TRAITEMENT D'INDUCTION DU MYELOME MULTIPLE DU SUJET JEUNE

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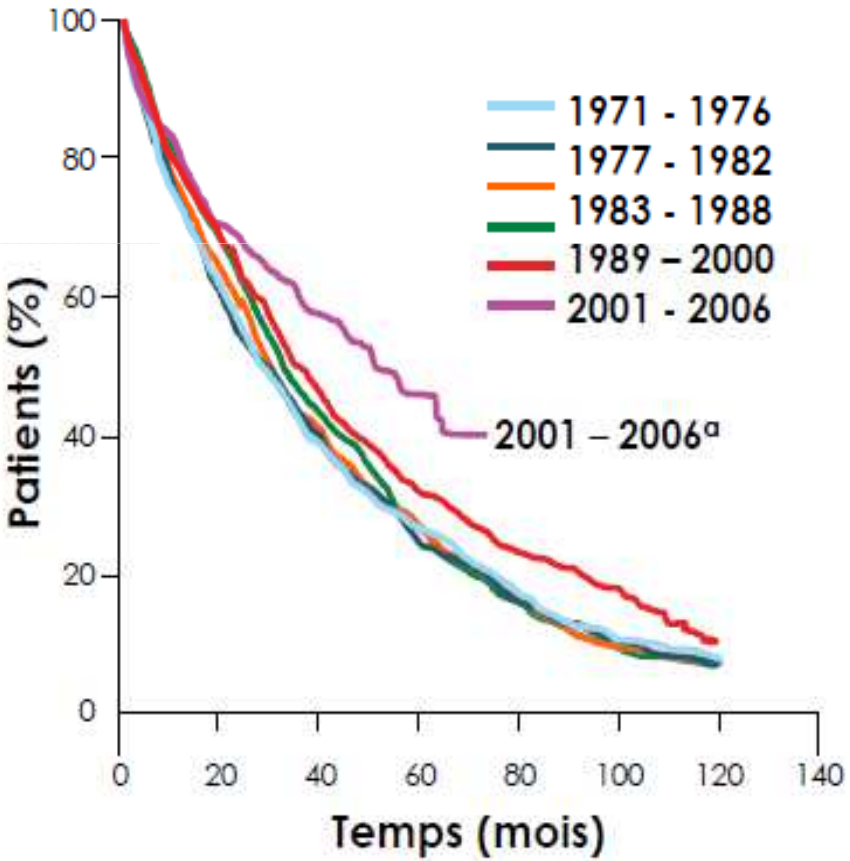
Groupe d'étude de myélome multiple

Journée scientifique du 4 juin 2016

L'arrivée de nouvelles molécules a permis d'augmenter la survie globale

Survie globale suivant la période à laquelle le diagnostic a été réalisé 1971–2006



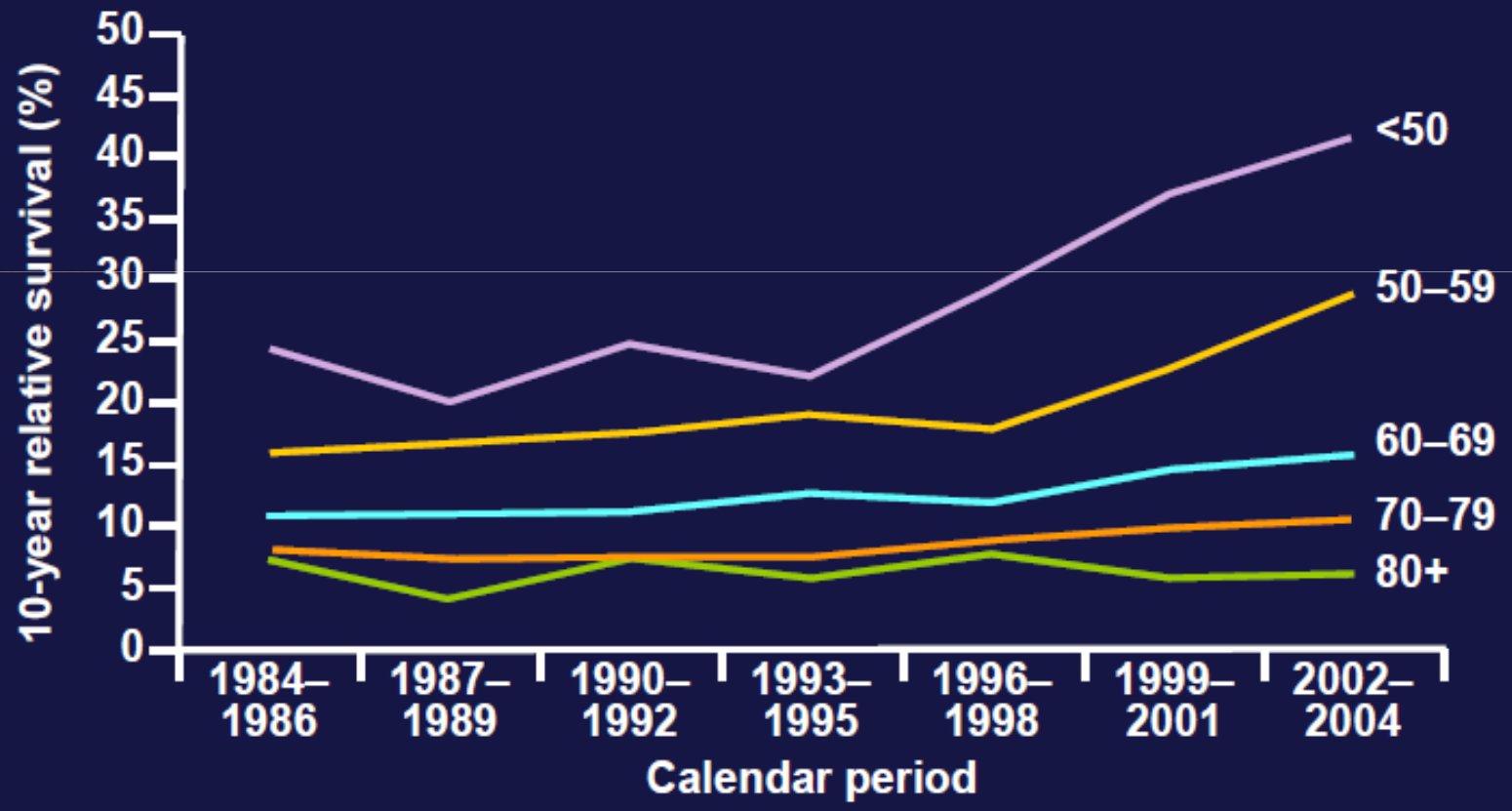
Période de diagnostic	OS médiane	p value
1971–1996[1]	30 mois	p < 0.001
1996–2006[1,a]	45 mois	
2001–2005[2]	55 mois	p = 0.002
2006-2010[2]	73 mois	

- Amélioration importante de la survie globale (OS) entre 2006 et 2010
- L'amélioration de la survie globale sur cette période est due à l'utilisation de nouvelles molécules et d'une autogreffe

1. Kumar SK, *et al. Blood.* 2008;111:2516-20.

Improvements in survival according to the age

Period estimates of 10-yr survival by major age groups in defined calendar periods



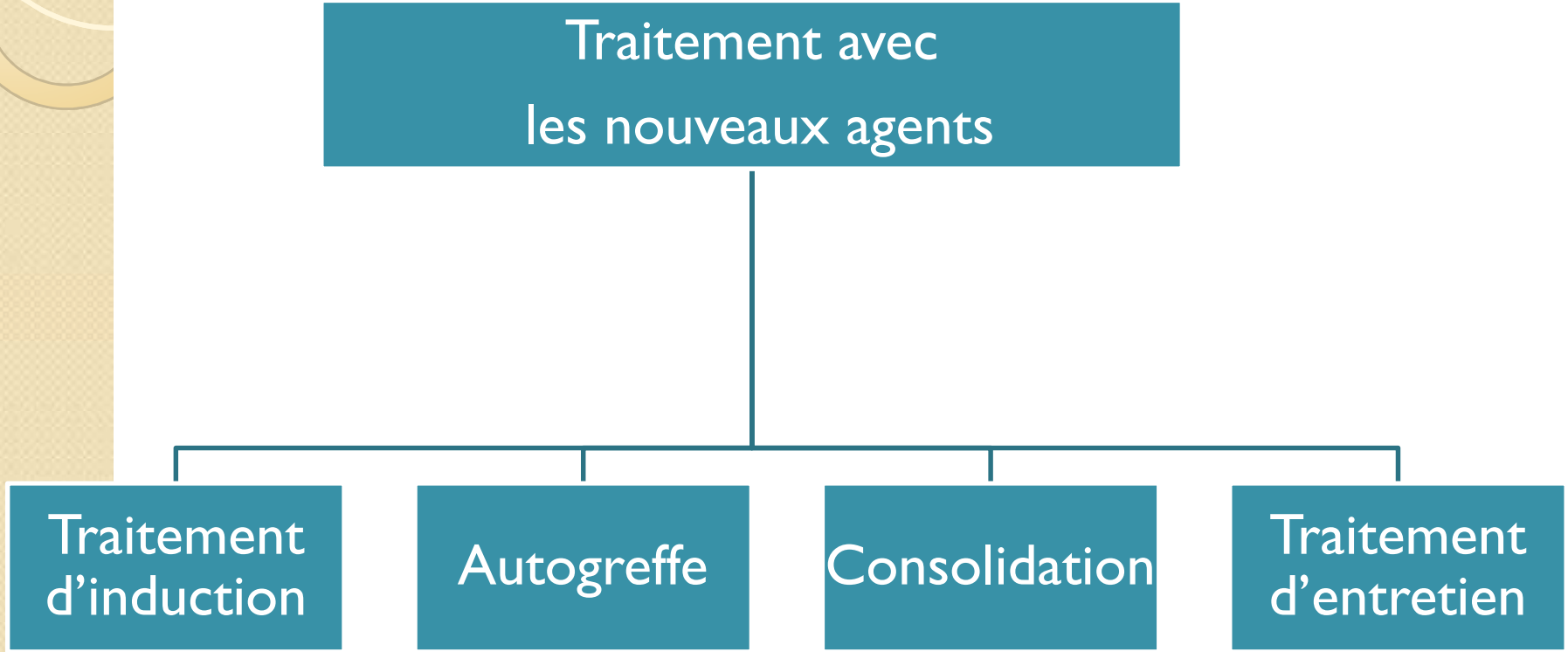
Improvements in survival for elderly patients expected with longer follow up of ongoing trials

Brenner *et al. Blood* 2008;111:2521–26

Objectifs principaux des traitements

- Obtenir une meilleure réponse possible (RP/VGPR/RC) après le traitement d'induction
- Réduire les symptômes
- Arriver à l'autogreffe avec la meilleure réponse
- Prolonger la survie sans progression et la survie globale du patient

Schéma thérapeutique actuel en Ière ligne des patients éligibles à une autogreffe



Les différents protocoles d'induction

	Basé sur *bortezomib*	**Basé sur *thalidomide***	**Basé sur *lenalidomide***	***Bortezomib*+ basé sur *IMiD***
Associations doubles	**VD**	***TD***	Rd ***RD***	
Associations triples	**PAD** **VCD**	TAD ***CTD***	RAD CRD	**VTD** VRD CRD/-TD Ixa-RD
Associations quadruples				VTDC RVCD RVDD

I. FAUT-IL- STRATIFIER NOS PATIENTS

Gold standard dans le monde: **VTD/VRD**

Contraintes économiques VRD>>VTD>>>>>TD

Oui pour la stratification

faible risque:

0 facteurs de

Mauvais pronostic

Haut risque

ISS=3 et/ou

IR et/ou

An cytg HR

II. QUEL OBJECTIF DU TRAITEMNET D'INDUCTION POUR NOS PATIENTS ?

• Critères de la réponse (IMWG/EBMT) :

Table 6: European Bone Marrow Transplant (EBMT) and International Myeloma Working Group (IMWG) Response Criteria

Category	EBMT Criteria	IMWG Criteria
Complete response (CR)	• No M protein detected in the serum or urine by IFE for ≥ 6 weeks • ≤ 5% abnormal bone marrow plasma cells	• Negative serum and urine IFE • Resolution of plasmacytomas • < 5% abnormal bone marrow plasma cells
Stringent CR (sCR)	Not used	• CR *plus* – Normal FLC ratio – No evidence of clonal abnormal bone marrow plasma cells by IHC or FISH
Very good partial response (VGPR)	Not used	• Serum and urine M protein detectable by IFE but not by SPEP *or* • ≥ 90% reduction in serum M protein plus urine M protein < 100 mg/24 hours
Partial response (PR)	• > 50% reduction in serum M protein *and/or* • 90% reduction in urine FLC excretion or reduction to < 200 mg/24 hours for 6 weeks	• 50% reduction in serum M protein and reduction in 24-hour urine protein by ≥ 90% or to < 200 mg/24 hours • If immeasurable M protein: – ≥ 50% reduction in difference between involved and uninvolved FLC – ≥ 50% reduction in the size of plasmacytoma, if present at baseline

FISH – fluorescence in situ hybridization; FLC – free light chain; IFE – immunofixation electrophoresis; IHC – immunohistochemistry; SPEP – serum protein electrophoresis.

Information from References 8,11,45–47.

blood®
2010 115: 2348-2353
doi:10.1182/blood-2009-07-235531 originally published online January 20, 2010

Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction

Morie A. Gertz, Shaji Kumar, Martha Q. Lacy, Angela Dispenzieri, David Dingli, Suzanne R. Hayman, Francis K. Buadi and William J. Hogan

Disease status at SCT	
Plateau	232 (81)
Never achieved PR (refractory)	29 (10)
Relapse on therapy	25 (9)
Median β_2-microglobulin at initial diagnosis (10-90th percentile), mg/L, n = 208	3.40 (1.83-9.70)
Median labeling index (10-90th percentile), n = 282	0.2 (0-2.0)
Induction therapy administered, N = 324	
Thalidomide dexamethasone	189 (66)
Lenalidomide dexamethasone	97 (34)

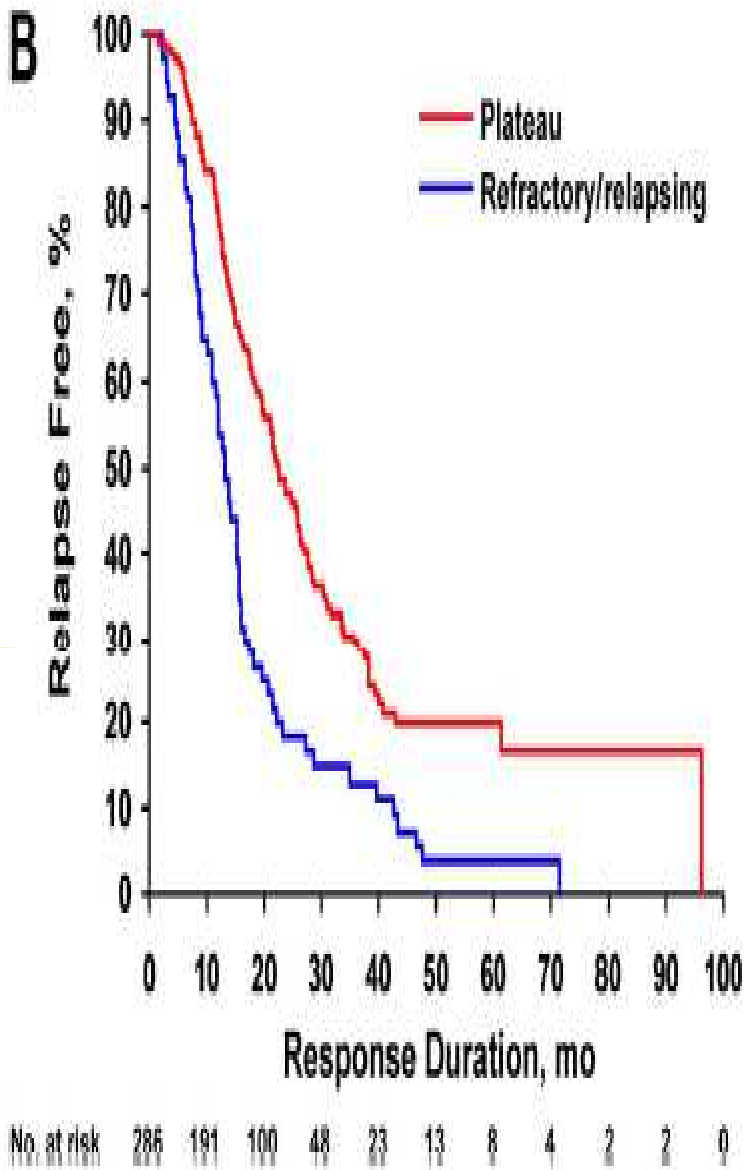


Figure 1. Failure to respond to thalidomide or lenalidomide induction leads to shorter posttransplantation progression-free survival (PFS). (A) PFS from day 0

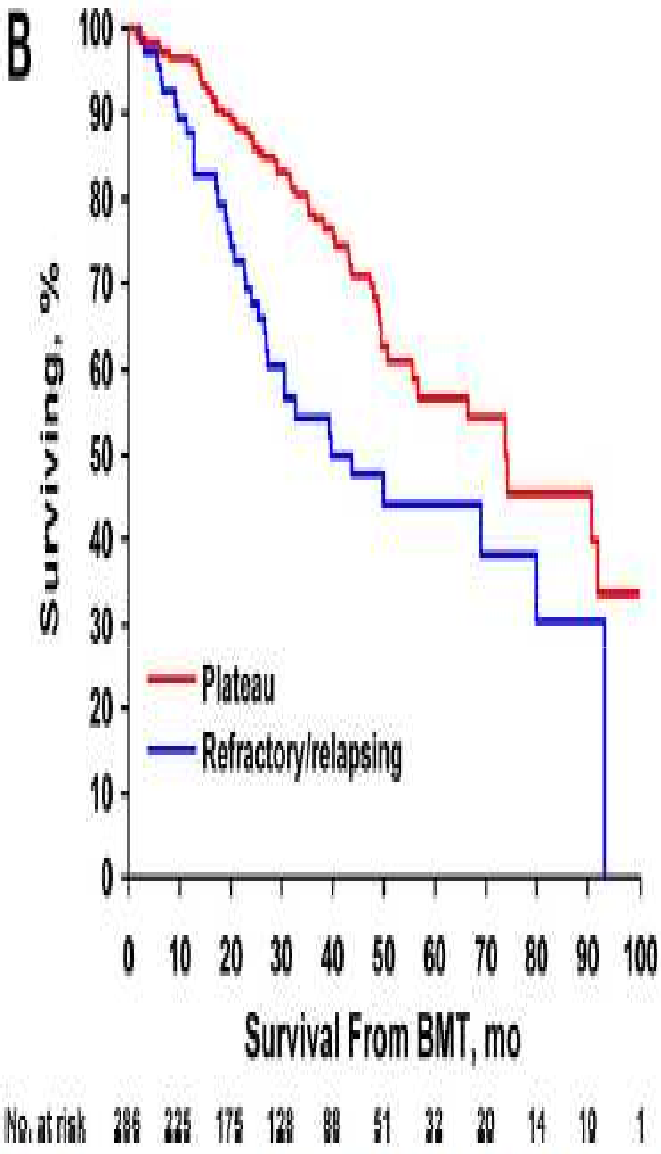
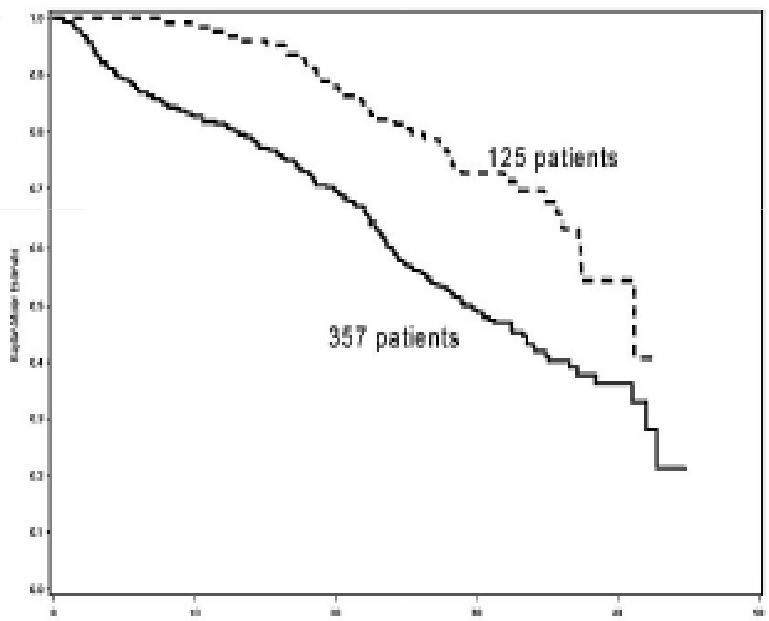


Figure 2. Failure to respond to thalidomide or lenalidomide induction leads to shorter posttransplantation overall survival. (A) Overall survival from day 0 of

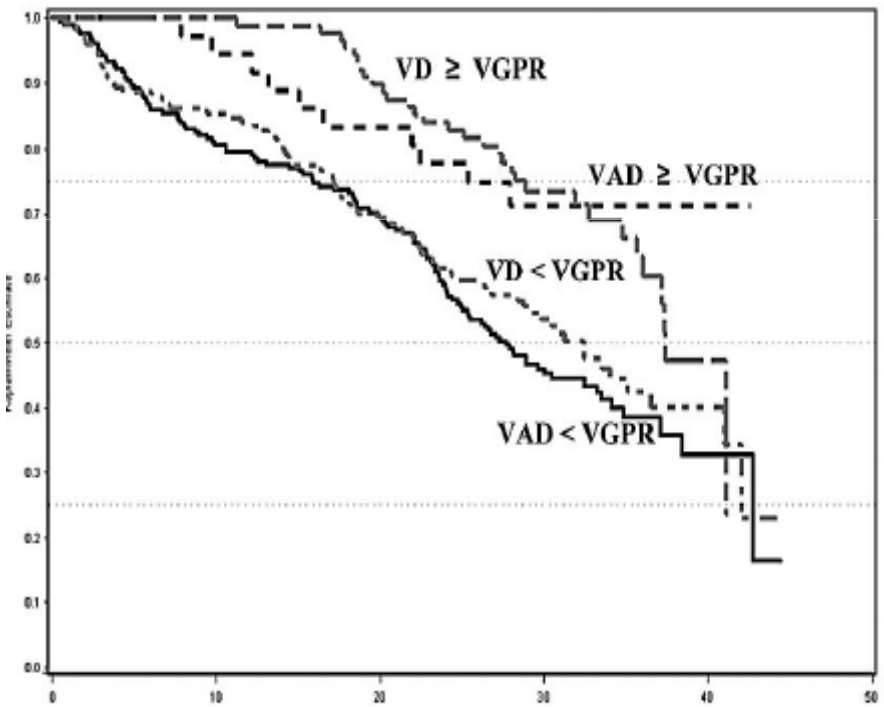
blood
2011 117: 3041-3044
doi:10.1182/blood-2010-08-300663 originally published online November 23, 2010

Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial

Philippe Moreau, Michel Attal, Brigitte Pégourié, Lucie Planche, Cyrille Hulin, Thierry Facon, Anne-Marie Stoppa, Jean-Gabriel Fuzibet, Bernard Grosbois, Chantal Doyen, Nicolas Ketterer, Catherine Sebban, Brigitte Kolb, Carine Chaletelx, Mamoun Dib, Laurent Voillat, Jean Fontan, Laurent Garderet, Jérôme Jaubert, Claire Mathiot, Dixie Essettine, Hervé Avet-Loiseau, Jean-Luc Harousseau and for the IFM 2005-01 study investigators*



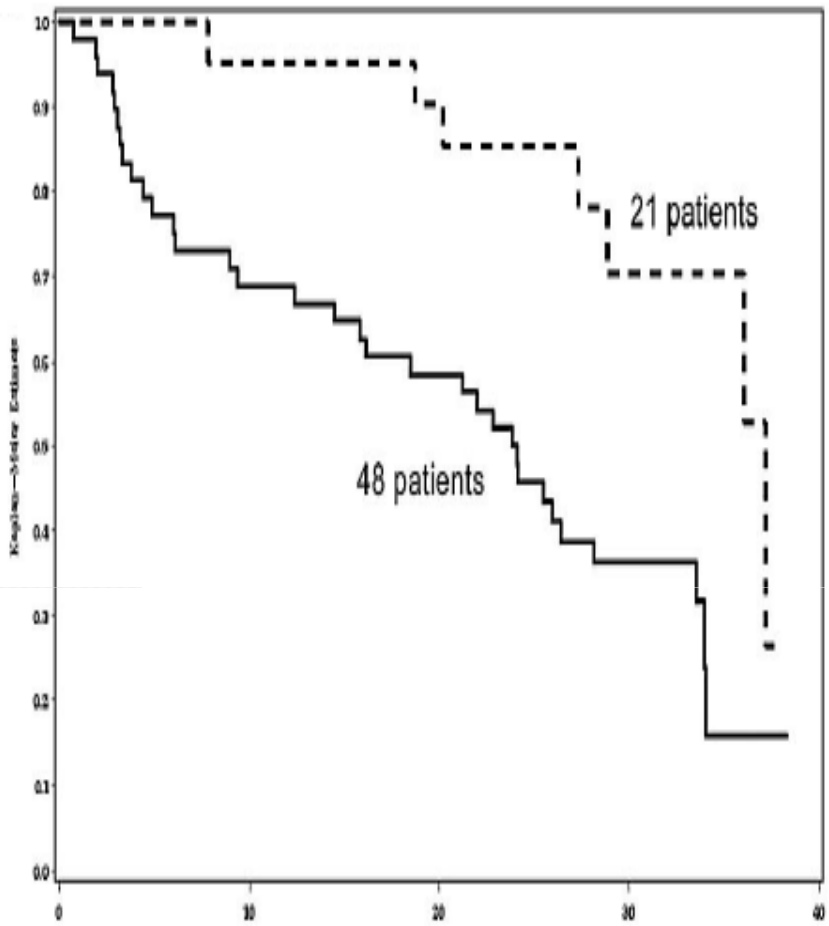
p < 0.0001



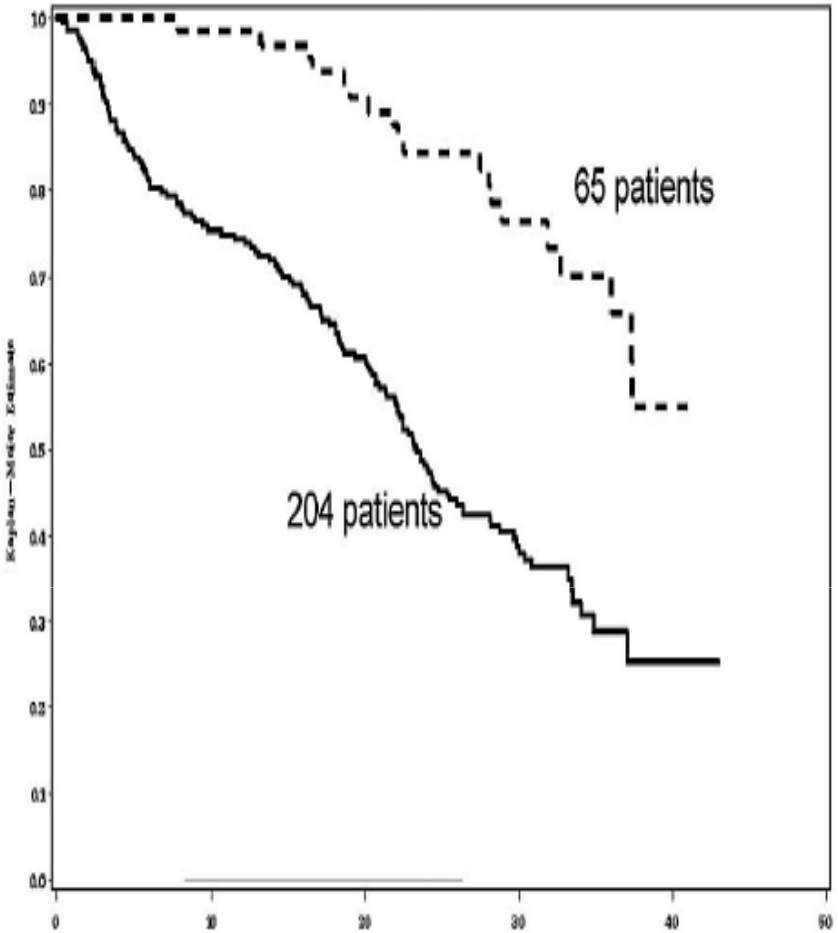
p < 0.0001

Obtention d'une VGPR in HDT

Obtention d'une VGPR in VAD/VD vs no Trt



p = 0.0036



p < 0.0001

Obtention d'une VGPR ISS 2/3 traités par VD vs no trt

Obtention d'une VGPR groupe anomalies cytogénétiques

Objectifs de réponse post induction pour nos patients

- **Haut risque:** ≥**RP**

pour les patients qui vont recevoir un traitement à base de velcade : **VTD** (> 90%)

- **Risque standard:** ≥**VGPR**

pour patients qui vont recevoir un traitement à base thalidomide: **CTD** (>50%)

III. QUELS PROTOCOLES POUR NOS PATIENTS? BI / TRI /QUADRI THERAPIE ?

- **Bithérapie:** n'as plus de place dans le traitement du myélome du sujet jeune
- **Quadrithérapie** ne fait pas mieux que trithérapie + plus de toxicités

→→ Pour nos patients: ***TRITHERAPIE :***

Quelle trithérapie??

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bortezomib-Based Versus Nonbortezomib-Based Induction Treatment Before Autologous Stem-Cell Transplantation in Patients With Previously Untreated Multiple Myeloma: A Meta-Analysis of Phase III Randomized, Controlled Trials

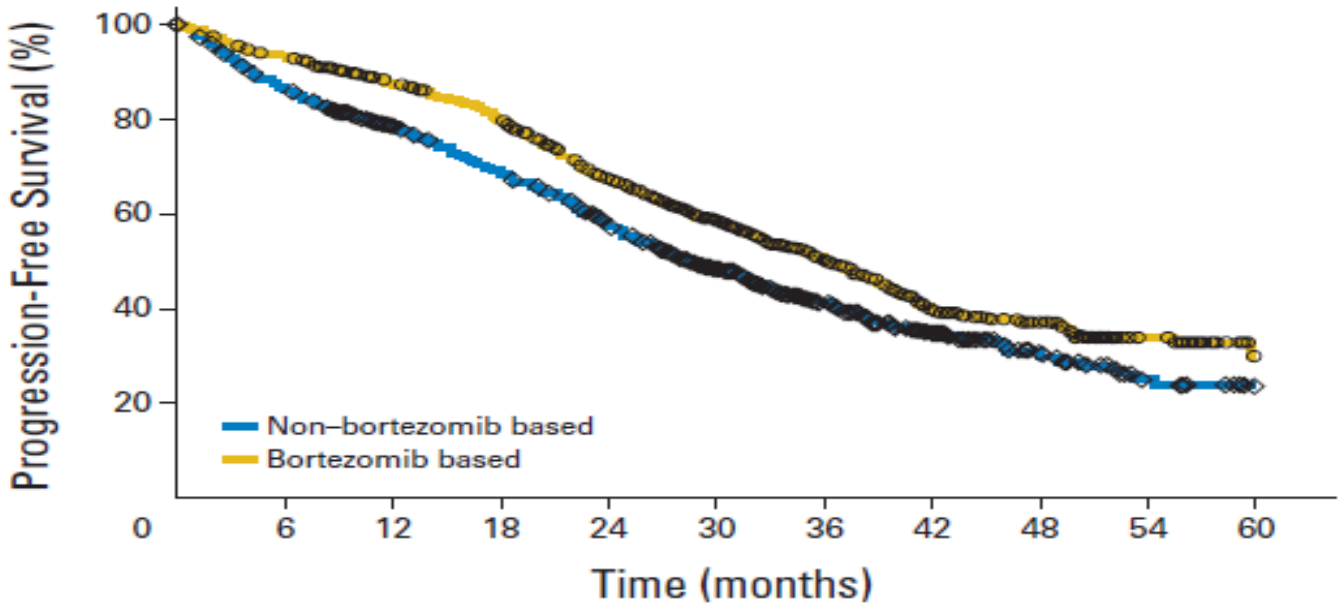
Pieter Sonneveld, Hartmut Goldschmidt, Laura Rosiñol, Joan Bladé, Juan José Lahuerta, Michele Cavo, Paola Tacchetti, Elena Zamagni, Michel Attal, Henk M. Lokhorst, Avinash Desai, Andrew Cakana, Kevin Liu, Helgi van de Velde, Dixie-Lee Esseltine, and Philippe Moreau

Patient-level data from the IFM 2005-01 (bortezomib-dexamethasone v vincristine-doxorubicin-dexamethasone [VAD] induction), HOVON-65/GMMG-HD4 (bortezomib-doxorubicin-dexamethasone v VAD), and PETHEMA GEM05MENOS65 (bortezomib-thalidomide-dexamethasone v thalidomide-dexamethasone) studies were pooled in an integrated analysis of efficacy and safety. Study-level data from the GIMEMA MM-BO2005 study (bortezomib-thalidomide-dexamethasone v thalidomide-dexamethasone) supplemented the integrated patient-level analysis. Key efficacy end points were post-transplantation complete plus near-complete response (CR+nCR) rate and progression-free survival (PFS).

Table 2. Postinduction and Post-Transplantation Response Rates for the Bortezomib-Based and Nonbortezomib-Based Induction Groups in the Integrated Analysis

	Bortezomib-Based Induction (n = 775)			Nonbortezomib-Based Induction (n = 772)					
Response	No.	%	95% CI	No.	%	95% CI	OR	95% CI*	P†
Postinduction									
CR	105	14	11 to 16	32	4	3 to 6	3.92	2.57 to 6.00	< .001
nCR	70	9	7 to 11	31	4	3 to 6	—		—
CR plus nCR	175	23	20 to 26	63	8	6 to 10	3.45	2.52 to 4.72	< .001
VGPR	187	24	21 to 27	76	10	8 to 12	—		
CR plus nCR plus VGPR‡	362	47	43 to 50	139	18	15 to 21	4.03	3.19 to 5.08	< .001
PR	284	37	33 to 40	341	44	41 to 48	—		—
ORR (≥ PR)	646	83	81 to 86	480	62	59 to 66	3.05	2.40 to 3.87	< .001
MR	35	5	3 to 6	109	14	12 to 17	—		—
SD	29	4	3 to 5	76	10	8 to 12	—		—
PD	24	3	2 to 5	55	7	5 to 9	—		—
Not evaluable	38	5	3 to 7	50	6	5 to 8	—		—

A



No. at risk											
Non–bortezomib based	785	671	571	497	404	286	164	89	46	20	8
Bortezomib based	787	723	647	587	472	344	206	98	56	30	10

B

Study	Hazard Ratio	95% CI	Non–bortezomib based Events	n	Median (months)	Bortezomib based Events	n	Median (months)	*P*
HOVON-65/GMMG-HD4	0.76	0.63 to 0.91	255	416	28.1	223	417	35.0	.0025
IFM 2005-01	0.78	0.60 to 1.01	128	242	29.7	110	240	36.1	.0577
PETHEMA GEM05MENOS65	0.65	0.45 to 0.92	70	127	27.9	55	130	55.5	.0152
Pooled (fixed effect)	0.75	0.65 to 0.85	453	785	28.6	388	787	35.9	< .001
Heterogeneity	$I^2 = 0\%$								
	Q = 0.76 with *df* = 2								
GIMEMA MM-BO2005	0.63	0.45 to 0.88							
Heterogeneity	$I^2 = 0\%$								
	Q = 1.75 with *df* = 3								

Favors bortezomib-based treatment | Favors non–bortezomib-based treatment

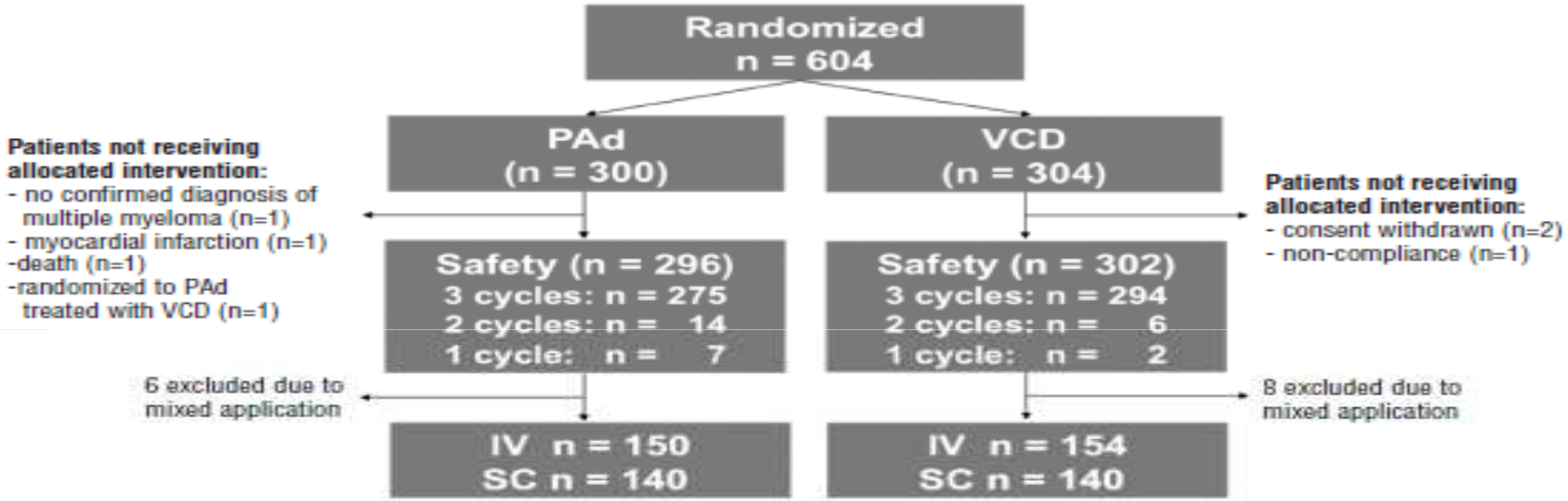
Conclusion de ces 4 études:

- Median ***PFS*** was ***35.9*** months versus 28.6 months with bortezomib-based versus nonbortezomib-based induction ***(P:0.001)***

- ***3-year overall survival (OS)*** rates were ***79.7%*** and 74.7% ***(P: 0.0402)***

haematologica | 2015; 100(7)

Subcutaneous *versus* intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial



	PAd n. (%)			VCD n. (%)		
All	IV	SC	*P*	IV	SC	*P*
≥ PR	109 (73)	99 (71)	0.79	120 (78)	115 (82)	0.39
≥ VGPR	55 (37)	44 (31)	0.39	64 (42)	40 (29)	**0.02**
nCR/CR	34 (23)	25 (18)	0.38	41 (27)	20 (14)	**0.01**

Table 2. Summary of adverse events, serious adverse events and deaths.

Adverse event	IV n (%)	SC n (%)	P
Any ≥ grade 2	198 (65)	156 (56)	**0.02**
Infections and infestations	77 (25)	54 (19)	0.09
Cycle 1	41 (14)	28 (10)	n.s.
Cycle 2	27 (9)	22 (8)	
Cycle 3	13 (5)	13 (5)	
Blood and lymphatic system disorders	49 (16)	30 (11)	0.06
Cycle 1	36 (12)	20 (7)	n.s.
Cycle 2	17 (6)	13 (5)	
Cycle 3	11 (4)	10 (4)	
Hematotoxicity			
Anemia	22 (7)	12 (4)	n.s.
Leukopenia	72 (24)	57 (20)	
Thrombocytopenia	17 (6)	13 (5)	
Metabolic and nutritional disorders	38 (13)	15 (5)	**<0.01**
Cycle 1	24 (8)	11 (4)	n.s.
Cycle 2	11 (4)	4 (1)	
Cycle 3	10 (4)	5 (2)	
Gastrointestinal disorders	30 (10)	11 (4)	**<0.01**
Cycle 1	18 (6)	4 (1)	**<0.01**
Cycle 2	11 (4)	4 (1)	n.s.
Cycle 3	5 (2)	3 (1)	
Peripheral neuropathy	35 (12)	23 (8)	0.21
Cycle 1	5 (2)	7 (3)	n.s.
Cycle 2	7 (2)	10 (4)	
Cycle 3	23 (8)	5 (2)	**<0.01**
Grading of neuropathy			
grade 2	26 (9)	19 (7)	n.s.
grade 3	9 (3)	4 (1)	
grade 4	0 (0)	0 (0)	

On propose à nos patients de haut risque

Un traitement à base de Velcade :

VTD (velcade ***sc***)

QUE FAUT-IL PROPOSER POUR LE RISQUE STANDARD?

Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results

haematologica | 2012; 97(3)

Table 1. Patients' characteristics (n=1,111).

Characteristic	CVAD (n=556)	CTD (n=555)
Age, years		
Median	59	59
Range	31-74	33-78
Female sex, n (%)	208 (37.4)	211 (38.0)
β_2 microglobulin, mg/L		
Median	4.1	3.9
Range	0.1-66.0	0.1-114.1
International Staging System stage, n (%)		
I	124 (22.3)	151 (27.2)
II	191 (34.4)	189 (34.1)
III	183 (32.9)	160 (28.8)
Missing data	58 (10.4)	55 (9.9)

CTD: cyclophosphamide, thalidomide, and dexamethasone; CVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

Table 2. Response after induction therapy (intent-to-treat population) and following high-dose therapy with ASCT (patients receiving ASCT).

Response, n (%)	After induction therapy		
	CVAD (n=556)	CTD (n=555)	*P* value*
	(71.2)	458 (82.5)	<0.0001†
	(8.1)	72 (13.0)	0.0083
	(19.4)	168 (30.3)	0.000030
	(43.7)	218 (39.3)	0.14

Table 2. Response rate to induction therapy according to treatment arm

	QT + V, n = 129	TD, n = 127	VTD, n = 130
CR, %	21*	14*	35*
VGPR, %	15	15	25
PR, %	39	33	25
SD, %	12	12	6
PD, %	12†	23	7‡
Early deaths, %	1	1	2

Treatment of autologous stem cell transplant-eligible multiple myeloma patients: ten questions and answers

Mohamad Mohty,[1,2,3] and Jean-Luc Harousseau[4]

haematologica | 2014; 99(3)

Table 1. Induction regimens.

Induction regimen	Response post-induction (%) CR	Response post-induction (%) ≥ VGPR	Response post-ASCT (%) CR	Response post-ASCT (%) ≥ VGPR
TAD *vs.* VAD[11]	3 2	37* 18	14 12	66* 54
CTD *vs.* CVAD[13]	13* 8	43‡ 27	50* 37	74‡ 62
Bortezomib/dex *vs.* VAD[12]	6* 1	38* 15	16* 9	54* 37
PAD *vs.* VAD[14]	7* 2	42* 14	21* 9	62* 36*
VTD *vs.* TD[6]	19* 5	62* 28	42* 30	82* 64
vTD *vs.* VD[15]	13 12	49* 36	29 31	74* 58
VTD *vs.* TD *vs.* VBMCP/VBAD+V[18]	35* 14 21	60‡ 29 36	46† 24 38	n/a n/a n/a

*ASCT: autologous stem-cell transplantation; CR: complete response; VGPR: very good partial response. *P value statistically significant; ‡Information regarding P-values not available; †P value VTD versus TD statistically significant.*

On propose

- ***Faible risque***: ***CTD***

CTD vs TD

Pas d'études comparatives directes

CTD> RC/VGPR/OR → > EFS/OS ?

- ***Haut risque:*** ***VTD***

IV. NOMBRE DE CYCLES DE TRAITEMENT D'INDUCTION?

- La littérature: 3 à 6 cycles

- Devant le délai relativement long dans notre série entre la fin du traitement et l'autogreffe :

On propose: 4 cycles

3cycles → RCSP → 4ème cycle → Auto

V. FAUT-IL RATTRAPER LES PATIENTS EN ECHEC SELON NOTRE OBJECTIF ? FAUT-IL RATTRAPER LES PATIENTS <RP (réfractaire primaire et/ou en rechute)

- ***Faible risque :*** ***<TBRP***

oui → 2 cycles VTD → Autogreffe

- ***Haut risque:*** ***<RP***

Non → Autogreffe? Ou

Oui → RD? Mais cout/survie

Impact of Pretransplant Therapy and Depth of Disease Response before Autologous Transplantation for Multiple Myeloma

Ravi Vij [1], Shaji Kumar [2], Mei-Jie Zhang [3,4], Xiaobo Zhong [3], Jiaxing Huang [3], Angela Dispenzieri [2], Muneer H. Abidi [5], Jennifer M. Bird [6], César O. Freytes [7], Robert Peter Gale [8], Tamila L. Kindwall-Keller [9], Robert A. Kyle [2], Daniel J. Landsburg [10], Hillard M. Lazarus [11], Reinhold Munker [12], Vivek Roy [13], Manish Sharma [14], Dan T. Vogl [10], Baldeep Wirk [15], Parameswaran N. Hari [3,*]

R. Vij et al. / Biol Blood Marrow Transplant 21 (2015) 335–341

Baseline Demographics and Characteristics at Transplant

Characteristics	NO SALVAGE	SALVAGE	P
Number of patients	215	324	
Number of centers	77	85	
Baseline Demographics			
Median age at transplant, yr (range)	57 (33-75)	56 (18-74)	
18-39	13 (6)	23 (7)	.872
40-49	40 (19)	67 (21)	
50-59	84 (39)	113 (35)	
60-69	70 (33)	107 (33)	
70+	8 (4)	14 (4)	

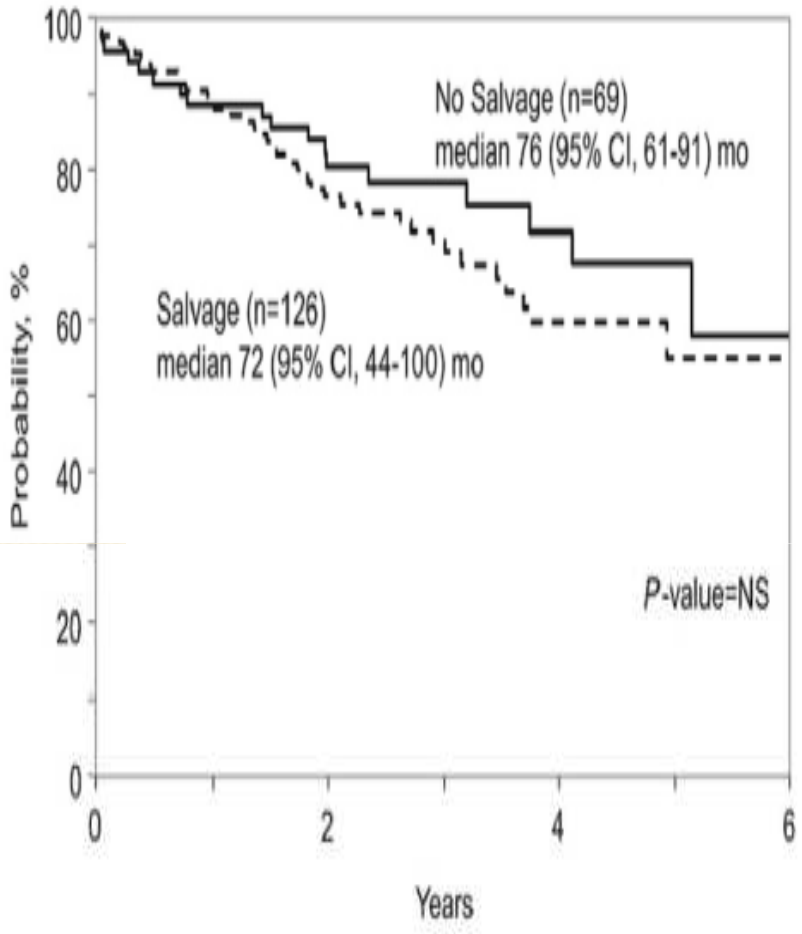


Figure 3. Effect of salvage on survival in patients with non-response to bortezomib/thalidomide/lenalidomide in first-line therapy.

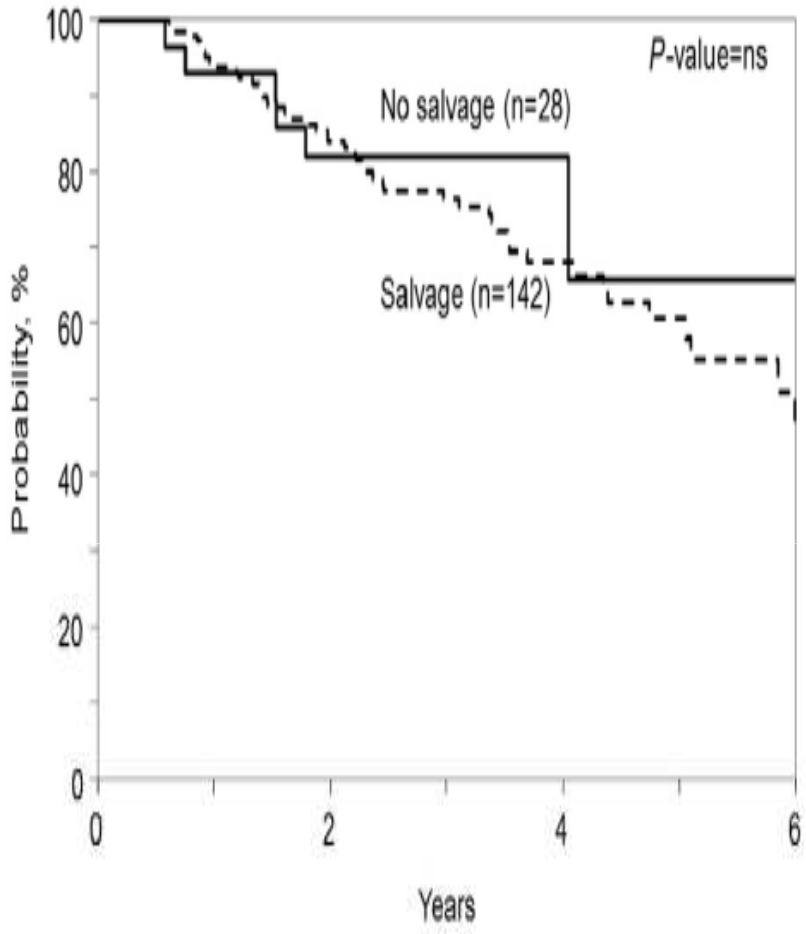


Figure 4. Effect of salvage on survival in patients receiving bortezomib and/or lenalidomide in first-line therapy.

Conclusions de cette étude

- On ***multivariate analysis:*** no impact of pretransplant salvage chemotherapy:
  - treatment-related mortality,
  - risk for relapse,
  - progression-free survival, or overall survival.
- ***In conclusion:*** (< PR to initial induction therapy, including with novel agent combinations, additional pre- ASCT salvage chemotherapy)
  - **improved** the **depth of response** and pre-ASCT **disease status**
  - ***not associated with survival benefit***

Merci