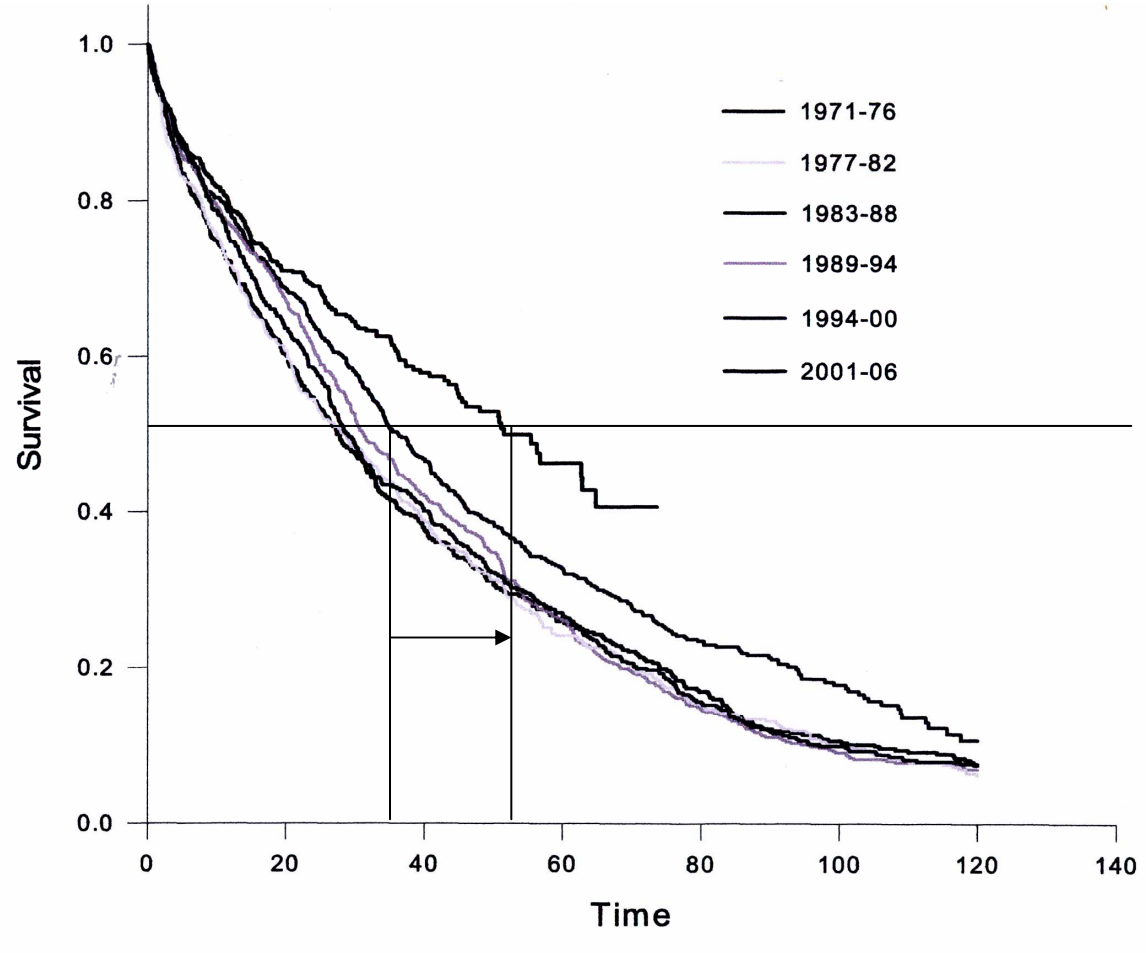
Actualités dans le myélome

Dr Bernard De Prijck - ULG

Fleurus - 20 Mai 2010

Le myélome, une maladie en pleine (r)évolution !



Définitions…

Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: Serum monoclonal protein <3 g/100 ml Clonal bone marrow plasma cells <10% and Absence of end-organ damage such as hypercalcemia, *r*enal insufficiency, *a*nemia and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met: Serum monoclonal protein (IgG or IgA) ⩾3 g/100 ml and/or clonal bone marrow plasma cells ⩾10% and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder
Multiple myeloma	All three criteria must be met except as noted: Clonal bone marrow plasma cells ⩾10% Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma) and Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically

Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma

RA Kyle and SV Rajkumar Leukemia 2009;23:3-9

(R)évolution…

- **Gammapathie monoclonale bénigne (« MGUS »)**
- **Génétique**
- **Chaînes légères libres**
- **Atteinte osseuse**
- **« Nouvelles drogues »**
- **Greffe de moëlle**

MGUS

Hérédité ?

Etat « pré-myélomateux »?

blood
2009 114: 791-795
Prepublished online Jan 30, 2009;
doi:10.1182/blood-2008-12-191676

Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden

Ola Landgren, Sigurdur Y. Kristinsson, Lynn R. Goldin, Neil E. Caporaso, Cecilie Blimark, Ulf-Henrik Mellqvist, Anders Wahlin, Magnus Bjorkholm and Ingemar Turesson

	First-degree relatives of MGUS patients (n = 14 621)	First-degree relatives of controls (n = 58 387)	RR (95% CI)*
MGUS	22	31	2.8 (1.4-5.6)†
Multiple myeloma	41	57	2.9 (1.9-4.3)†
Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia	8	8	4.0 (1.5-11)†
Chronic lymphocytic leukemia	23	46	2.0 (1.2-2.3)†
Non-Hodgkin lymphoma	44	161	1.1 (0.8-1.5)
Hodgkin lymphoma (< 45 y)	8	24	1.3 (0.6-2.9)
Hodgkin lymphoma (> 45 y)	1	18	0.2 (0.0-1.7)

*All estimates were adjusted for sex of first-degree relative.

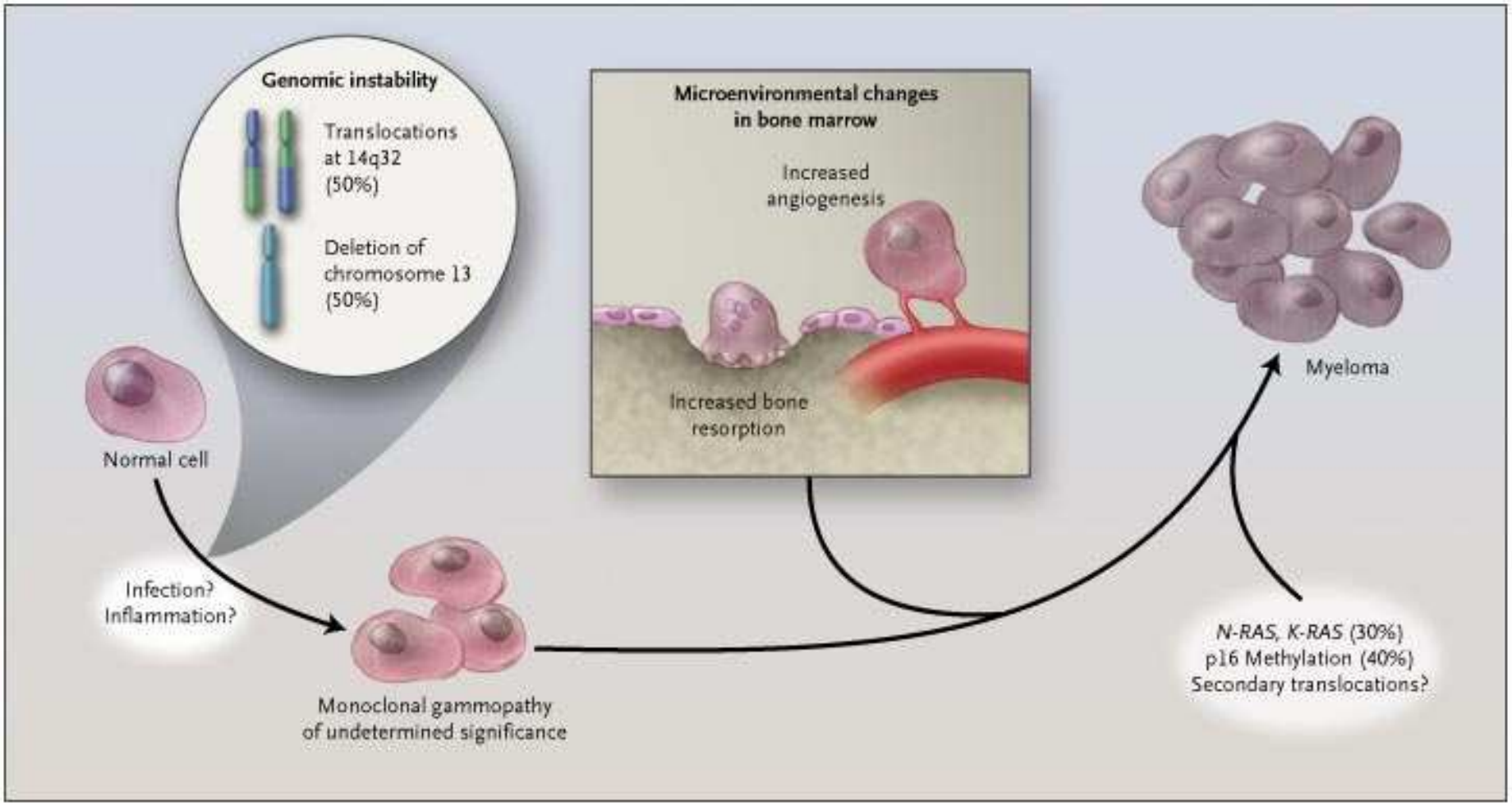
†Statistically significant (2-sided *P* value < .05).

MGUS patient ➔ risque relatif descendance

- MGUS ➔ RR x 2.8 MGUS, x 2.9 MM, x 4 Waldenström et x 2 LLC
- MGUS IgG/A ➔ RR x 4 MGUS, x 2.9 MM, x 20 Waldenström
- MGUS IgM ➔ RR x 5 LLC

➔ Hérédité ou environnement …?!

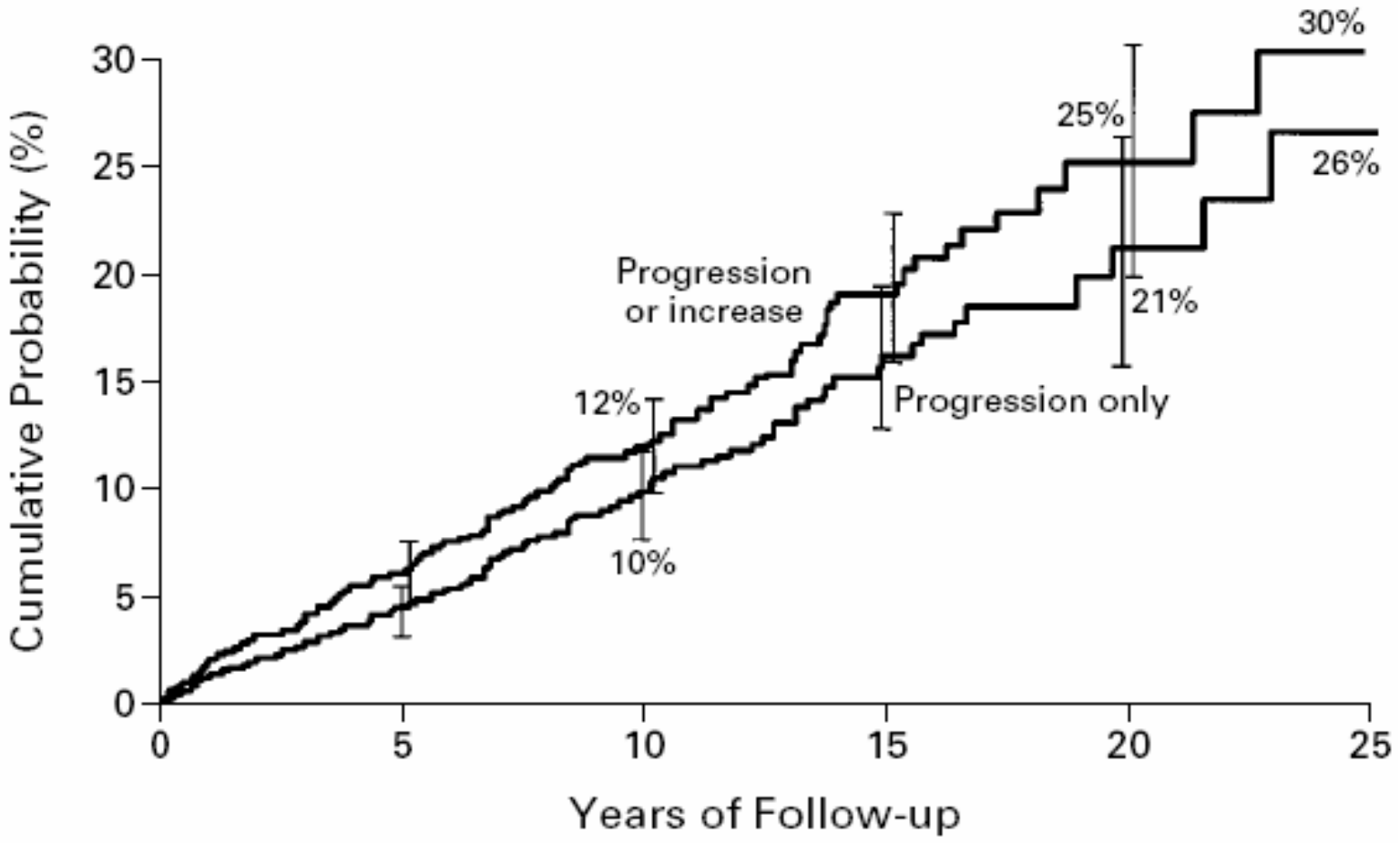
Etat pré-myélomateux ?



Kyle RA and Rajkumar SV. N Engl J Med 2004;351:1860-73

A LONG-TERM STUDY OF PROGNOSIS IN MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

ROBERT A. KYLE, M.D., TERRY M. THERNEAU, PH.D., S. VINCENT RAJKUMAR, M.D., JANICE R. OFFORD, B.S., DIRK R. LARSON, M.S., MATTHEW F. PLEVAK, B.S., AND L. JOSEPH MELTON III, M.D.



NEJM 2002;346:564

blood

2009 113: 5412-5417
Prepublished online Jan 29, 2009;
doi:10.1182/blood-2008-12-194241

Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study

Ola Landgren, Robert A. Kyle, Ruth M. Pfeiffer, Jerry A. Katzmann, Neil E. Caporaso, Richard B. Hayes, Angela Dispenzieri, Shaji Kumar, Raynell J. Clark, Dalsu Baris, Robert Hoover and S. Vincent Rajkumar

MGUS précède MM

- Pic MC décelable 8 ans avant dans 75% des MM
- Si FLC ratio aNl ou pic > 15 gr/l, risque de 58% à 20 ans, sinon 5%...
- Deux modalités évolutives des MGUS:
  - Augmentation régulière du pic ou du FLC ratio
  - Pic ou ratio stable

  → **Imprévisible !**

Leukemia (2009) 23, 2210–2221
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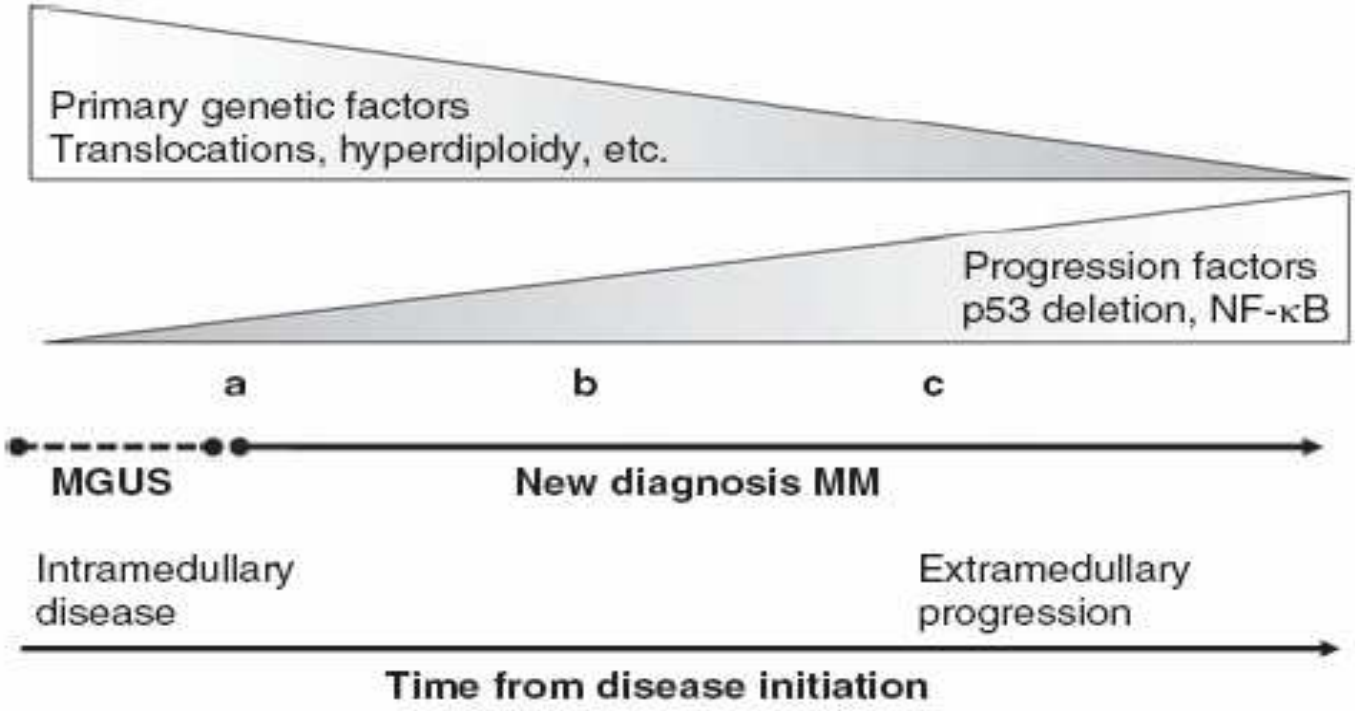
www.nature.com/leu

SPOTLIGHT REVIEW

International Myeloma Working Group molecular classification of multiple myeloma: spotlight review

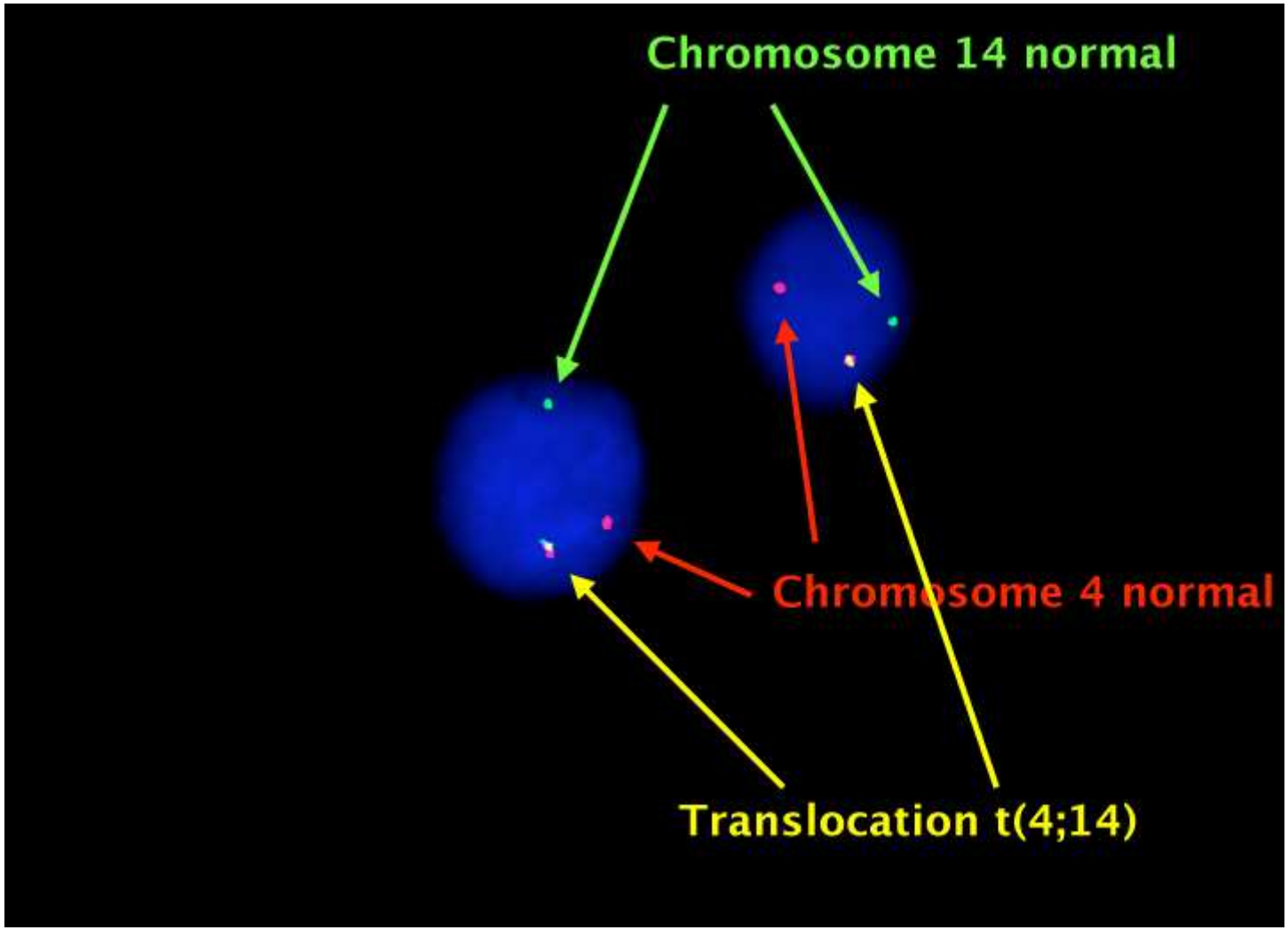
R Fonseca[1], PL Bergsagel[1], J Drach[2], J. Shaughnessy[3], N Gutierrez[4], AK Stewart[1], G Morgan[5], B Van Ness[6], M Chesi[1], S Minvielle[7], A Neri[8], B Barlogie[3], WM Kuehl[9], P Liebisch[10], F Davies[5], S Chen-Kiang[11], BGM Durie[12], R Carrasco[13], Orhan Sezer[14], Tony Reiman[15], Linda Pilarski[16] and H Avet-Loiseau[7]



Apports de la génétique

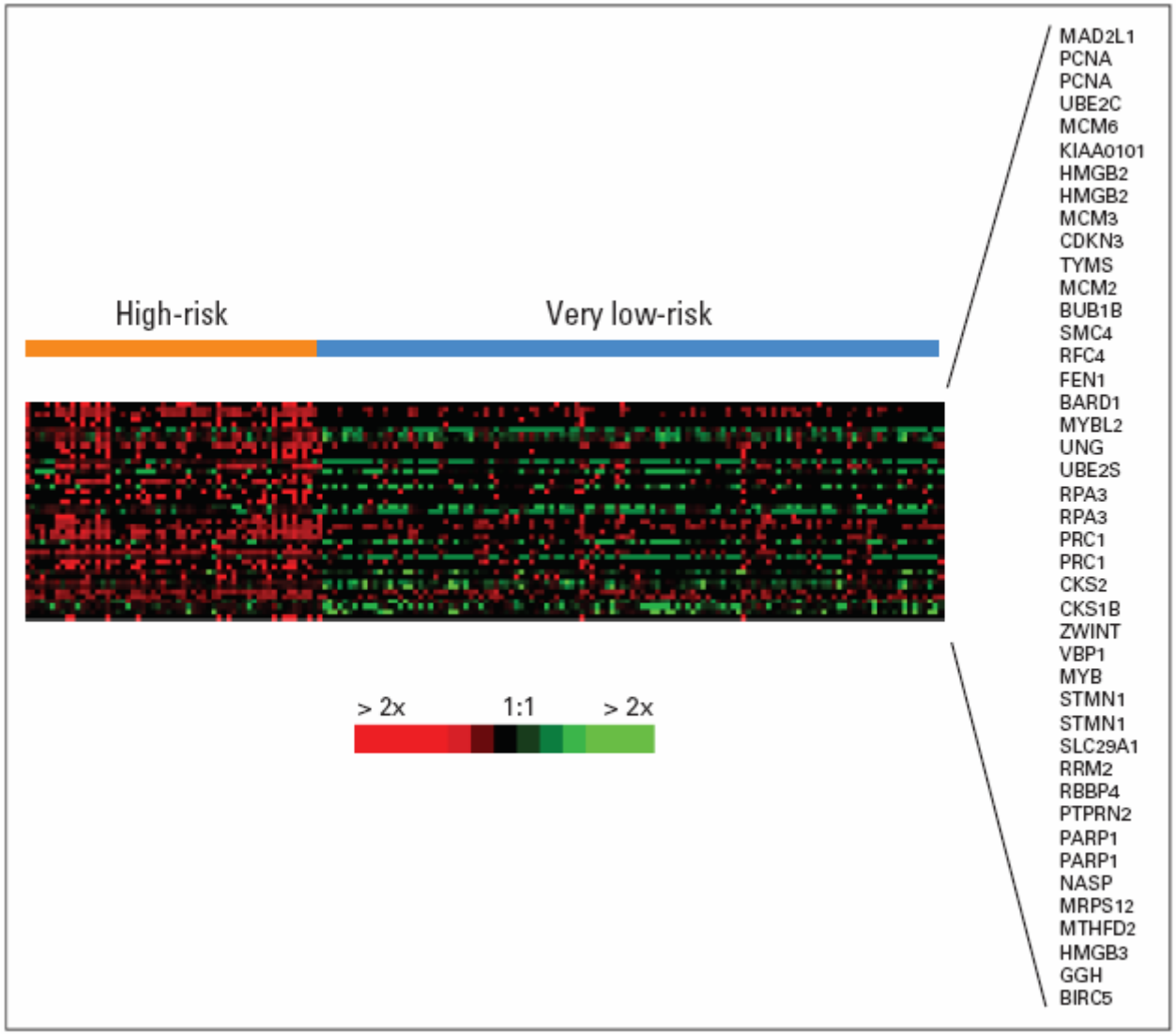
- FISH sur plasmocytes purifiés
  - → t(4;14)
  - → t(14;16)
  - → 17p13 deletion
  - → t(11;14)
  - → del13
  - → anom 1
  - → ploïdie

…


Chromosome 14 normal
Chromosome 4 normal
Translocation t(4;14)

Apports de la génétique

- FISH sur plasmocytes purifiés
- Explosion des études grâce au « GEP » !
  → Etiopathogénie
  → Facteurs pronostiques
  → ??? Traitements ciblés…!!!



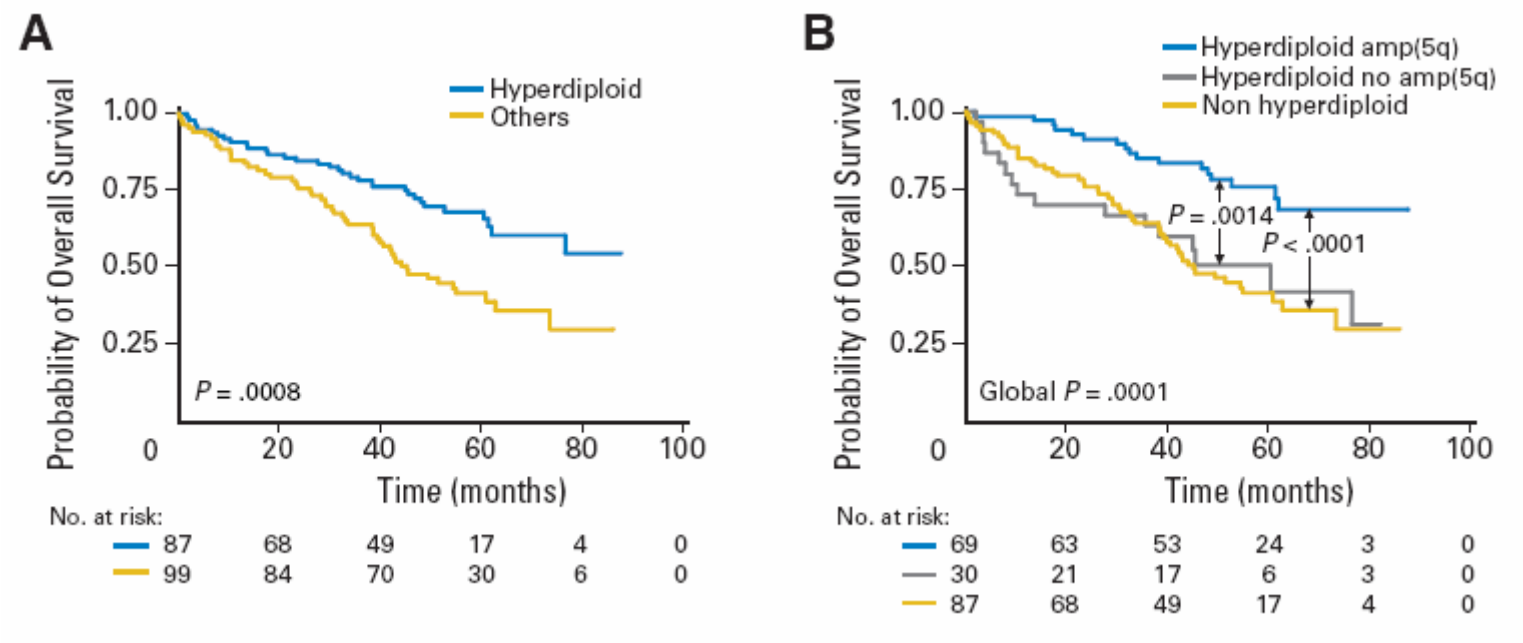
Decaux, JCO 2008,26:4798

New proposed International Myeloma Working Group molecular cytogenetic classification

	Percentage of patients	*Clinical and laboratory features*
Hyperdiploid	45	More favorable, IgG-κ, older patients.
Non-hyperdiploid	40	Aggressive, IgA-λ, younger individuals
Cyclin D translocation	18	
t(11;14)(q13;q32)	16	Upregulation of CCND1; favorable prognosis; bone lesions. Two subtypes by GEP
t(6;14q)(p21;32)	2	Probably same as CCND1
t(12;14)(p13;q32)	<1	Rare
MMSET translocation	15	
t(4;14)(p16;q32)	15	Upregulation of MMSET; upregulation of FGFR3 in 75% unfavorable prognosis with conventional therapy; bone lesions less frequent
MAF translocation	8	Aggressive
t(14;16)(q32;q23)	5	Confirmed as aggressive by at least two series
t(14;20)(q32;q11)	2	One series shows more aggressive disease.
t(8;14)(q24;q32)	1	Unknown effect on outcome but presumed aggressive.
Unclassified (other)	15	Various subtypes and some with overlap

Prognostic Significance of Copy-Number Alterations in Multiple Myeloma

Hervé Avet-Loiseau, Cheng Li, Florence Magrangeas, Wilfried Gouraud, Catherine Charbonnel, Jean-Luc Harousseau, Michel Attal, Gerald Marit, Claire Mathiot, Thierry Facon, Philippe Moreau, Kenneth C. Anderson, Loïc Campion, Nikhil C. Munshi, and Stéphane Minvielle

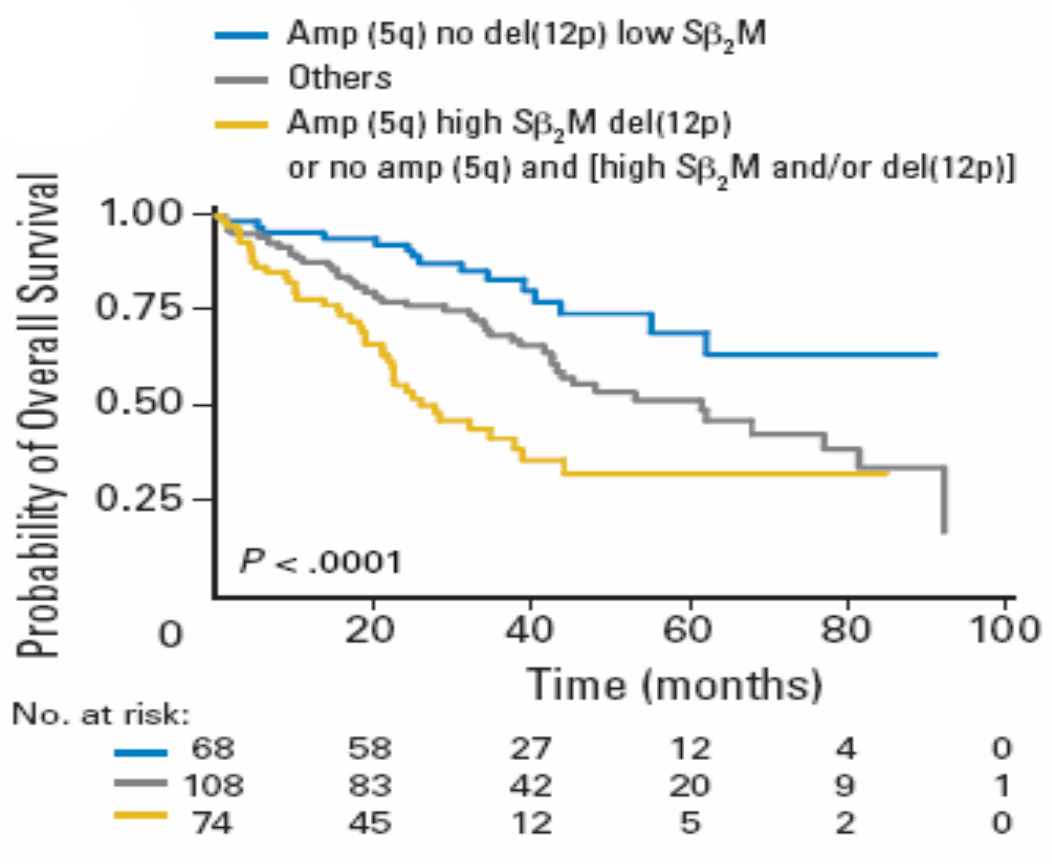


VOLUME 27 · NUMBER 27 · SEPTEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Significance of Copy-Number Alterations in Multiple Myeloma

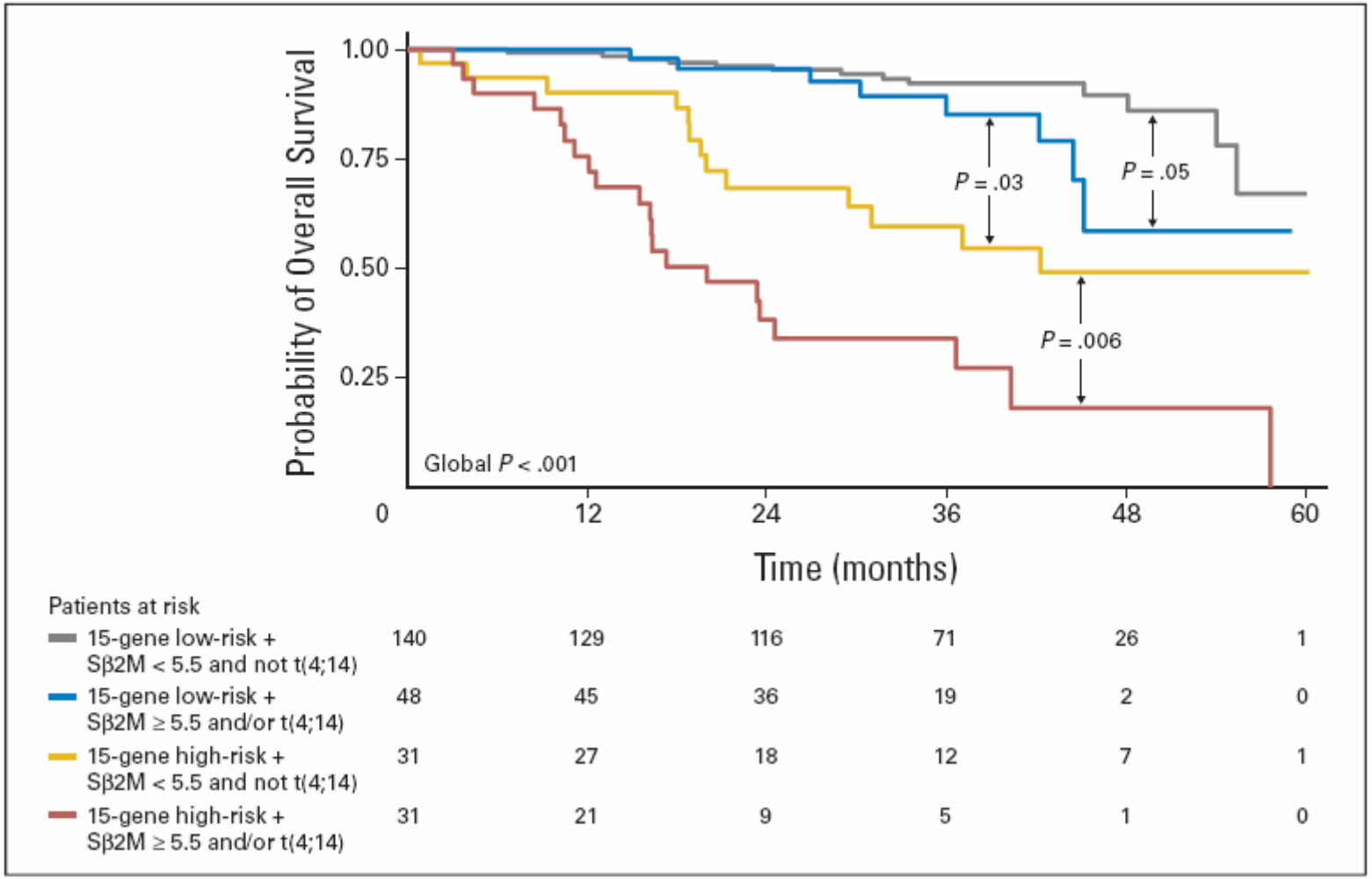
Hervé Avet-Loiseau, Cheng Li, Florence Magrangeas, Wilfried Gouraud, Catherine Charbonnel, Jean-Luc Harousseau, Michel Attal, Gerald Marit, Claire Mathiot, Thierry Facon, Philippe Moreau, Kenneth C. Anderson, Loïc Campion, Nikhil C. Munshi, and Stéphane Minvielle



VOLUME 27 · NUMBER 27 · SEPTEMBER 20 2009

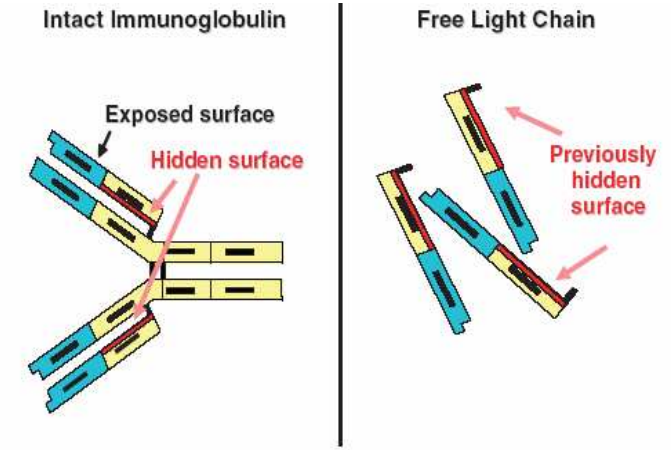
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Decaux, JCO 2008,26:4798

Les chaînes légères libres



Leukemia (2009) 23, 215–224
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www.nature.com/leu

SPOTLIGHT REVIEW

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders

A Dispenzieri[1], R Kyle[1], G Merlini[2], JS Miguel[3], H Ludwig[4], R Hajek[5], A Palumbo[6], S Jagannath[7], J Blade[8], S Lonial[9], M Dimopoulos[10], R Comenzo[11], H Einsele[12], B Barlogie[13], K Anderson[14], M Gertz[1], JL Harousseau[15], M Attal[16], P Tosi[17], P Sonneveld[18], M Boccadoro[6], G Morgan[19], P Richardson[14], O Sezer[20], MV Mateos[3], M Cavo[17], D Joshua[21], I Turesson[22], W Chen[23], K Shimizu[24], R Powles[25], SV Rajkumar[1] and BGM Durie[26] on behalf of the International Myeloma Working Group[27]

Dosage des chaînes légères libres

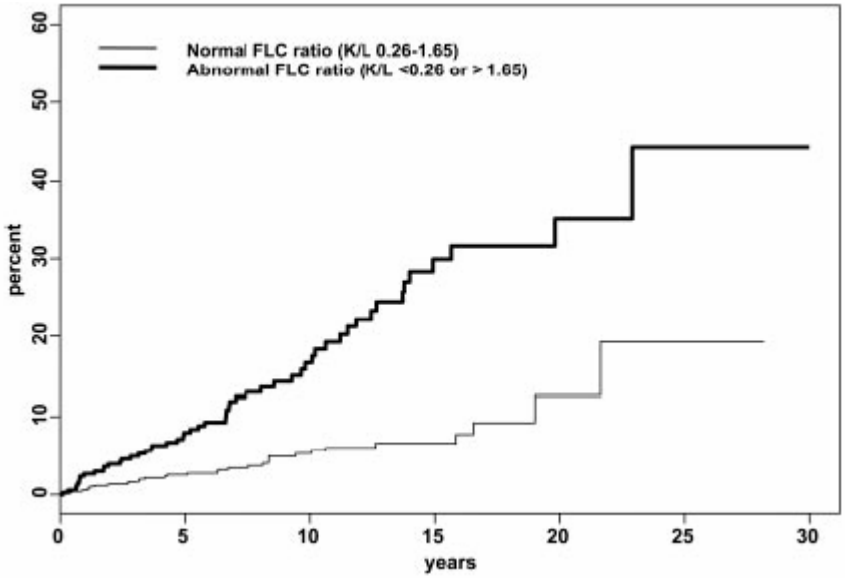
Uses of serum immunoglobulin free light chain assay
Screening in combination with immunofixation electrophoresis[20]
Baseline values prognostic
Monoclonal gammopathy of undermined significance[17]
Smoldering myeloma[16]
Symptomatic myeloma[9,12,29,32]
Plasmacytoma[31]
AL amyloidosis[28]
Hematologic response
AL amyloidosis[19,28,34–36]
'Non-secretory' myeloma[a 13]
Stringent complete response in multiple myeloma[a 37]
Light chain deposition disease (Personal experience of authors)

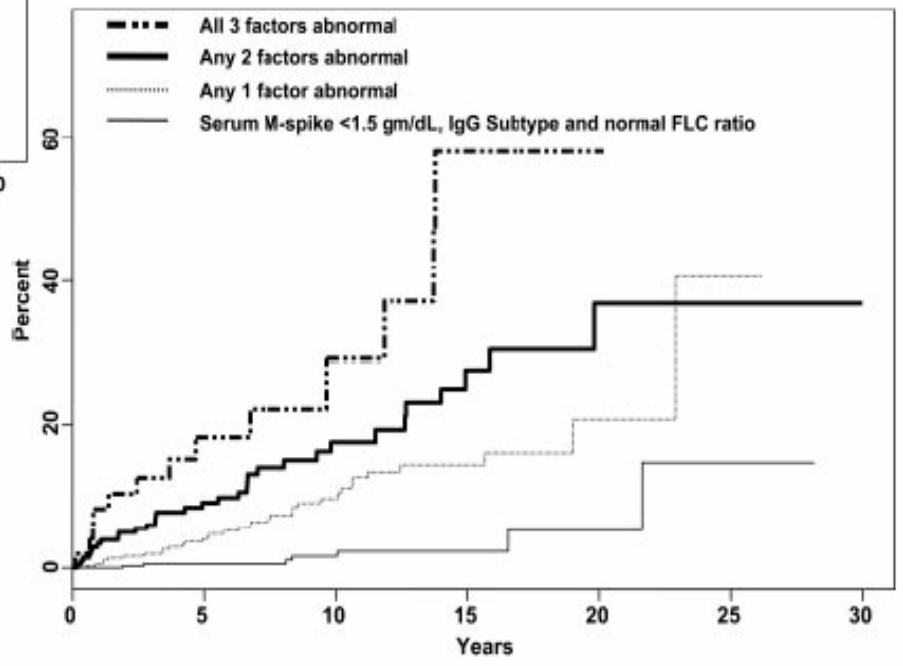
[a]Not yet validated.

Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance

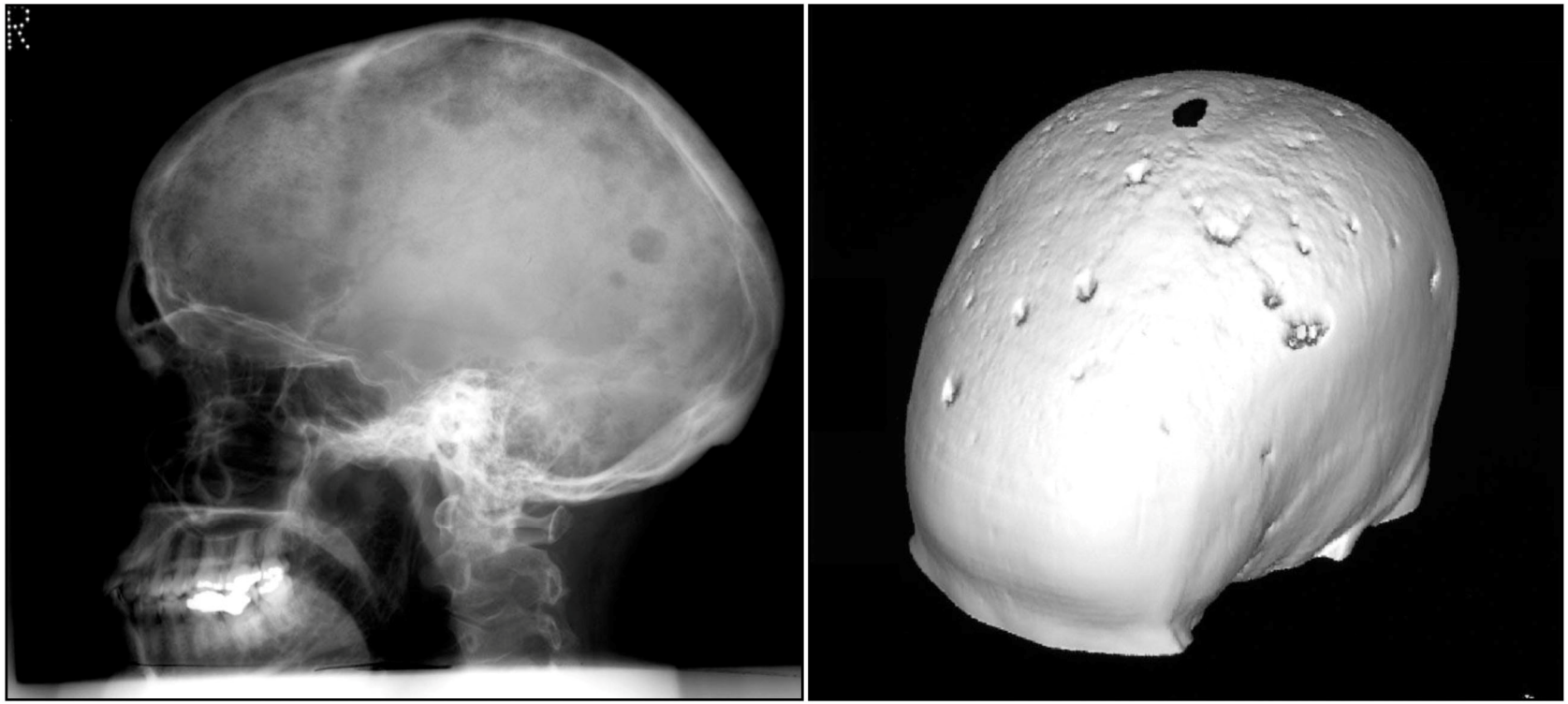
S. Vincent Rajkumar, Robert A. Kyle, Terry M. Therneau, L. Joseph Melton III, Arthur R. Bradwell, Raynell J. Clark, Dirk R. Larson, Matthew F. Plevak, Angela Dispenzieri, and Jerry A. Katzmann

BLOOD, 1 AUGUST 2005 • VOLUME 106, NUMBER 3



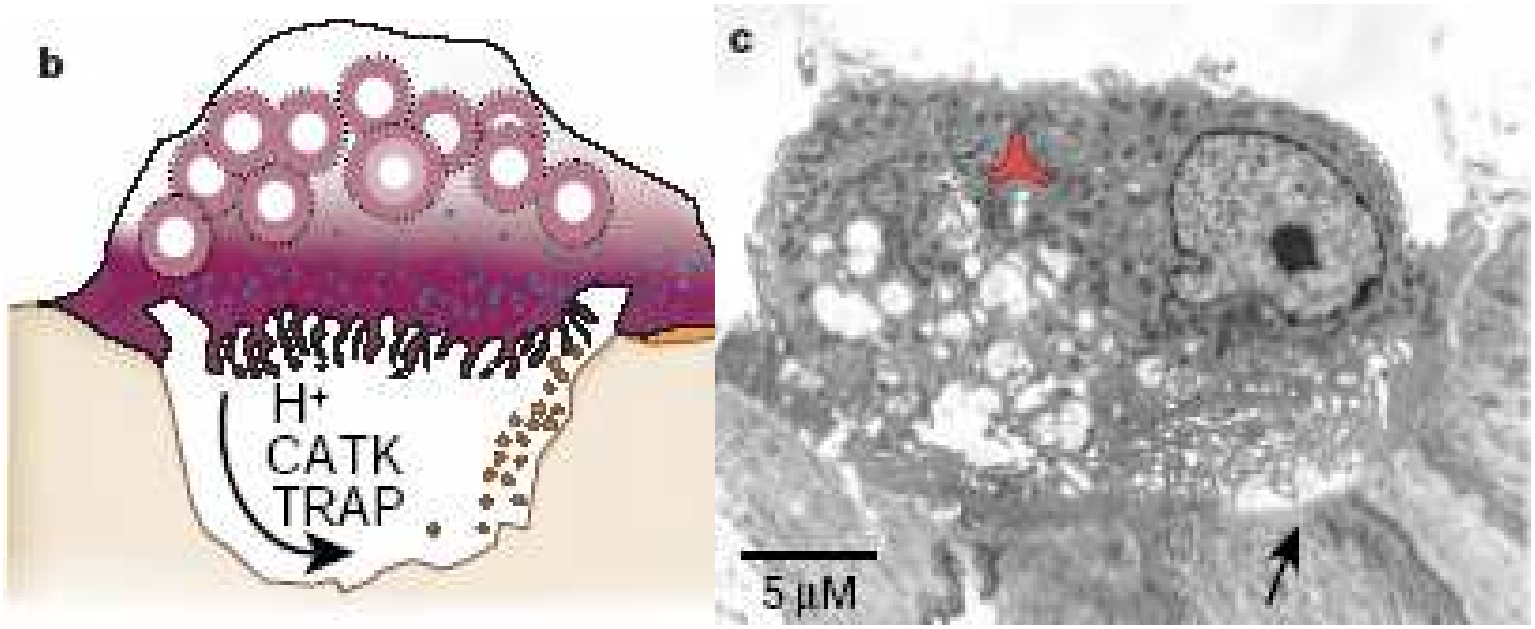


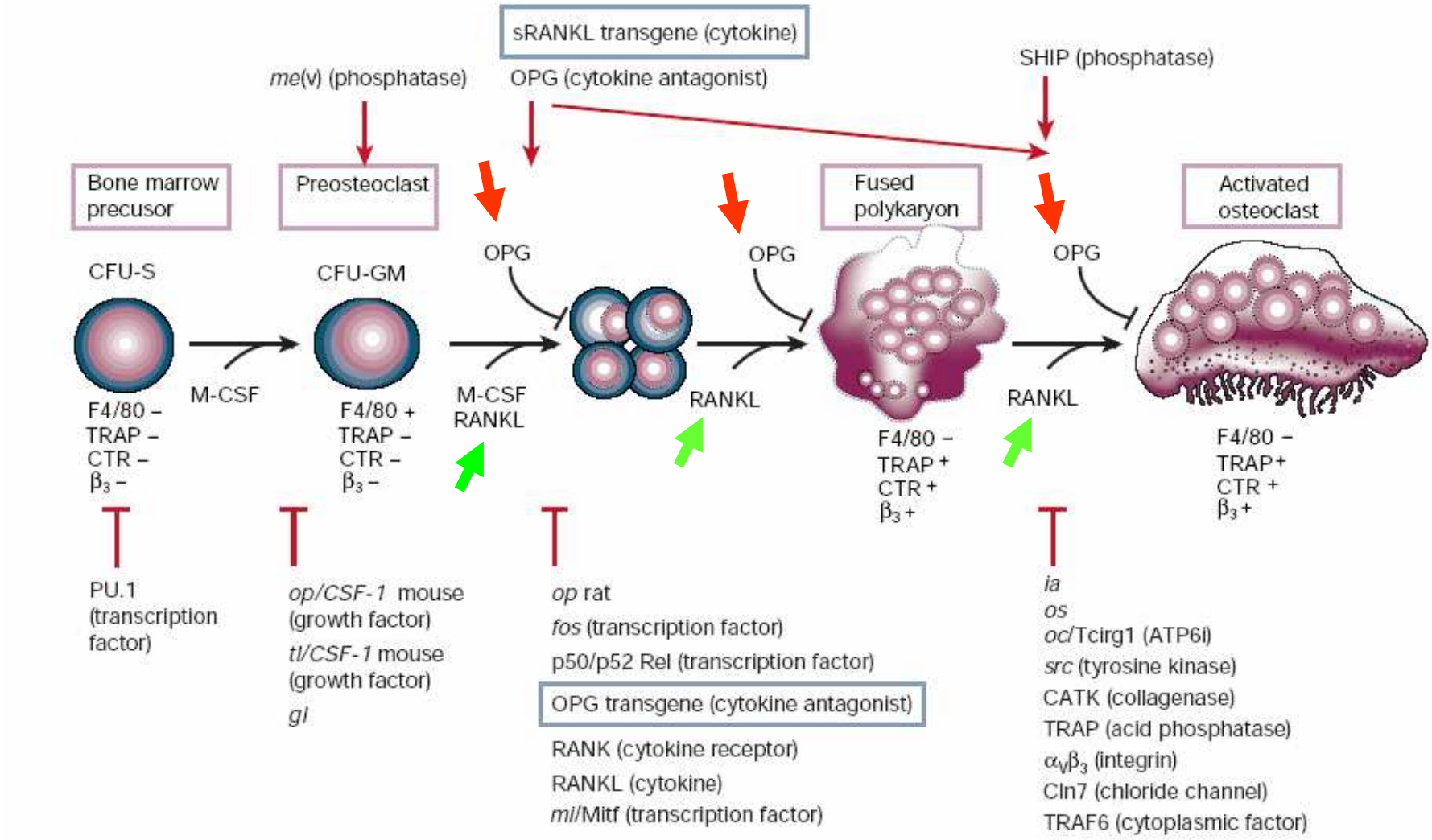
L’atteinte osseuse



La « petite main » du plasmocyte pour faire le sale boulot…

→ ***l'ostéoclaste ☹ !***




sRANKL transgene (cytokine)
me(v) (phosphatase)
OPG (cytokine antagonist)
SHIP (phosphatase)
Bone marrow precusor
Preosteoclast
Fused polykaryon
Activated osteoclast
OPG
OPG
OPG
CFU-S
CFU-GM
M-CSF
M-CSF
RANKL
RANKL
RANKL
F4/80 –
TRAP –
CTR –
β3 –
F4/80 +
TRAP –
CTR –
β3 –
F4/80 –
TRAP +
CTR +
β3 +
F4/80 –
TRAP +
CTR +
β3 +
PU.1 (transcription factor)
op/CSF-1 mouse (growth factor)
tl/CSF-1 mouse (growth factor)
gl
op rat
fos (transcription factor)
p50/p52 Rel (transcription factor)
OPG transgene (cytokine antagonist)
RANK (cytokine receptor)
RANKL (cytokine)
mi/Mitf (transcription factor)
ia
os
oc/Tcirg1 (ATP6i)
src (tyrosine kinase)
CATK (collagenase)
TRAP (acid phosphatase)
αVβ3 (integrin)
Cln7 (chloride channel)
TRAF6 (cytoplasmic factor)

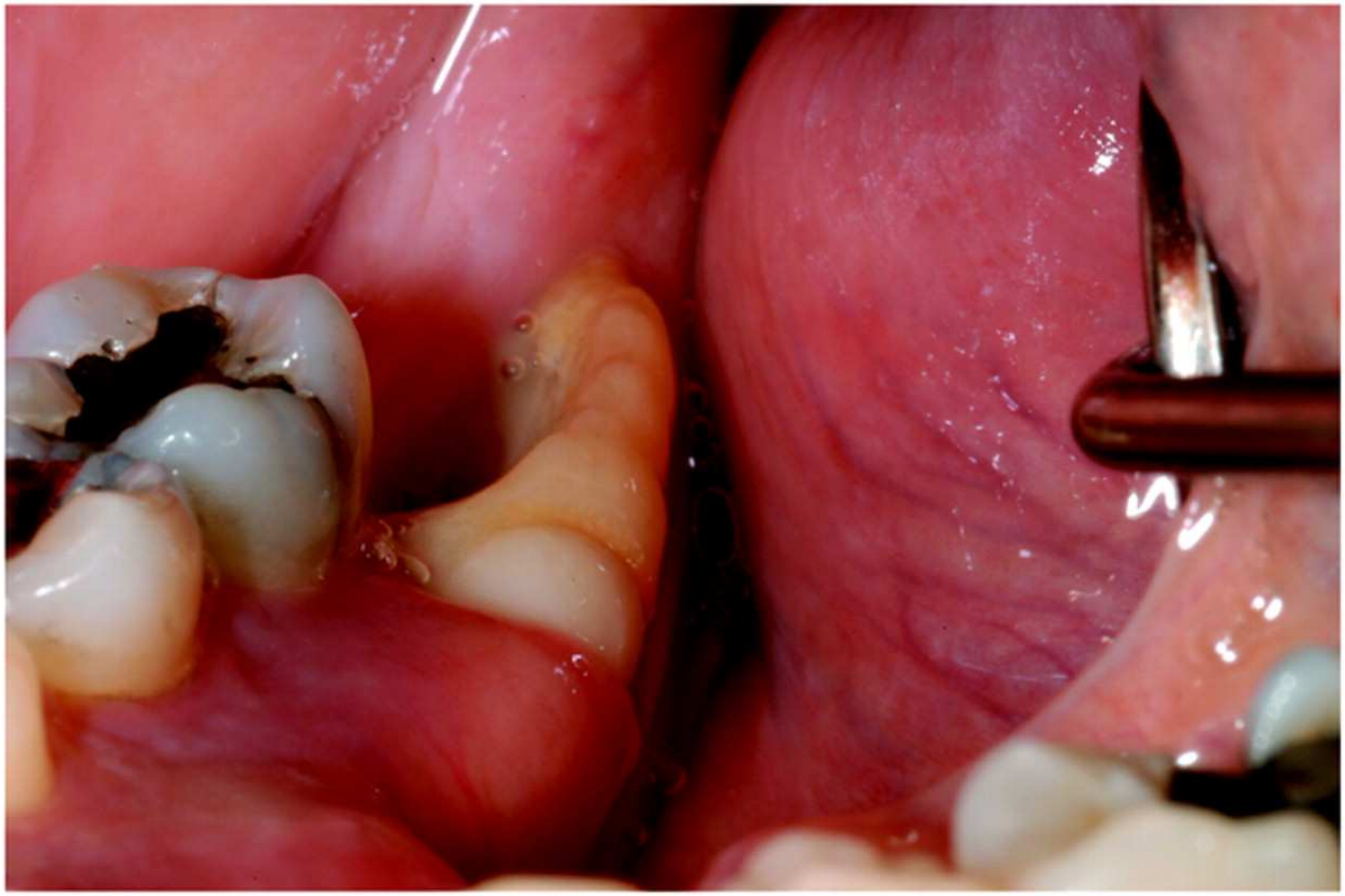
Les bi-phosphonates

- Poisons des ostéoclastes

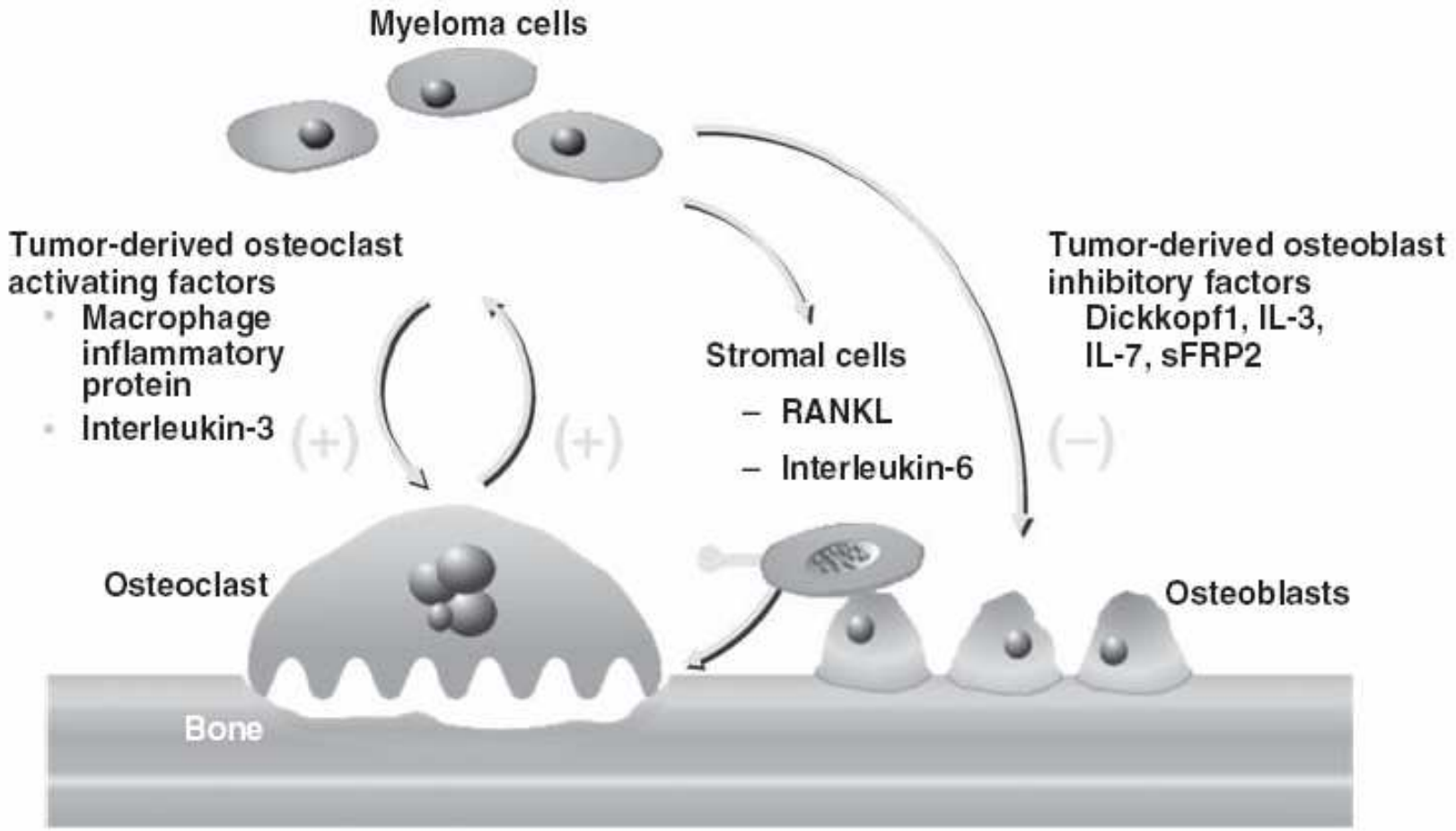
→ Zoledronate, Pamidronate, Alendronate, …

… MAIS …

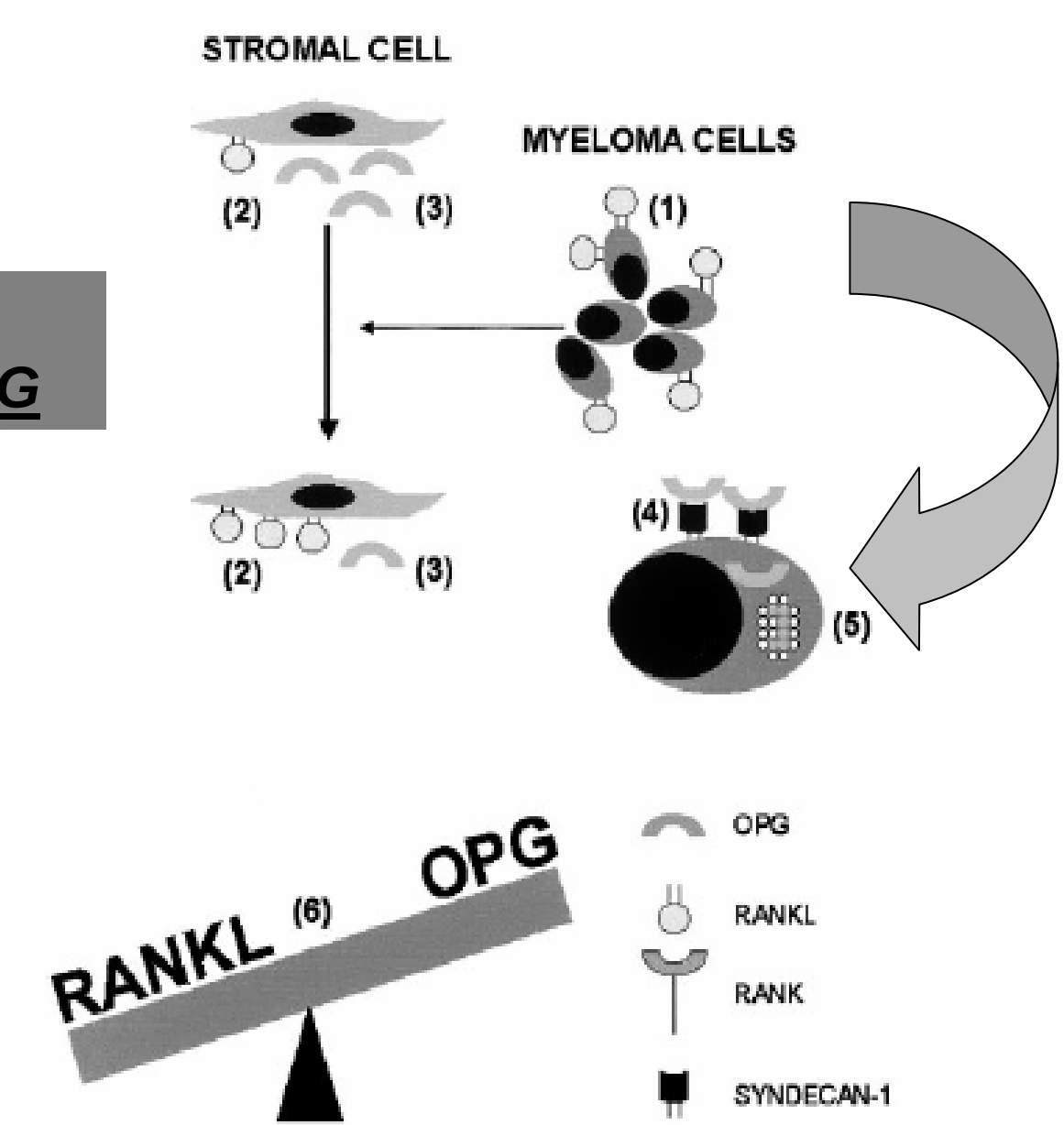
Ostéonécrose de la machoire



RANK-RANKL-OPG, MIP1α



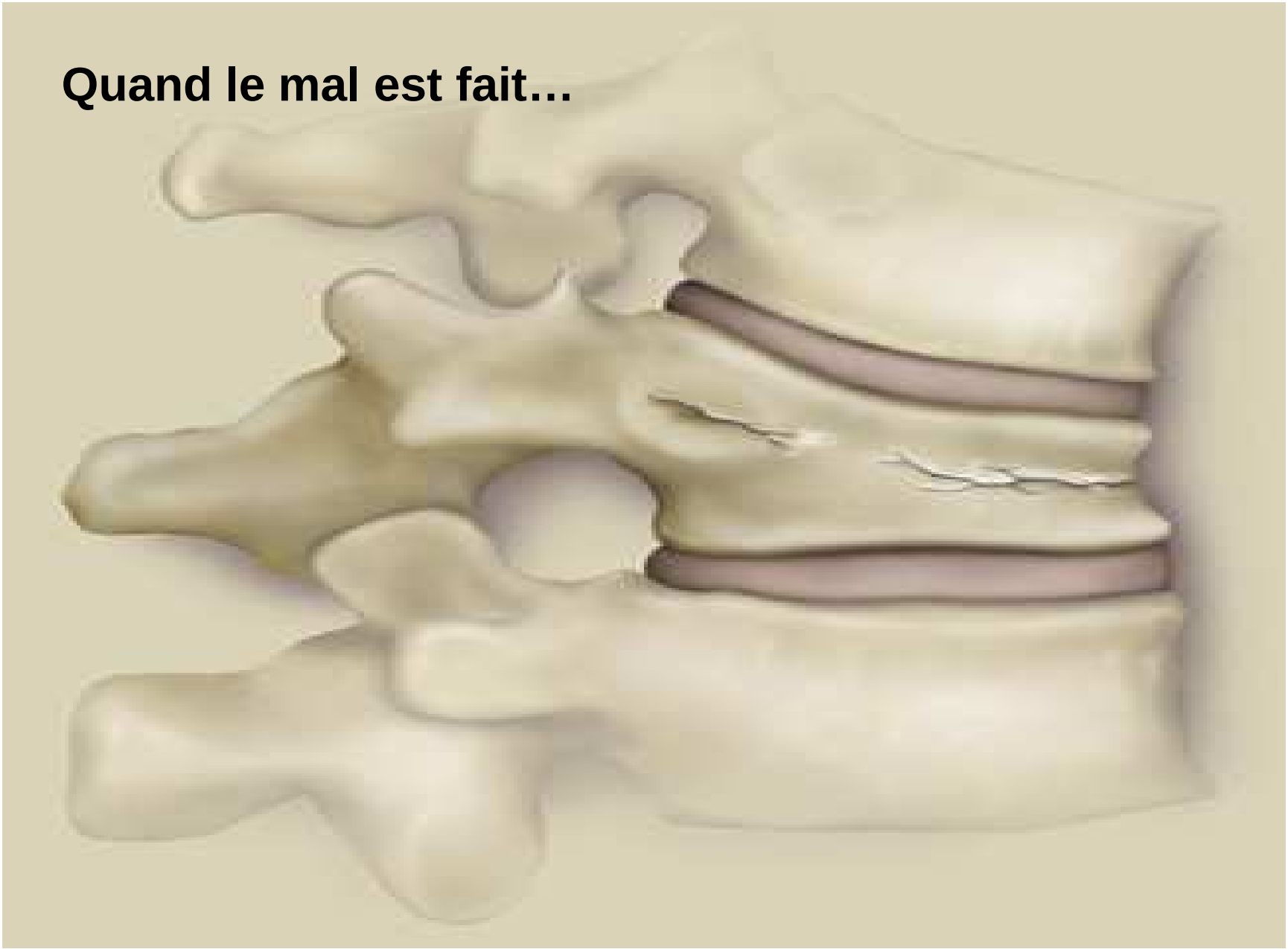
L'axe RANK-RANKL-OPG



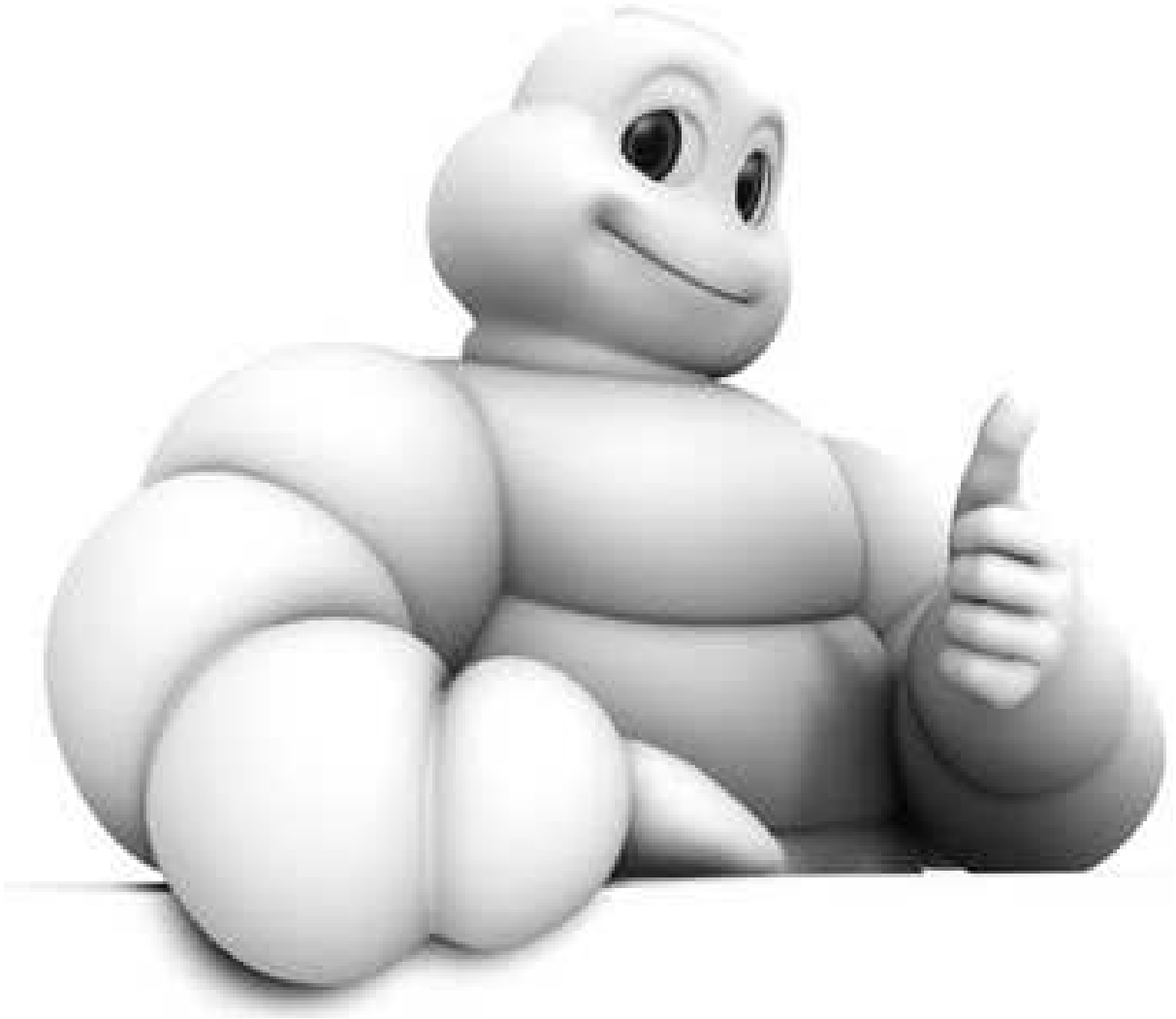
Nouvelles approches thérapeutiques via des AC monoclonaux

- → anti-RANKL (DENOSUMAB).
- → anti MIP1α
- → anti DKK1

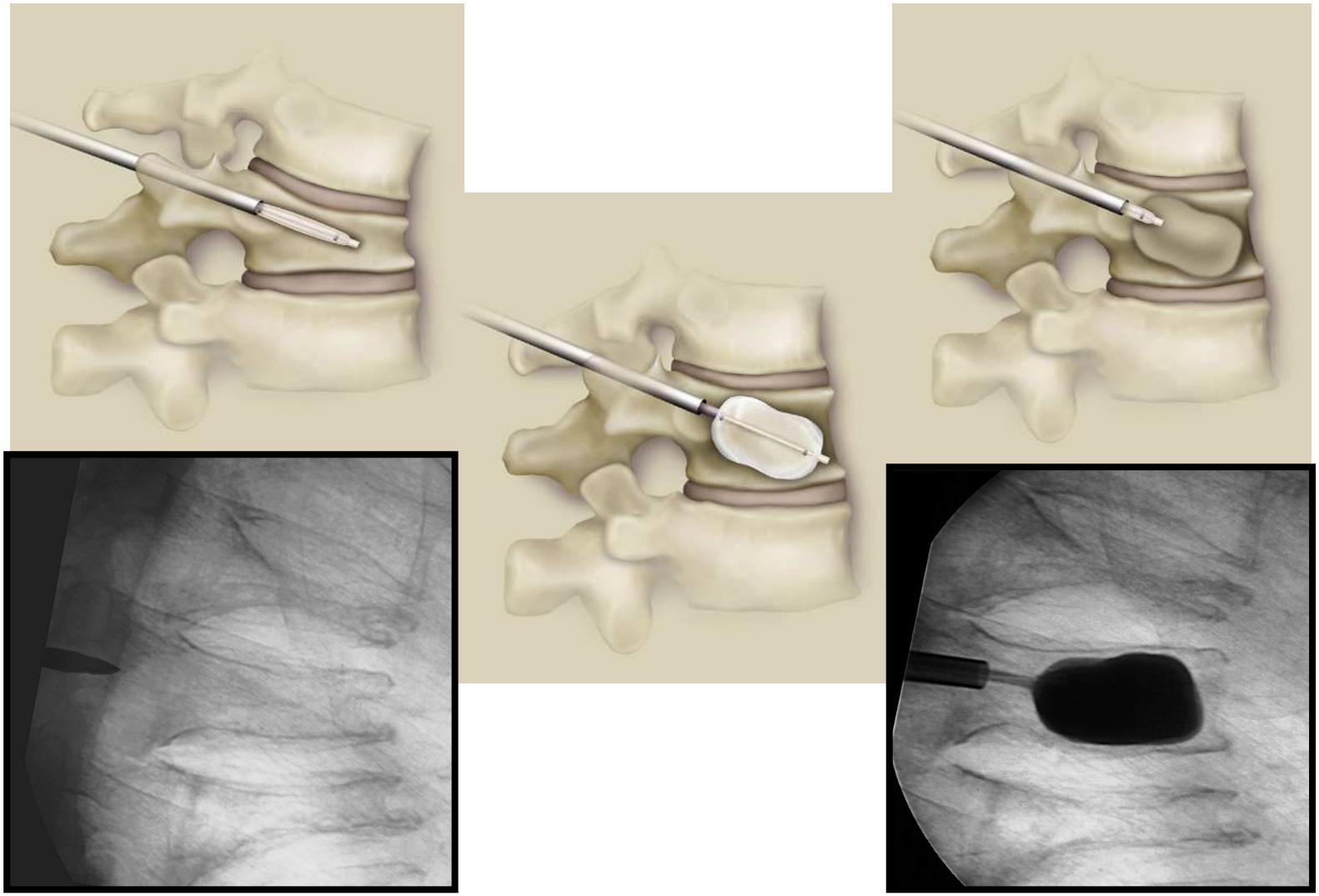
Quand le mal est fait…



Un p’tit coup de gonflette…



Kyphoplastie



Kyphoplastie: indications

- # tassement aigu et douloureux
- # tassement avec risque compressif
- # tassement avec cyphose +++

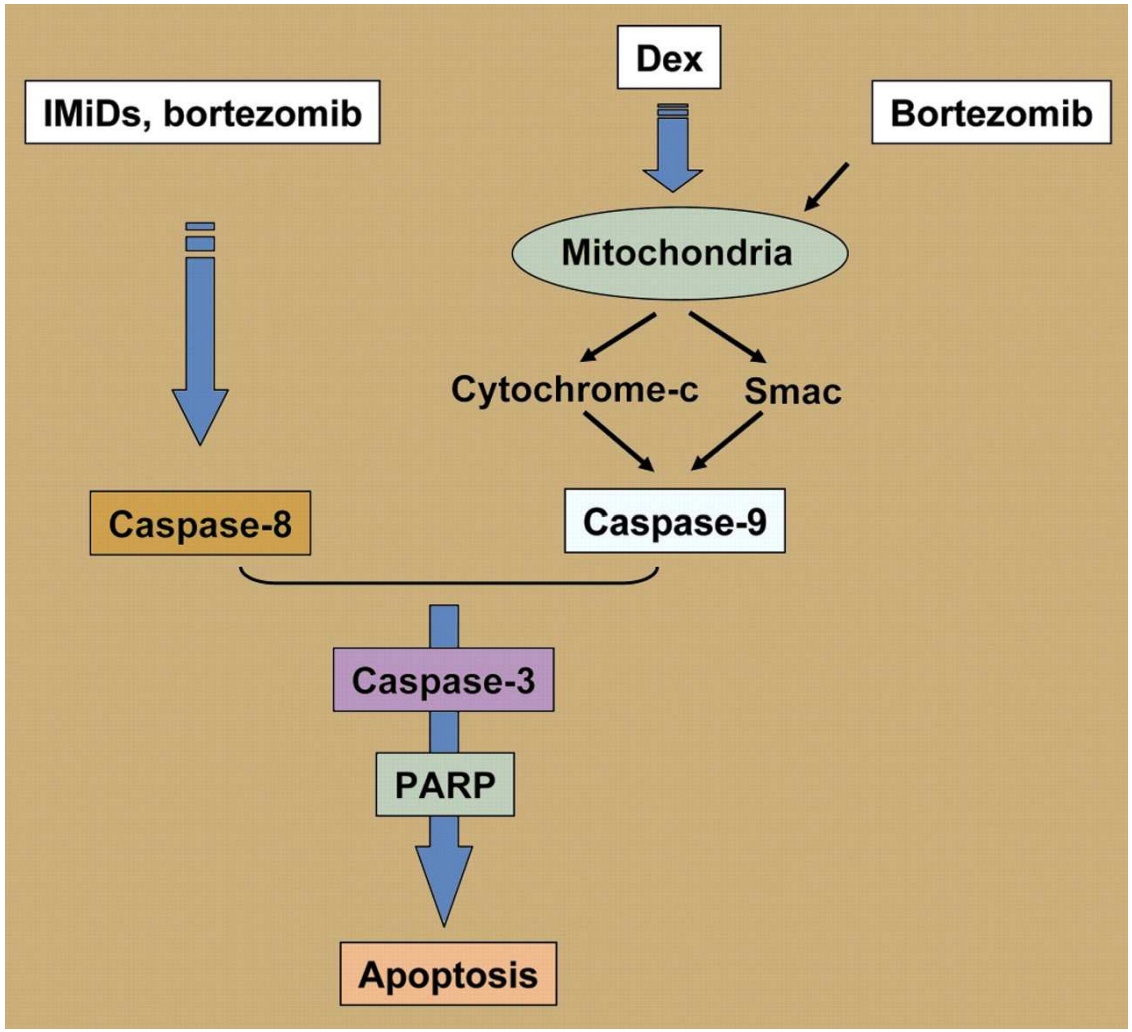
- 3 à 4 vertèbres « kyphoplastiables » par procédure!
- Association possible avec radiothérapie et/ou chimiothérapie
- Si compression symptomatique → chirurgie

Les « nouvelles drogues »

ou « *comment dépasser le concept de chimiothérapie classique* »…

blood
JOURNAL OF
THE AMERICAN
SOCIETY OF
HEMATOLOGY

Toward a new therapeutic backbone in myeloma



Richardson, P. Blood 2007;109:2672-2673

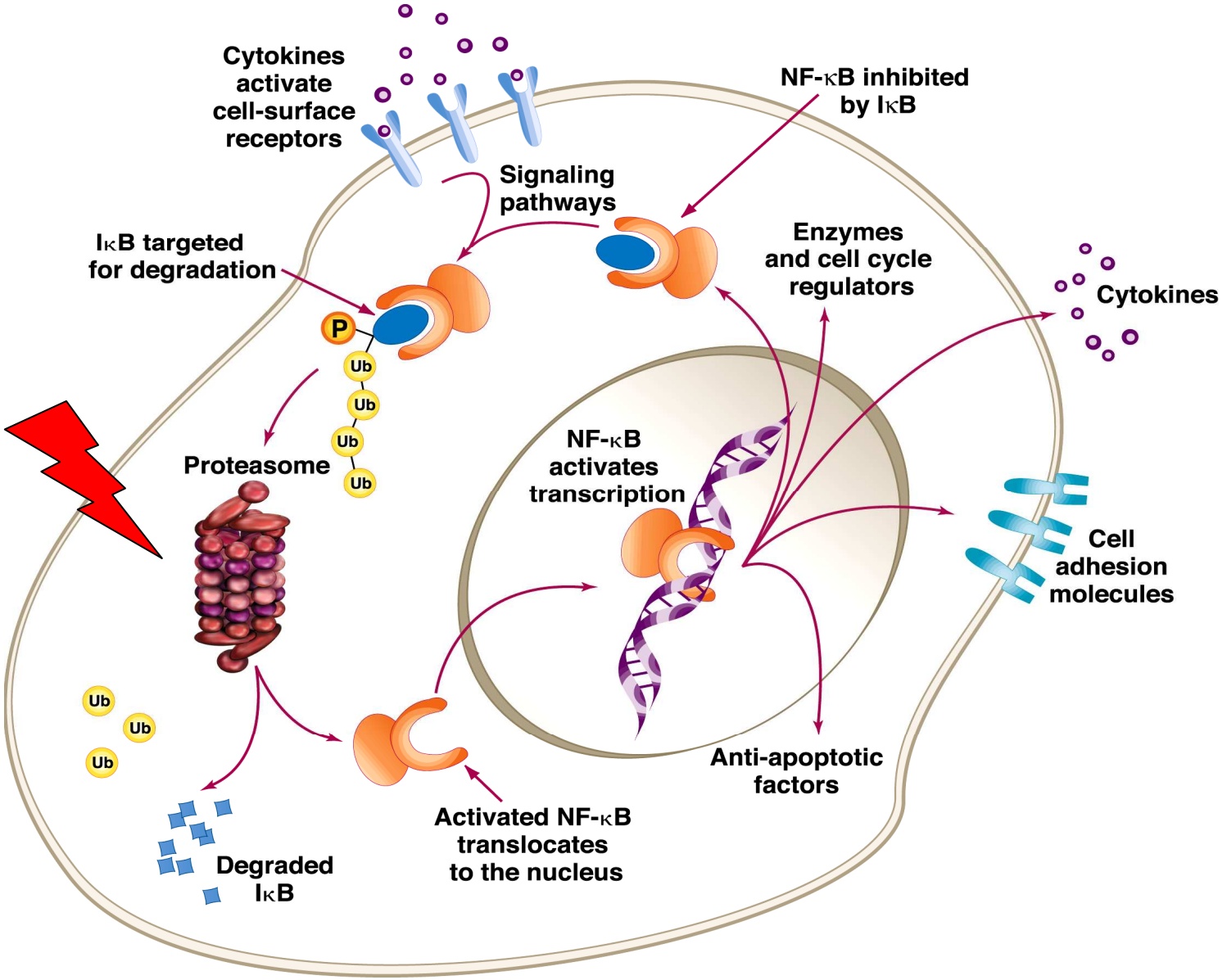
Les « nouvelles drogues »

- Les inhibiteurs du protéasome: Bortezomib
- Les IMiDs: Thalidomide, Lenalinomide

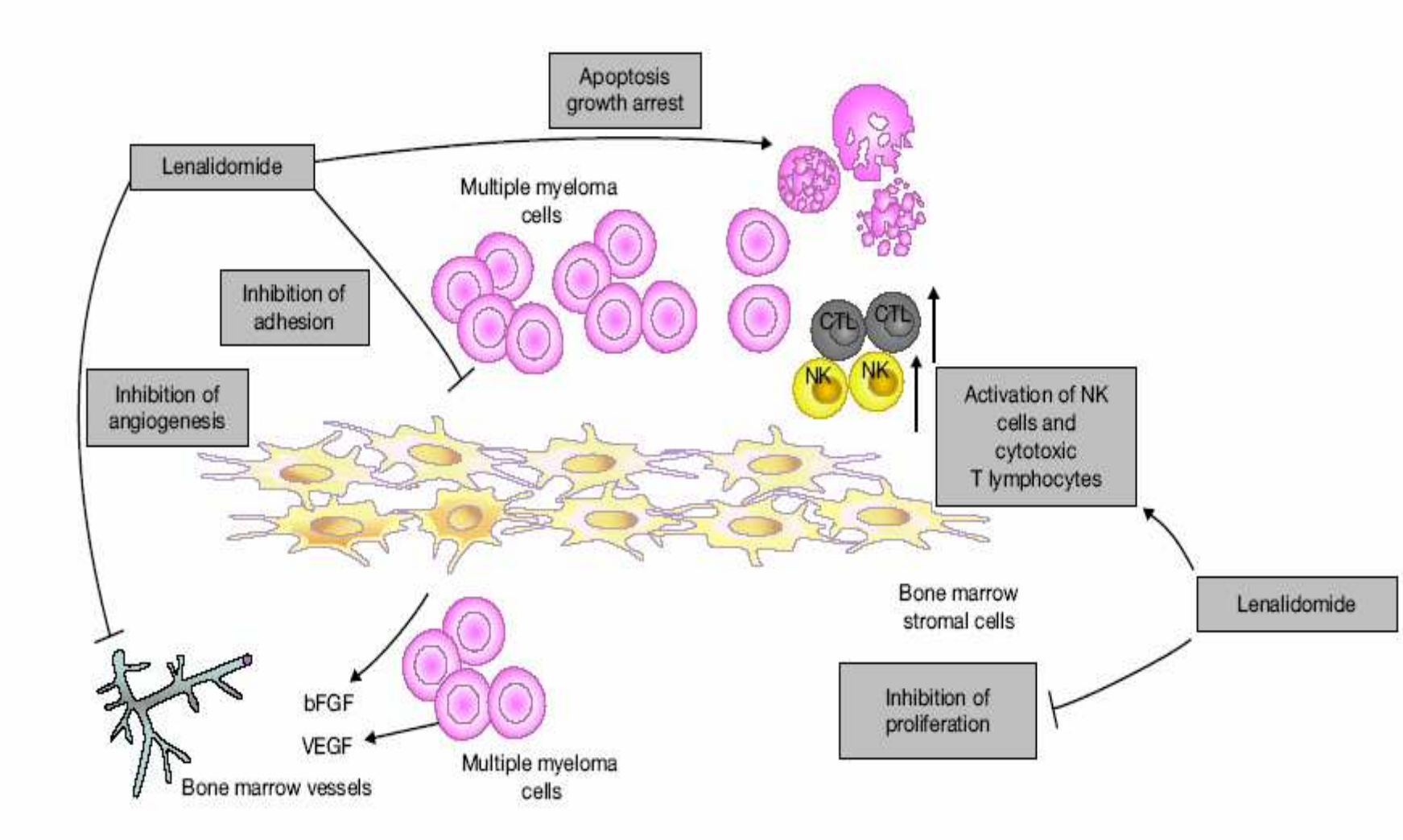
<u>Les futures nouvelles drogues…</u>

- Autres inhibiteurs du protéasome: Carfilzomib
- Autres IMiDs: Pomalinomide
- Les inhibiteurs des histone deacetylases: Vorinostat, Panobinostat
- Et d’autres, encore…

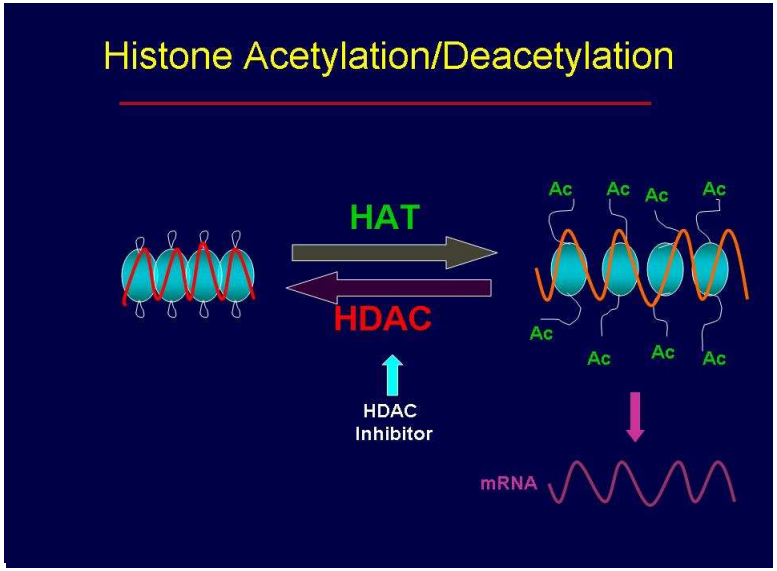
Inhibiteurs du protéasome

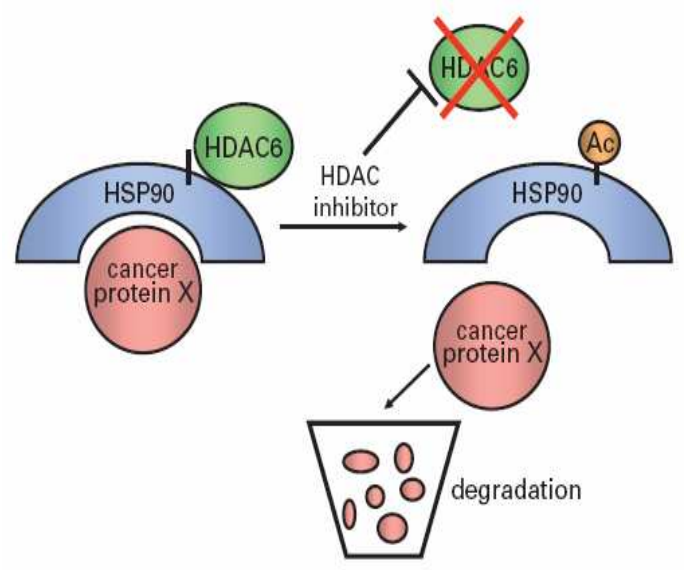


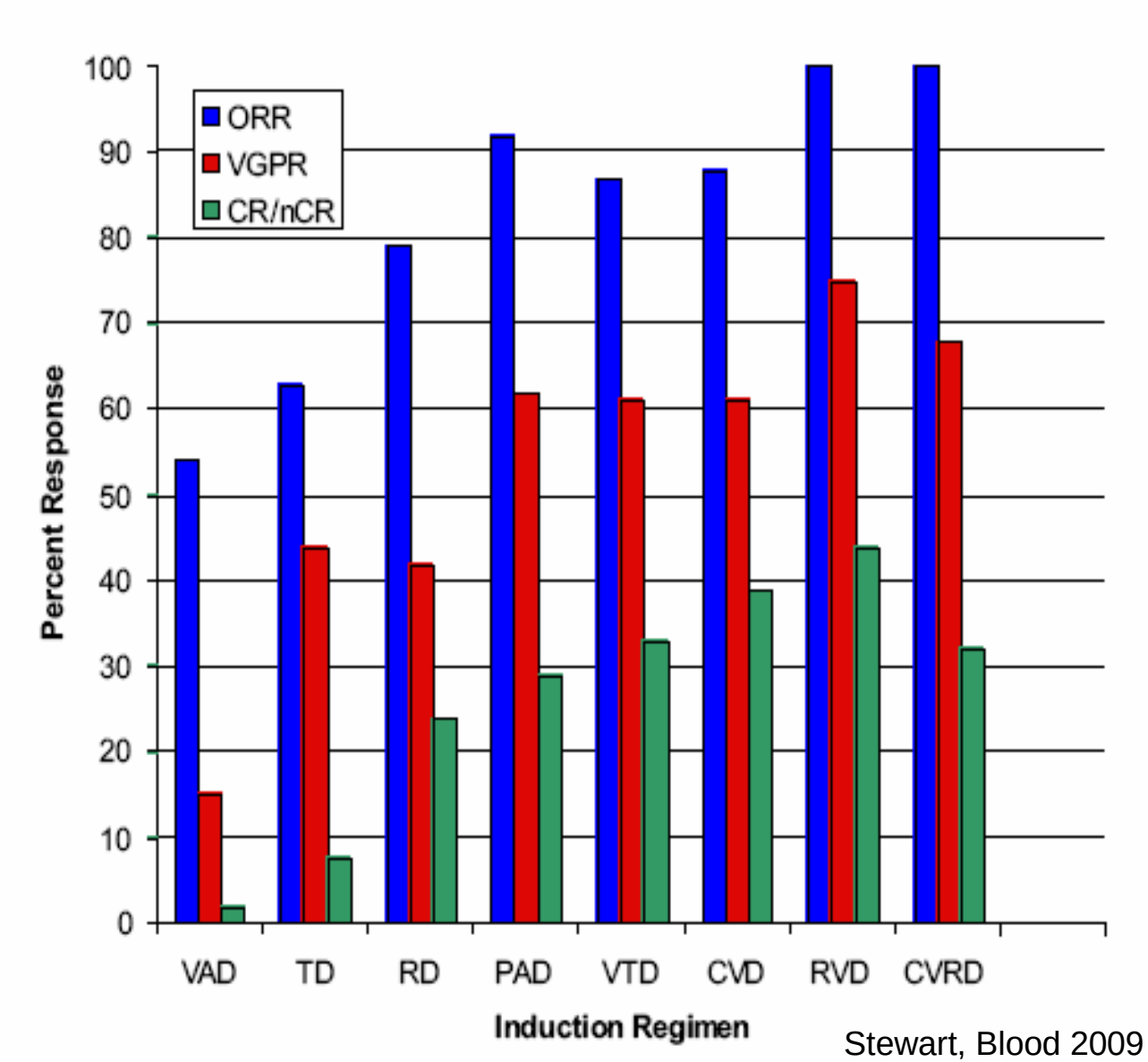
IMiDs


Apoptosis
growth arrest
Lenalidomide
Multiple myeloma
cells
Inhibition of
adhesion
Inhibition of
angiogenesis
CTL
CTL
NK
NK
Activation of NK
cells and
cytotoxic
T lymphocytes
Bone marrow
stromal cells
Lenalidomide
Inhibition of
proliferation
bFGF
VEGF
Multiple myeloma
cells
Bone marrow vessels

HDACi


Histone Acetylation/Deacetylation
HAT
HDAC
HDAC
Inhibitor
Ac
Ac
Ac
Ac
Ac
Ac
Ac
Ac
mRNA

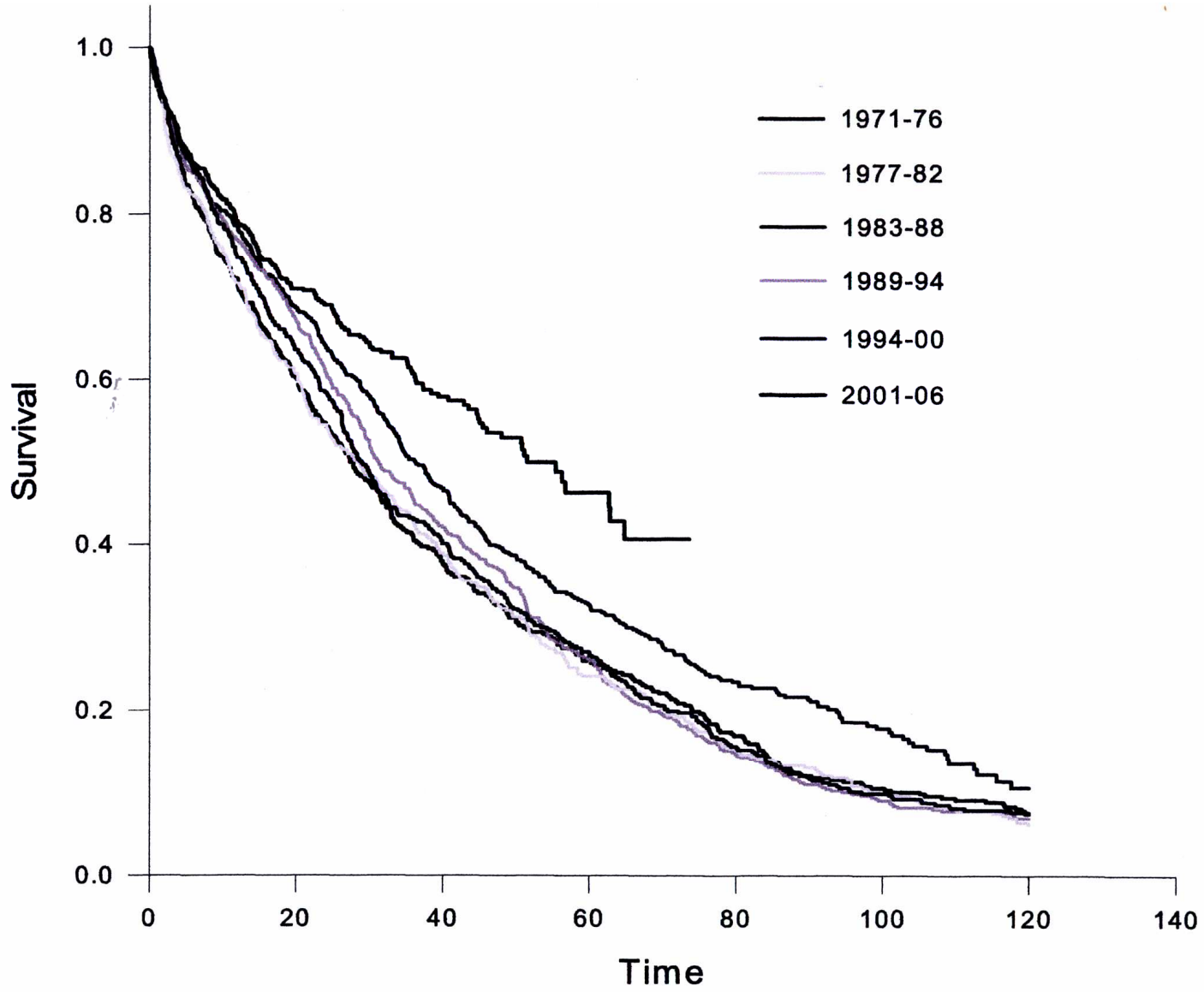

HDAC6
HDAC6
HSP90
cancer
protein X
HDAC
inhibitor
Ac
HSP90
cancer
protein X
degradation



Stewart, Blood 2009 114:5436

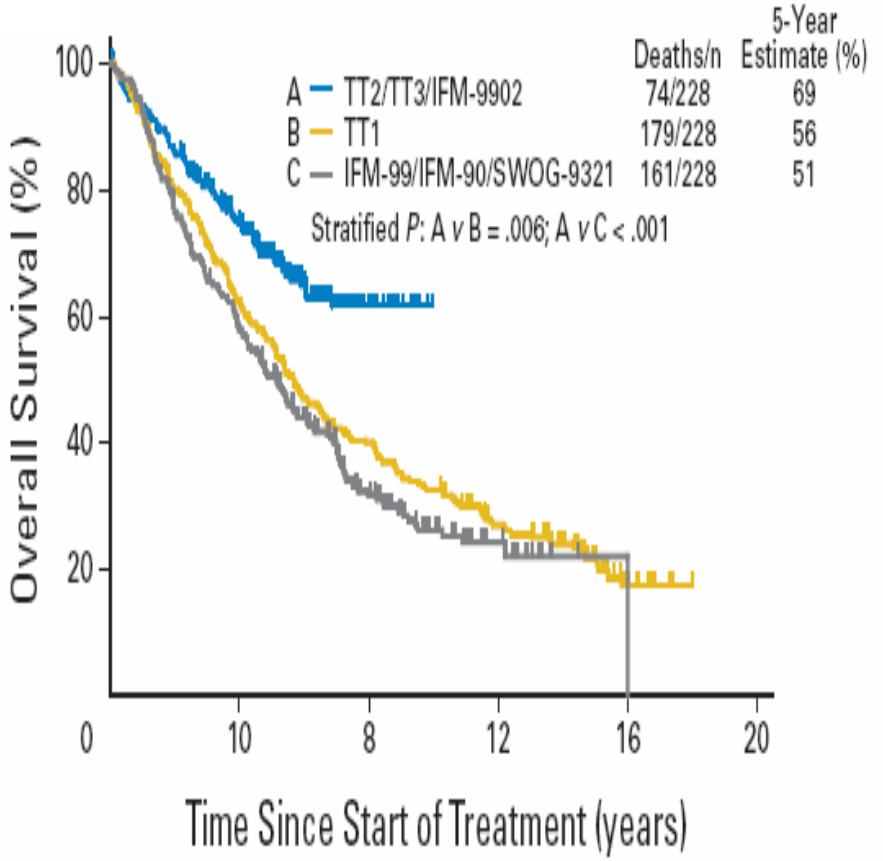
Les nouvelles drogues

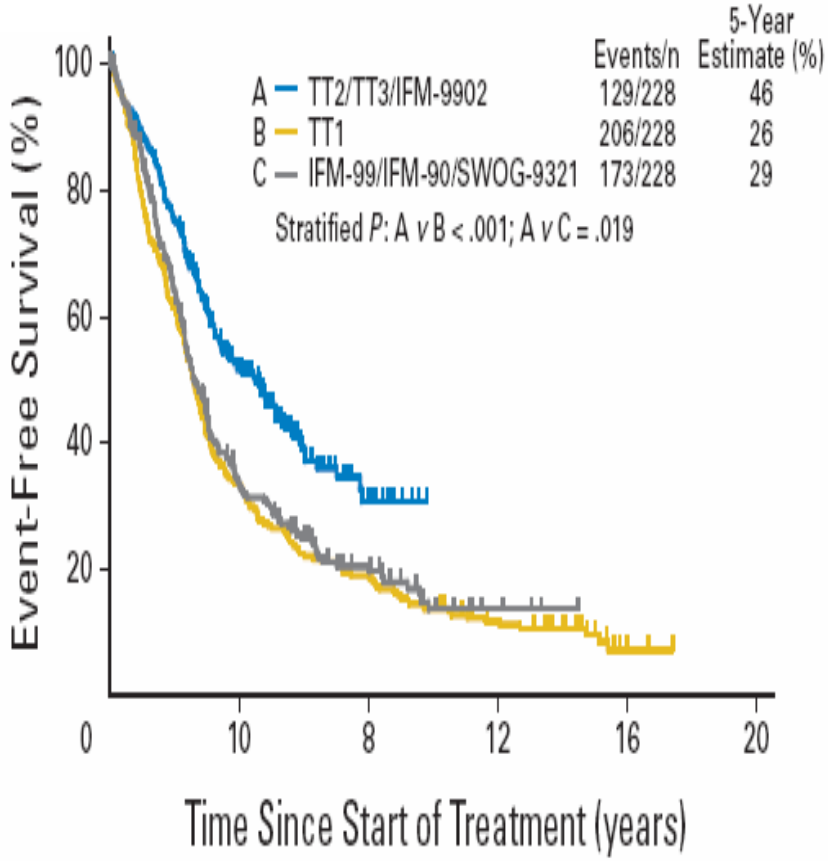
- Monothérapie versus combinaison
- Avant, pendant, après, sans greffe
- Concept de consolidation, de maintenance


1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
20
40
60
80
100
120
140
Time
1971-76
1977-82
1983-88
1989-94
1994-00
2001-06

Long-Term Follow-Up of Autotransplantation Trials for Multiple Myeloma: Update of Protocols Conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical Sciences

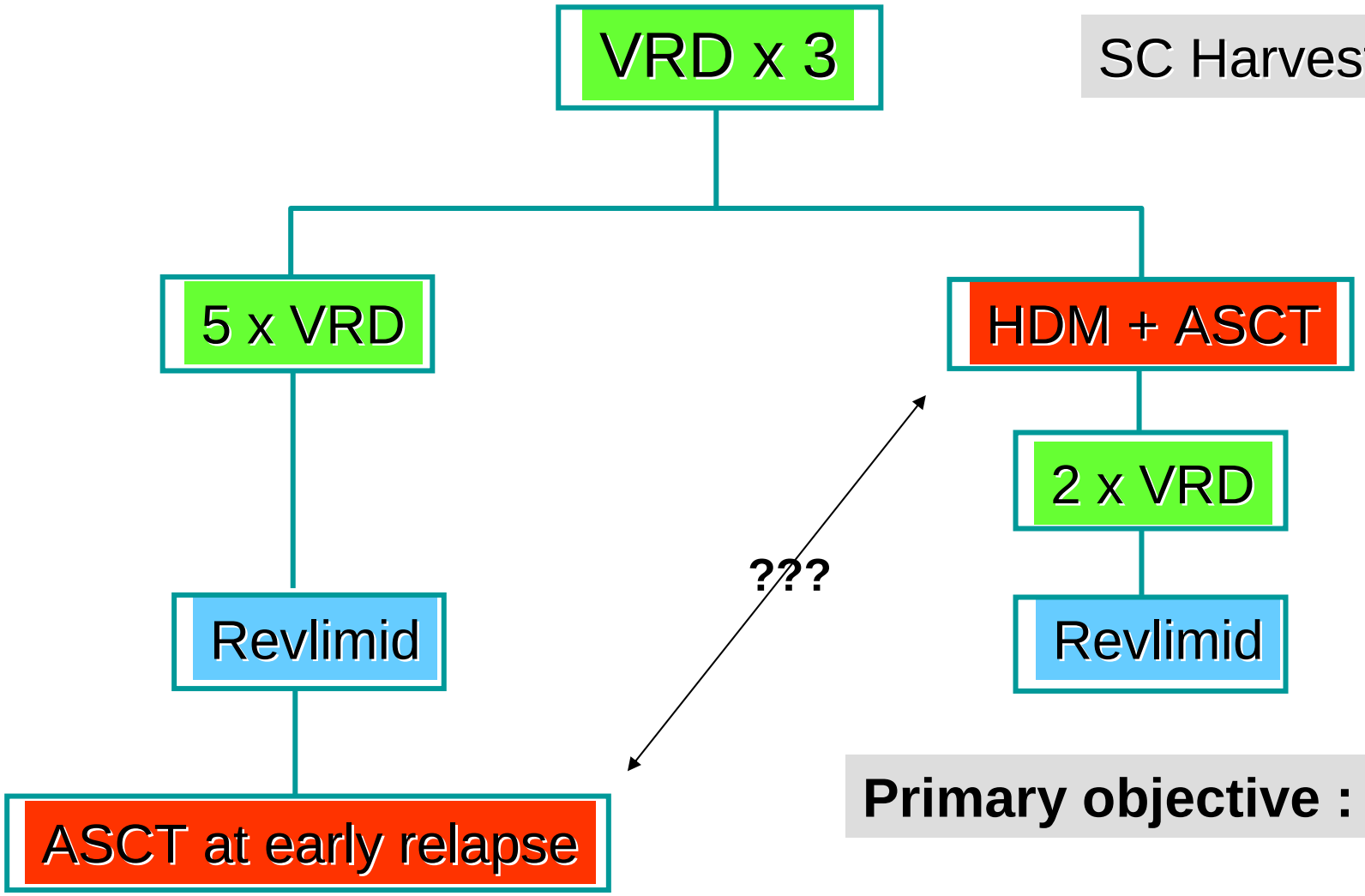
Bart Barlogie, Michel Attal, John Crowley, Frits van Rhee, Jackie Szymonifka, Philippe Moreau, Brian G.M. Durie, and Jean-Luc Harousseau





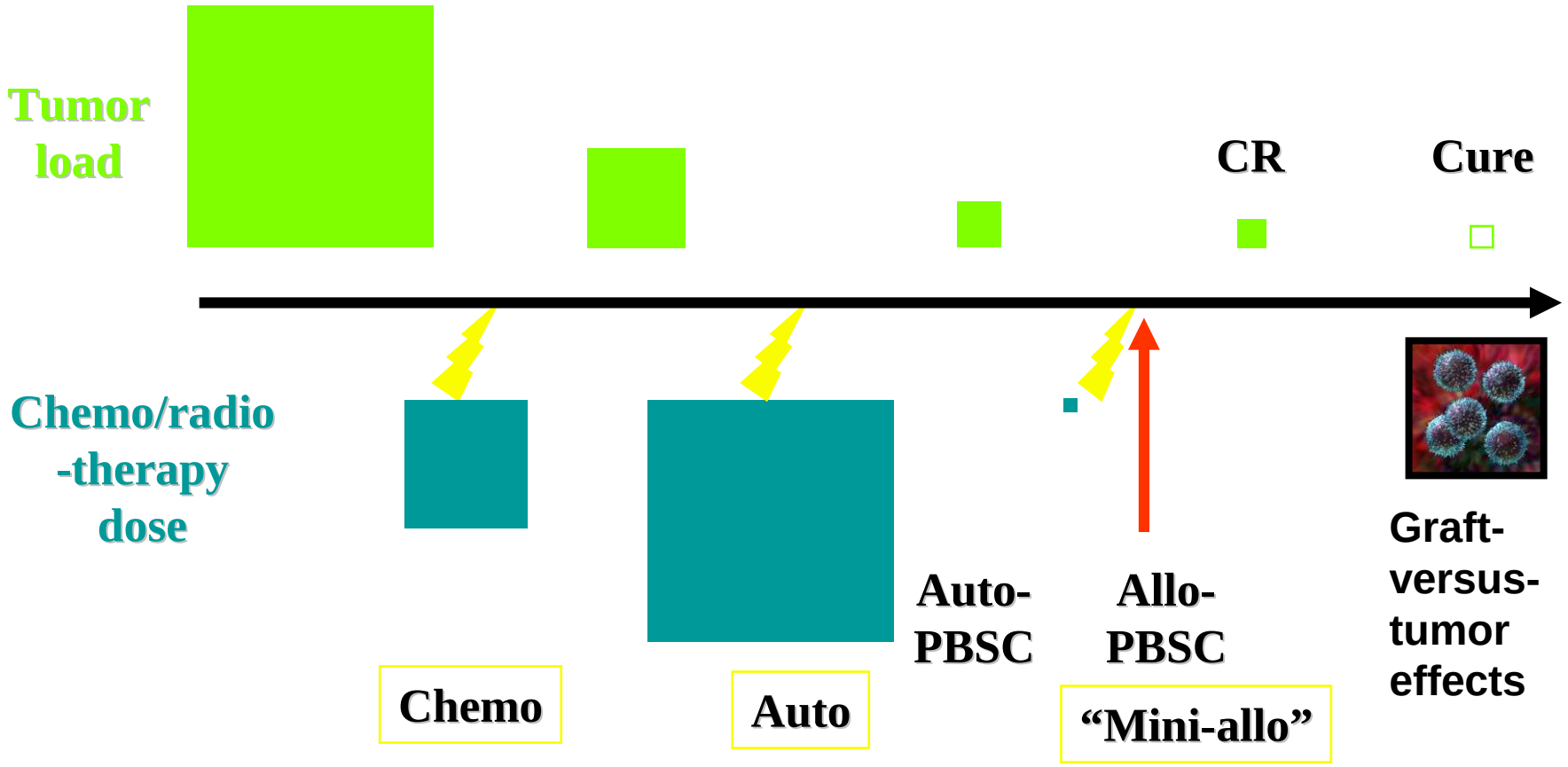
J Clin Oncol 28:1209-1214. © 2010

MYELOMA IFM 2009



Primary objective : EFS

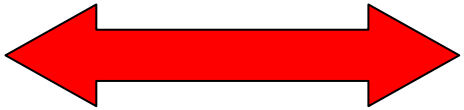
Tandem auto-Mini HCT: the concept!



Mini-greffe… Maxi-effets?

« Bof »…

- ~ 15% de décès « toxique » à 5 ans
- ~ 60% de maladie chronique du greffon contre l'hôte
- ~ 30% toujours sous immuno-suppresseurs à 5 ans

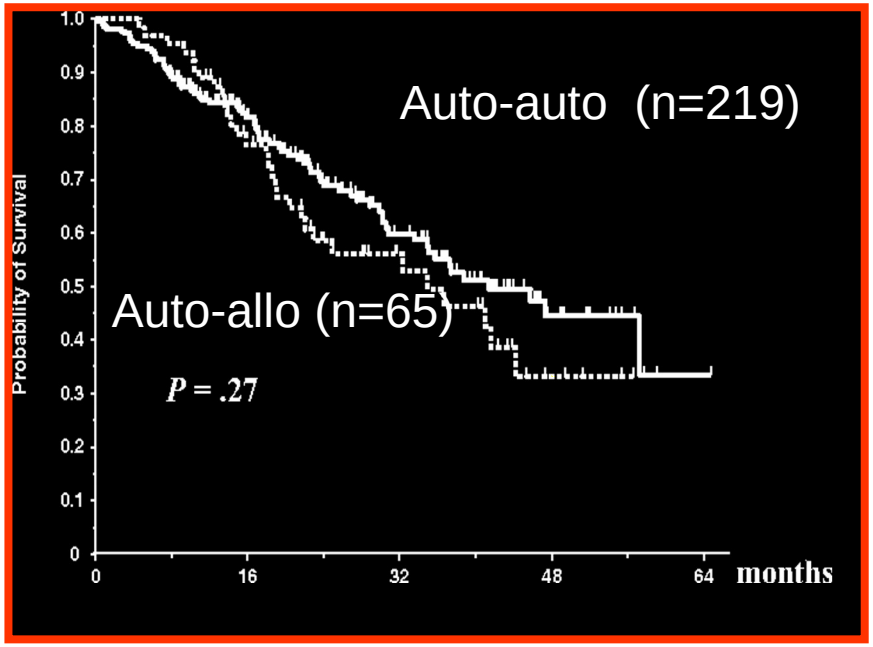


« Yes! »

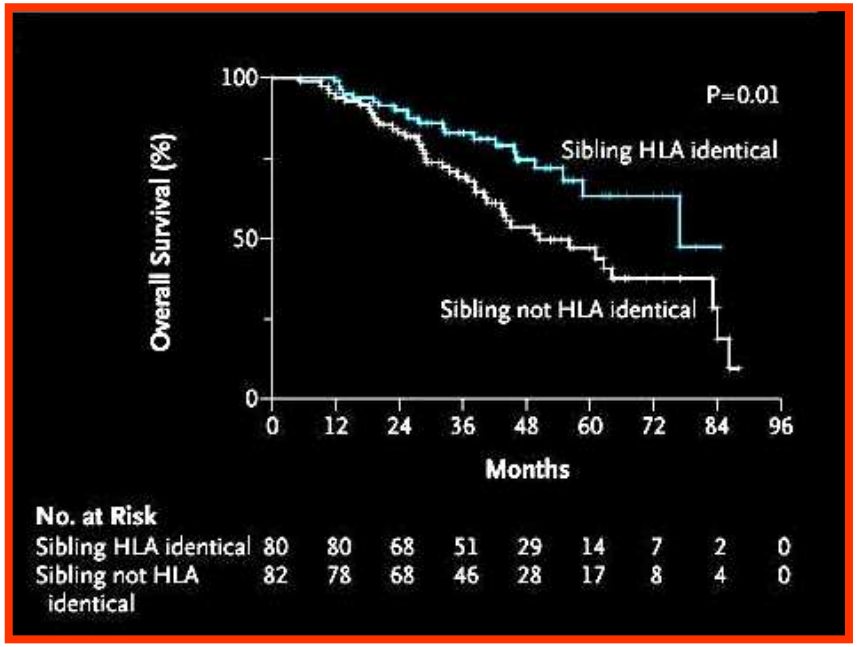
- Effet GVM
- Plateau sur la courbe de survie

  → guérison ?!

Tandem auto vs tandem auto-minigreffe



Garban, F. et al. Blood 2006

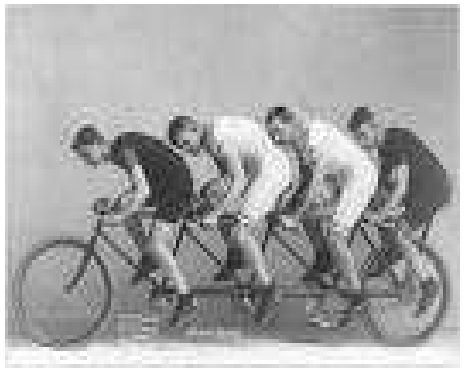


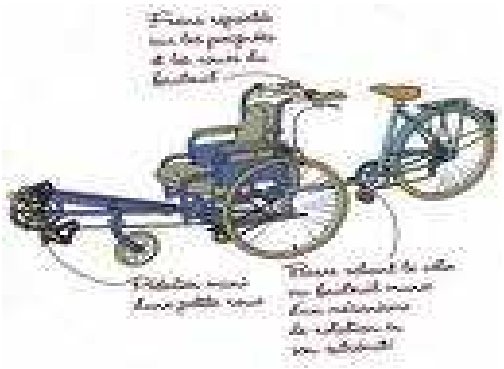
Bruno, B. et al. NEJM07

« Asking a transplanter if he wants to transplant a patient is like asking a monkey if he wants a banana »

Georges Cannellos, MD

Science et état d’âme…

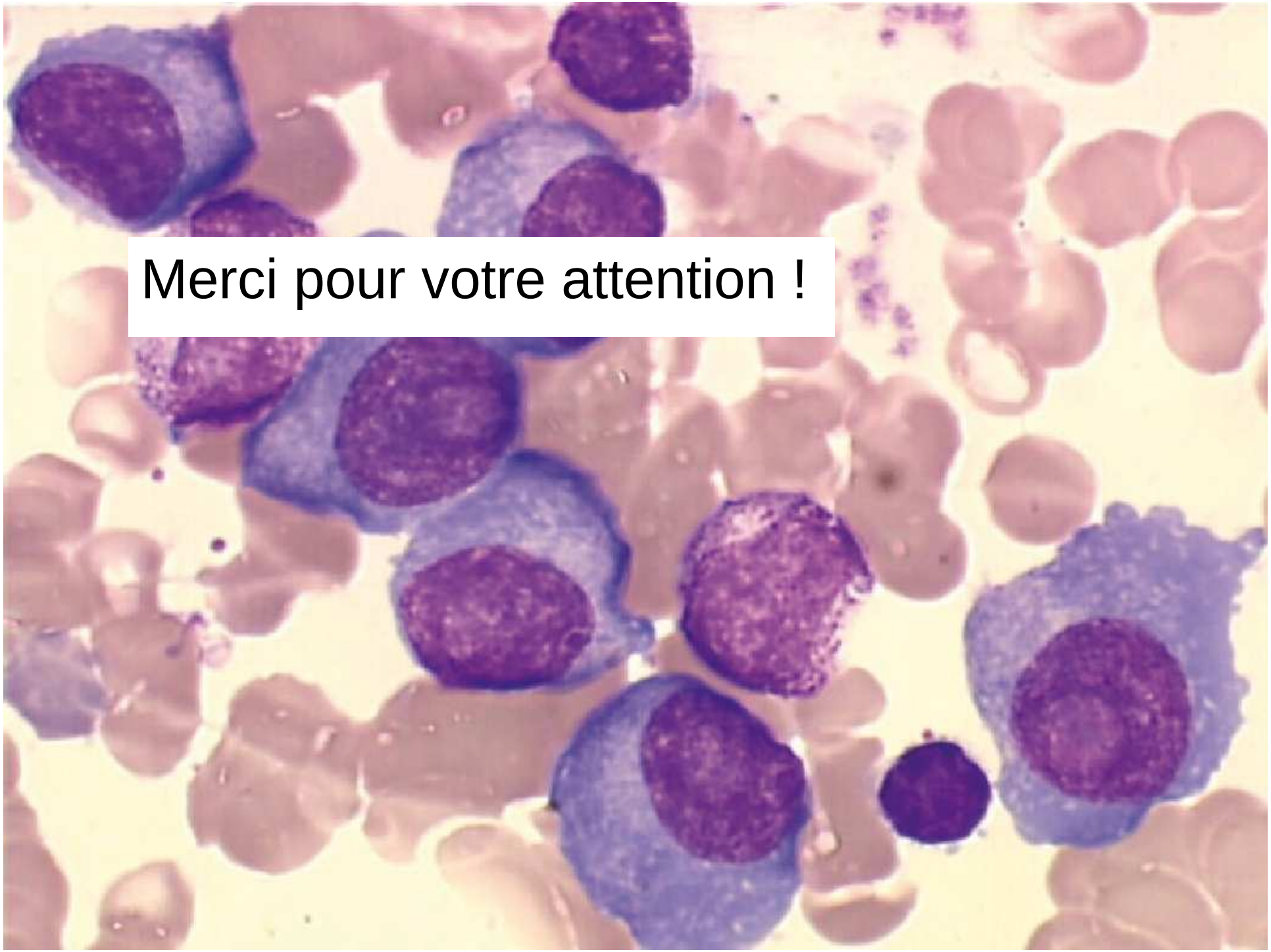




Bruno, Rajkumart, Barlogie, Stewart, Rosinol, Bensinger, Moreau, Gratwohl,…

En conclusion

- MGUS → risque de lymphopathie.
- MGUS = état prémyélomateux, évolution imprévisible.
- Apports des études génétiques: balbutiements cliniques.
- Contribution du dosage des chaînes légères libres au diagnostic et dans le suivi.
- Importance de l'axe RANK-RANKL-OPG → nouveaux traitements des lésions osseuses.
- Apport des techniques non invasives (kyphoplastie).
- Modifications radicales du traitement avec les « nouvelles drogues »
- Allogreffe avec conditionnement atténué (RIC, « mini ») toujours expérimentale.


Merci pour votre attention !