National University Cancer Institute, Singapore

NUHS National University Health System

Multiple Myeloma: Risk Stratified Treatment Strategies

A/Prof Chng Wee Joo
Head, Haematologic Malignancies
Department of Haematology-Oncology
National Cancer Institute of Singapore
National University Health System
Deputy Director and Senior Principle Investigator
Cancer Science Institute, Singapore
National University of Singapore

Research

Clinical Care

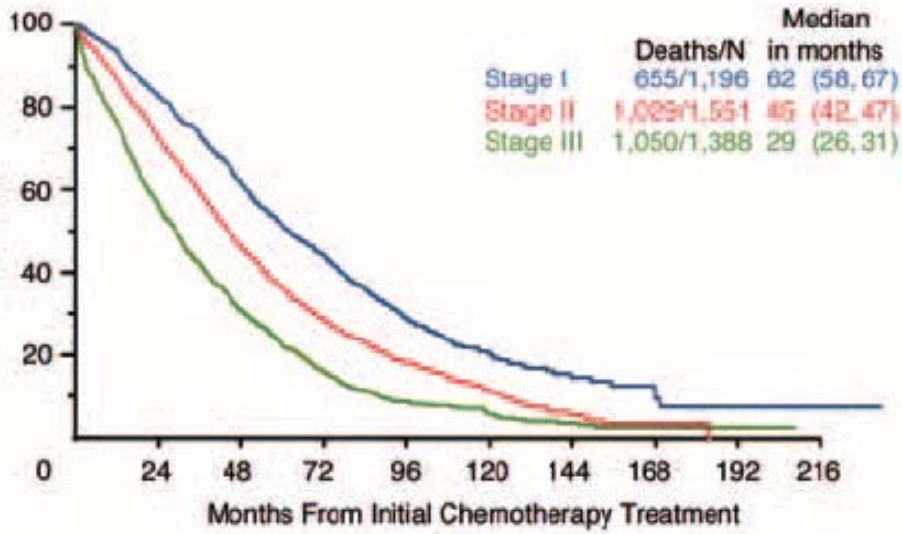
Education

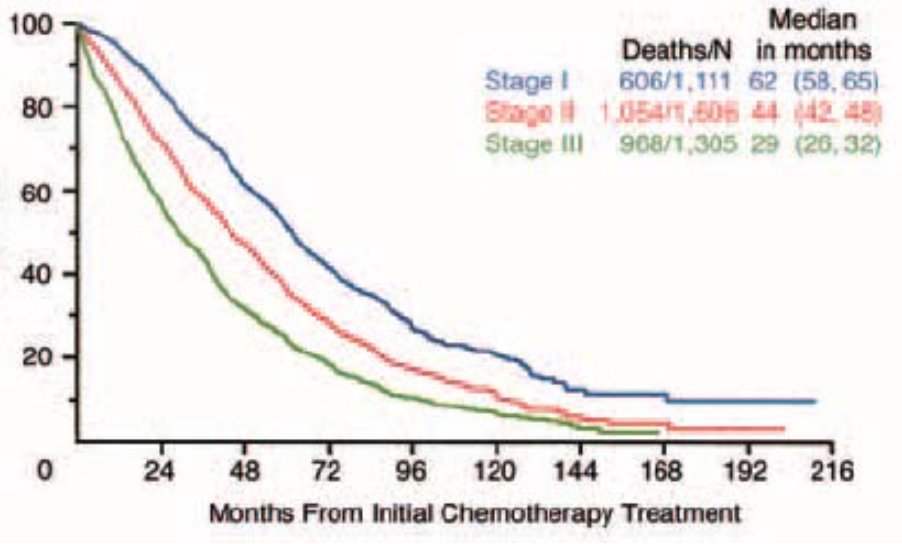
CSI SINGAPORE

International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

*There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.





Greipp et al JCO 2005;23:3142

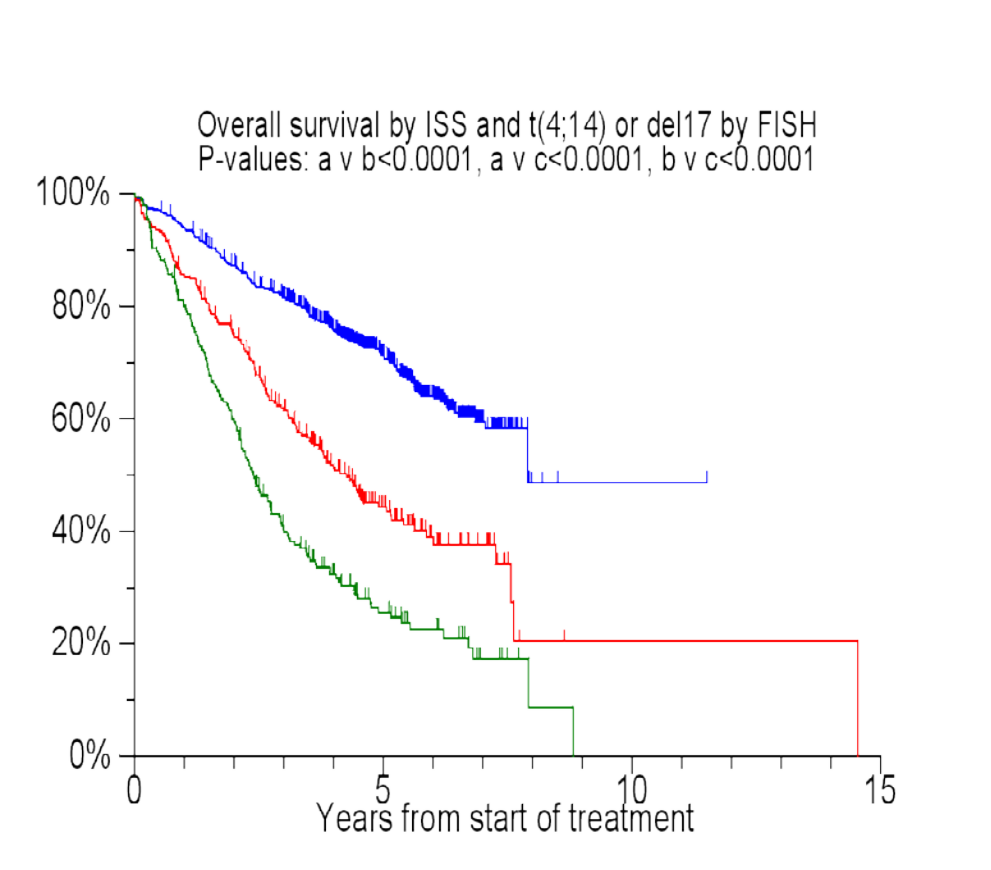
Genetic Abnormalities Detected by FISH

Abnormalities	Frequencies	Prognosis
t(4;14)	10-15%	Poor
t(11;14)	15-20%	Neutral
t(14;16)	3-5%	Poor
1q21 Gain	30-35%	Poor
13q14 del	45-50%	Neutral
17p13 del	5-10%	Poor

Summary of Prognostic Factors

	Pre-treatment	Post-treatment
Host	Age Albumin	
Tumor Burden	MRI/PET-CT Durie-Salmon Beta-2 microglobulin	MRI/PET-CT
Tumor Biology	PCLI Genetics	Response

Prognostic impact of t(4;14)/del(17p) with ISS



	Deaths/N	4-year estimate
a ISS I or ISS II and Normal FISH	193/610	76% (72,79)
b ISS I and Abnormal FISH/ISS III and Normal FISH	140/252	52% (45,58)
c ISS II or ISS III and Abnormal FISH	146/196	32% (26,39)

Avet-loiseau et al. ASH 2009

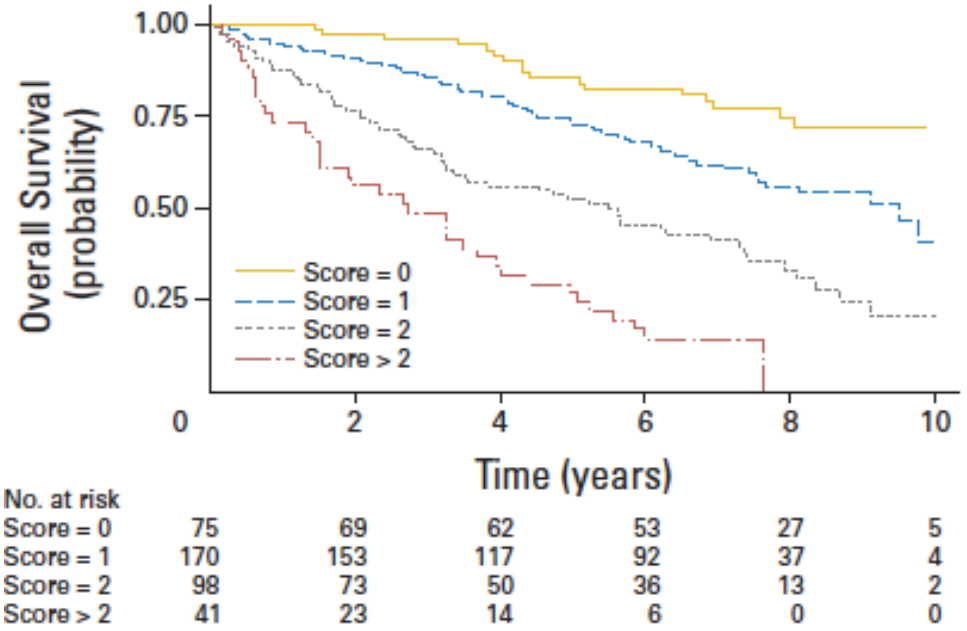
		IMWG[64]	MRC[53]	German[65]
Treatment		Include both young patients (transplant) and older patients (chemotherapy only)	Young (intensive) and old patients (non-intensive) with thalidomide-based combination at induction and thalidomide maintenance on MRC IX trials	Chemo-based induction followed by HD Mel ASCT and maintenance
N		2637	629	315
Low Risk	Parameter	ISS[1] I/II with no adverse FISH[2]	ISS I/II with no adverse FISH[3] Or ISS I with 1 adverse FISH lesions	ISS I with no adverse FISH[2]
	% Patients	51%	38%	42%
	OS	76% at 4 yrs	Median 67.8 mths	72% at 5 yrs
Int Risk	Parameter	ISS III with no adverse FISH Or ISS I and t(4;14) / 17p13 del	ISS I with >1 adverse FISH lesions Or ISS II / III with 1 adverse FISH lesions Or ISS III and no adverse FISH	ISS II / III with no adverse FISH Or ISS I and t(4;14) / 17p13 del
	% Patients	29%	48%	44%
	OS	45% at 4 yrs	Median 41.3 mths	62% at 5 yrs
High Risk	Parameter	ISS II / III and t(4;14) / 17p13 del	ISS II / III with >1 adverse FISH lesions	ISS II / III and t(4;14) / 17p13 del
	% Patients	20%	14%	14%
	OS	33% at 4 yrs	Median 19.4 mths	41% at 5 yrs

[1] ISS stage I = Beta-2 microglobulin < 3.5 mg/L and Albumin ≤ 3.5 g/dL; ISS stage III = Beta-2 microglobulin ≥ 5.5 mg/L; ISS stage II = Not ISS I or ISS III.
[2] Adverse FISH here refers to t(4;14) and/or 17p13 del
[3] Adverse FISH here refers to Adverse IgH translocations (t(4;14) or t(14;16) or t(14;20)), 17p13 del and/or 1q21 gain

Long-Term Analysis of the IFM 99 Trials for Myeloma: Cytogenetic Abnormalities [t(4;14), del(17p), 1q gains] Play a Major Role in Defining Long-Term Survival

Hervé Avet-Loiseau, Michel Attal, Loic Campion, Denis Caillot, Cyrille Hulin, Gerald Marit, Anne-Marie Stoppa, Laurent Voillat, Marc Wetterwald, Brigitte Pegourie, Eric Voog, Mourad Tiab, Anne Banos, Jerome Jaubert, Didier Bouscary, Margaret Macro, Brigitte Kolb, Catherine Traulle, Claire Mathiot, Florence Magrangeas, Stephane Minvielle, Thierry Facon, and Philippe Moreau

	Univariate Analysis			Multivariate Analysis		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Age, years						
> 55 *v* ≤ 55	1.63	1.25 to 2.13	< .001	1.71	1.22 to 2.40	.002
β_2-microglobulin, mg/L						
> 5.5 v ≤ 5.5	2.19	1.65 to 2.90	< .001	2.68	1.89 to 3.82	< .001
Creatinine, μmol/L						
> 180 *v* ≤ 180	1.96	1.30 to 2.96	.001	—	—	—
Calcemia, mmol/L						
> 2.8 *v* ≤ 2.8	1.95	1.31 to 2.88	.001	—	—	—
Platelets, g/L						
≤ 120 *v* > 120	2.34	1.37 to 3.90	.001	—	—	—
Hemoglobin, g/dL						
≤ 11 *v* > 11	1.42	1.08 to 1.86	.011	—	—	—
t(4,14)						
Yes *v* no	2.73	1.95 to 3.82	< .001	3.04	1.97 to 4.68	< .001
del17p						
> 60 *v* ≤ 60	3.33	2.01 to 5.21	< .001	3.04	1.71 to 5.39	< .001
del13						
> 40 *v* ≤ 40	1.74	1.35 to 2.24	< .001	—	—	—
1q gain						
Yes *v* no	2.00	1.56 to 2.58	.001	1.58	1.14 to 2.19	.006



JCO 2012 epub

Can novel agents modulate risk?

Novel Drugs and High Risk cytogenetics: Two different concepts

- **To overcome adverse Prognosis:**

With the use of novel drugs the survival of patients with high risk cytogentics is similar to that of standard risk patients

- **To Improve Outcome:**

The treatment with novel drugs is able to improve the outcome so far observed with standard treatments in high risk patients

Talidomide Combo: do not seem to overcome the adverse prognosis of High Risk Cytogentics:

Impact of cytogenetic abnormalities in patients treated with thalidomide/dex + double ASCT

- Retrospective study of 2 trials investigating thal/dex + double ASCT
- Patients (n=593) followed for median 36 months
- FISH analysis at diagnosis
  - del(13q) 45%
  - t(4;14) 16%
  - del(17p) 7%
- Results

	Presence of t(4;14) and/or del(17p)	Absence of t(4;14) and/or del(17p)	*P*
5-year TTP	30%	53%	<0.0001
5-year PFS	28%	45%	<0.0001
5-year OS	53%	69%	<0.0001

  - Multivariate analysis: presence of del(17p) and high β_2M at baseline most important variables adversely influencing TTP, PFS and OS

Zamagni *et al*. ASH 2010 (Abstract 3562)

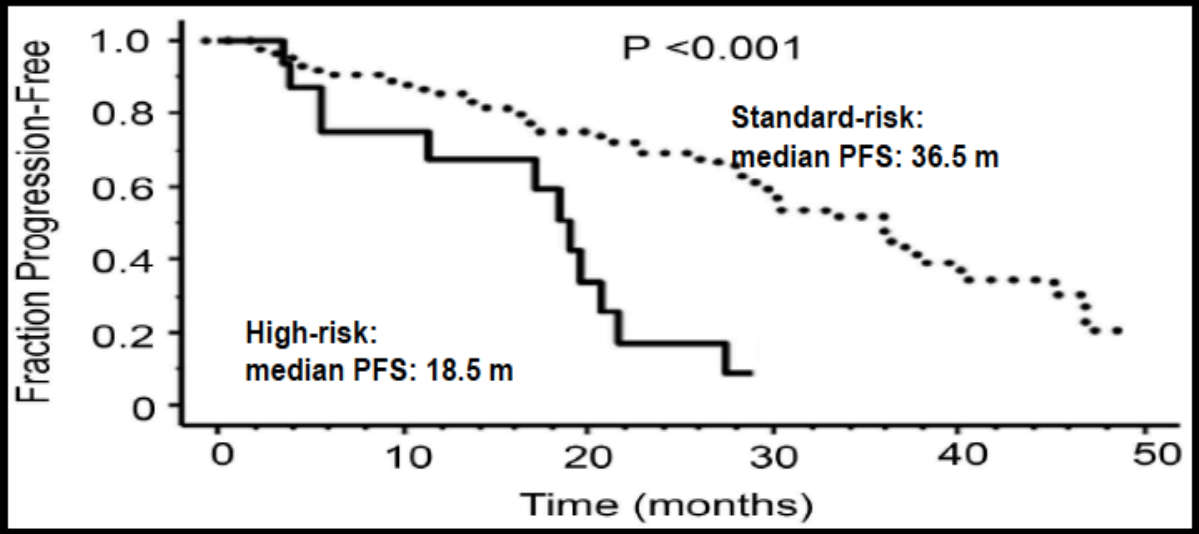
Lenalidomide/Dex in newly diagnosed MM

High Response Rate but short PFS

- **Patients** (n=100 newly diagnosed): *16% high-risk* *[hypodiploidy, del(13) (cytogenetics), del p53 , PCLI ≥ 3%, t(4;14), t(14;16)*
- **Treatment:** Lenalidomide (25mg/day), days 1-21 of 4-week cycle + Dex
- **Results** (median follow up: 36 months)

Response	High-risk	Standard risk	*P*
≥ PR	81%	89%	0.56
≥ VGPR	38%	45%	0.36

PFS



This has not so far resulted in a significantly different 3-year OS (77% vs86%)

Kapoor *et al*. Blood. 2009;114:518-521.

Lenalidomide maintenance in high-risk cytogenetics

- Patients treated in 2005-01 trial: Vel/dex vs VAD
- Patients achieving ≥ PR post-transplantation enrolled in 2005-02 trial: 2 months consolidation with lenalidomide followed by lenalidomide maintenance or placebo
- Chromosomal data available for 488 patients:
  - t(4;14) in 13.3%
  - del(17p) in 6.6%

The median PFS of the total group of Len treated patients was 42m

	Lenalidomide maintenance	Placebo
Median PFS for pts with t(4;14)	28 months	24 months
Median PFS for pts with del(17p)	29 months	14 months

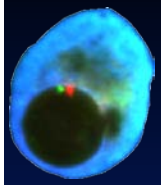
Len mainten doesn't either overcome or improve the adverse prognosis of t(4;14)

Lenalidomide doesn't overcome the adverse prognosis of del17p, but improved the PFS as compared with no maintenance.

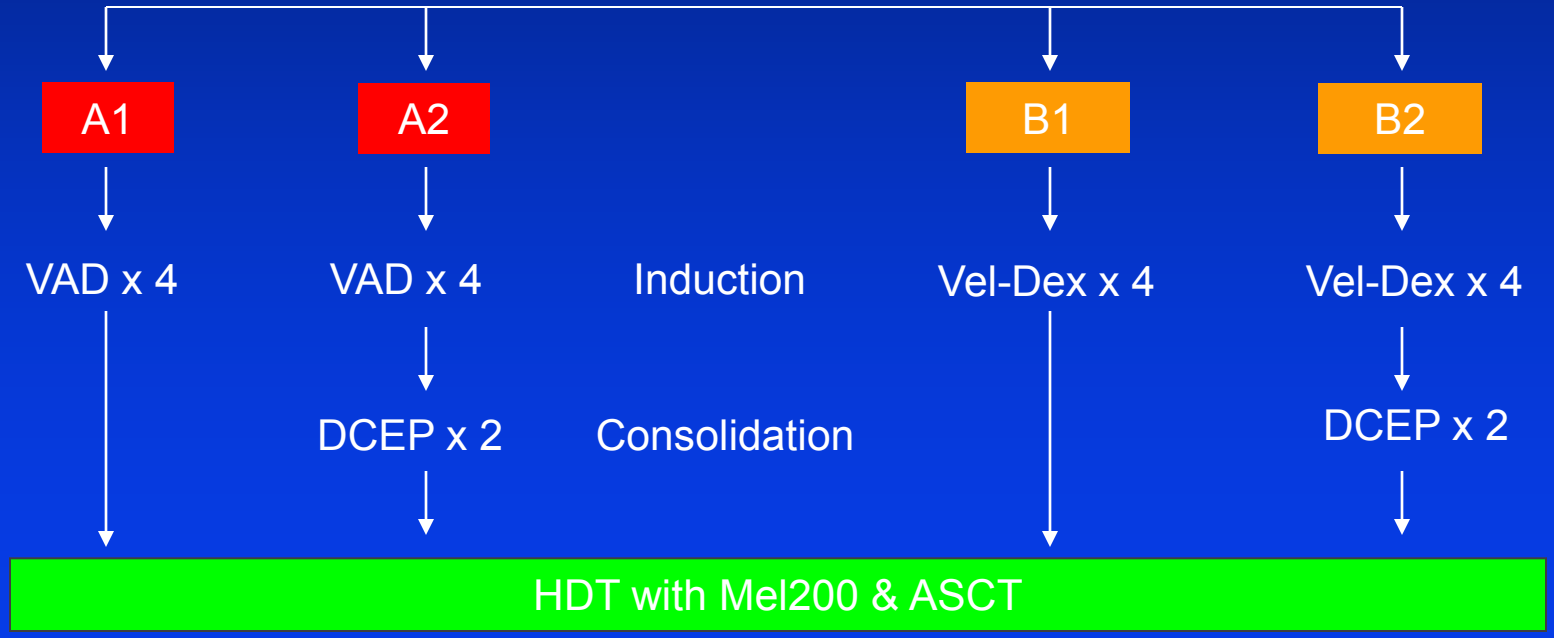
Avet-Loiseau *et al*. ASH 2010 (Abstract 1944)

Bortezomib Plus Dexamethasone Induction Improves Outcome of Patients With t(4;14) Myeloma but Not Outcome of Patients With del(17p)

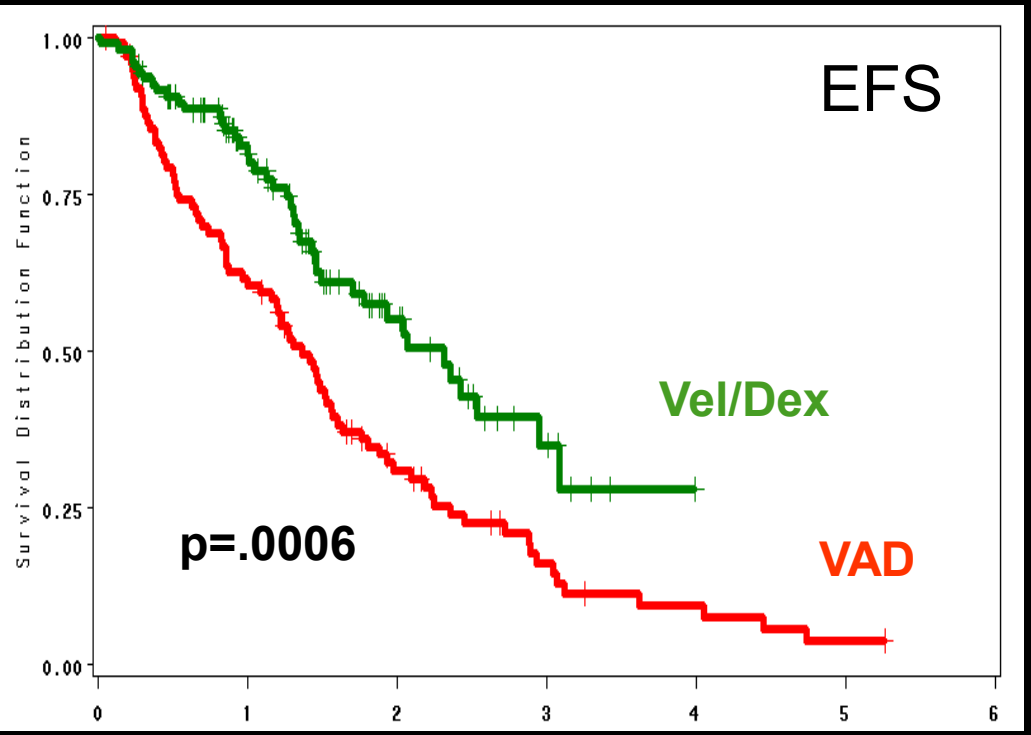
Hervé Avet-Loiseau, Xavier Leleu, Murielle Roussel, Philippe Moreau, Catherine Guerin-Charbonnel, Denis Caillot, Gérald Marit, Lotfi Benboubker, Laurent Voillat, Claire Mathiot, Brigitte Kolb, Margaret Macro, Loïc Campion, Marc Wetterwald, Anne-Marie Stoppa, Cyrille Hulin, Thierry Facon, Michel Attal, Stéphane Minvielle, and Jean-Luc Harousseau

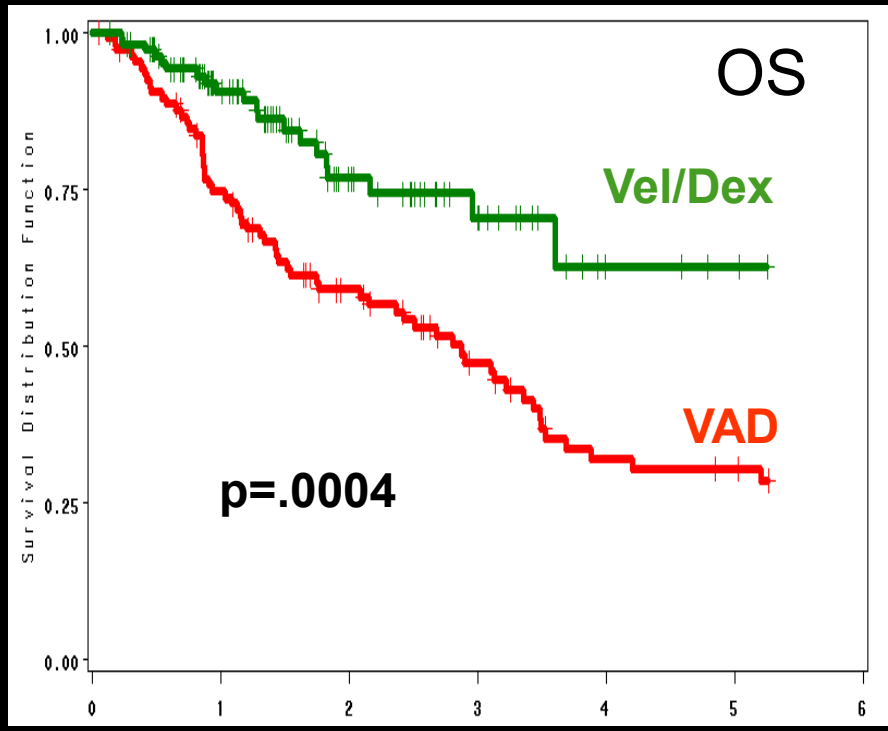


JCO 2010; 28; 4630-4634



t(4;14) with Velcade®

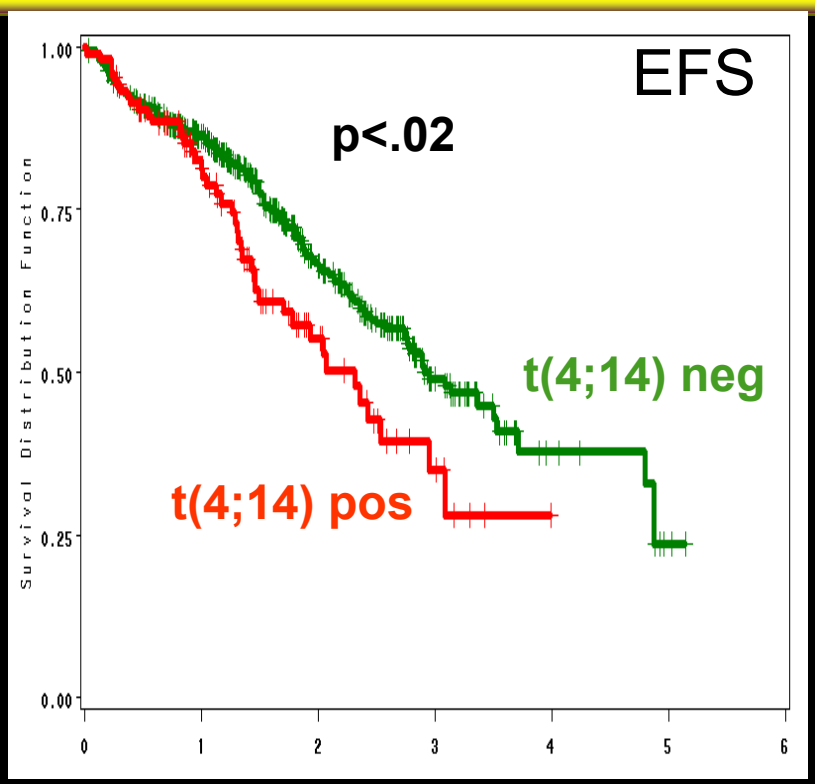


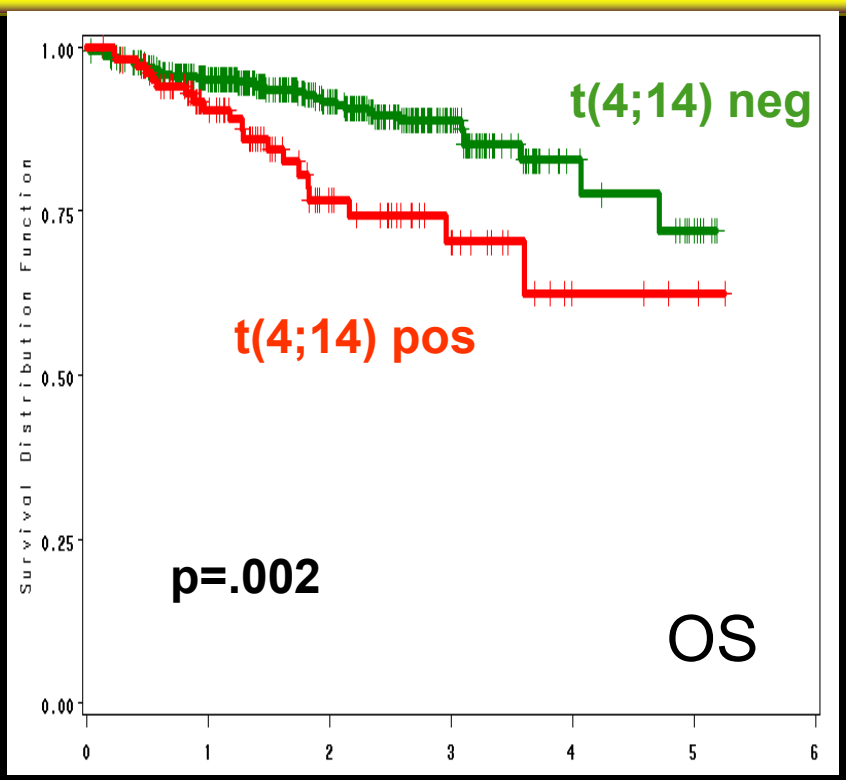


treatment	VAD	Vel/Dex	pvalue (logrank)
Patients	98	106	0.0006
Relapses	82	43	
Median EFS (years) [IC 95%]	1.36 [1.08 ; 1.56]	2.32 [1.49 ; 2.95]	

treatment	VAD	Vel/Dex	pvalue (logrank)
Patients	106	107	0.0004
Deaths	70	20	
Median OS (years) [IC 95%]	2.87 [1.76 ; 3.48]	---* [3.60 ; ---*]	

t(4;14) with Velcade®

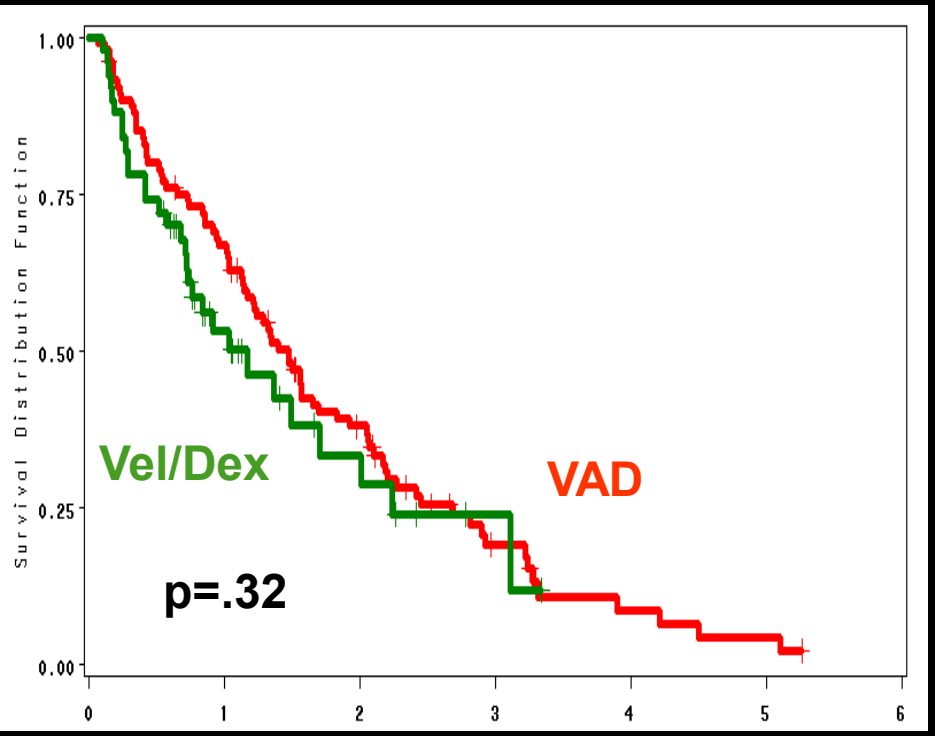


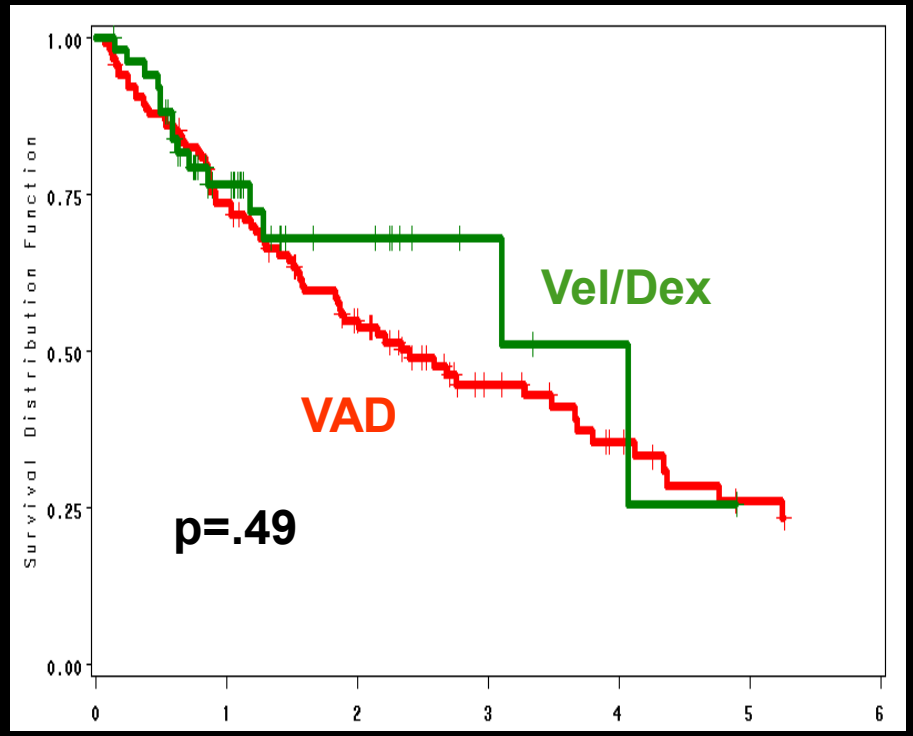


t(4 ;14)	neg	pos	pvalue (logrank)
Patients	396	106	0.0178
Relapses	141	43	
Median EFS (years) [IC 95%]	2.90 [2.74 ; 3.53]	2.32 [1.49 ; 2.95]	

t(4 ;14)	neg	pos	pvalue (logrank)
Patients	400	107	0.0020
Deaths	38	20	
Median OS (years) [IC 95%]	---* [---* ; ---*]	---* [3.60 ; ---*]	

Del(17p) with Velcade®

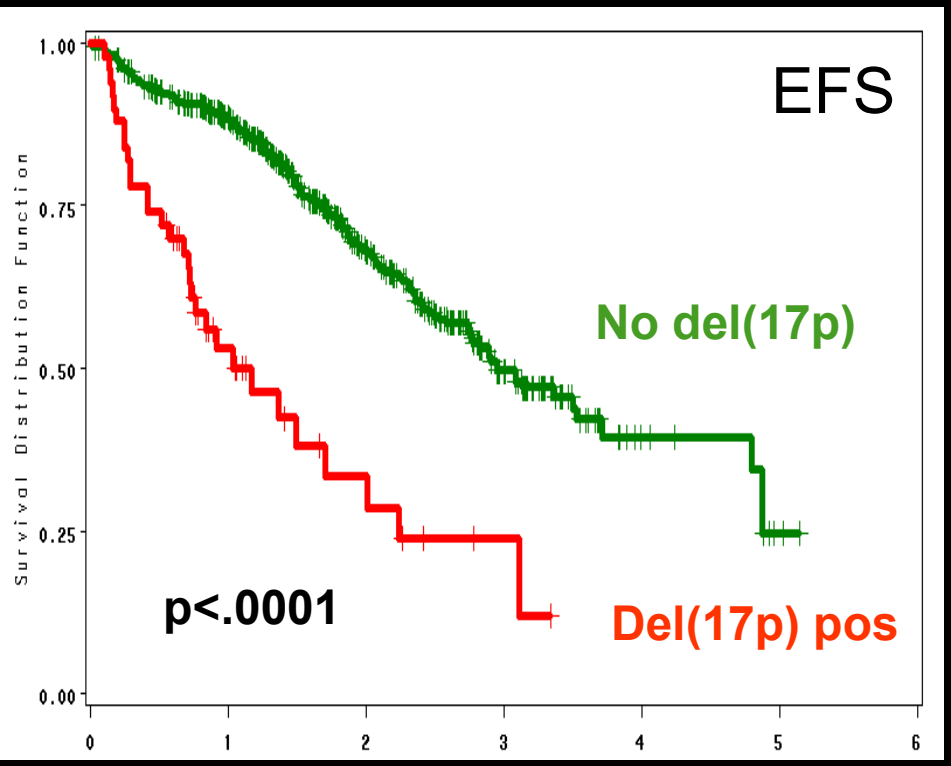


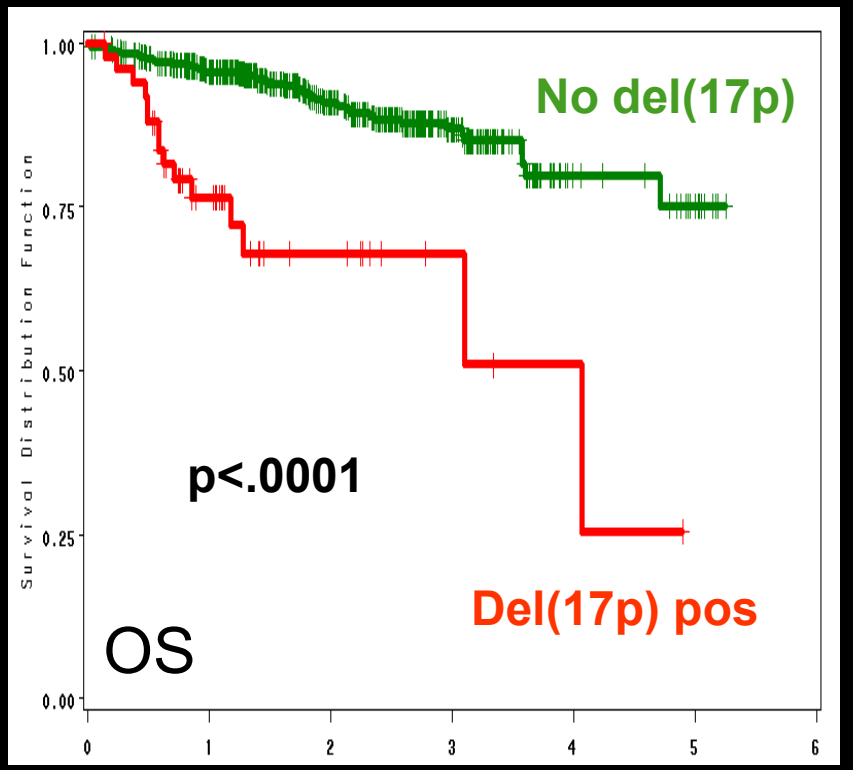


treatment	VAD	Vel/Dex	pvalue (logrank)
Patients	101	50	0.3156
Relapses	82	30	
Median EFS (years) [IC 95%]	1.47 [1.17 ; 1.83]	1.17 [0.72 ; 2.01]	

treatment	VAD	Vel/Dex	pvalue (logrank)
Patients	115	51	0.4857
Deaths	70	15	
Median OS (years) [IC 95%]	2.40 [1.83 ; 3.66]	4.07 [3.10 ; --*]	

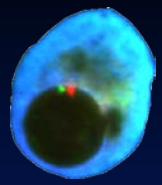
Del(17p) with Velcade®





Del(17p)	≤ 60%	> 60%	pvalue (logrank)
Patients	475	50	< 0.0001
Relapses	166	30	
Median EFS (years) [IC 95%]	2.95 [2.75 ; 3.71]	1.17 [0.72 ; 2.01]	

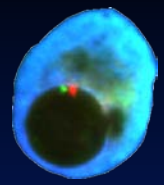
Del(17p)	≤ 60%	> 60%	pvalue (logrank)
Patients	480	51	< 0.0001
Deaths	48	15	
Median OS (years) [IC 95%]	---* [---* ; ---*]	4.07 [3.10 ; ---*]	



Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study

*Michele Cavo, Paola Tacchetti, Francesca Patriarca, Maria Teresa Petrucci, Lucia Pantani, Monica Galli, Francesco Di Raimondo, Claudia Crippa, Elena Zamagni, Antonio Palumbo, Massimo Offidani, Paolo Corradini, Franco Narni, Antonio Spadano, Norbert Pescosta, Giorgio Lambertenghi Deliliers, Antonio Ledda, Claudia Cellini, Tommaso Caravita, Patrizia Tosi, Michele Baccarani, for the GIMEMA Italian Myeloma Network**

Lancet 2010; 376: 2075-2085



	Events*/number of patients		Hazard ratio (95% CI)	p value†
	VTD	TD		
Presence of del(13q)	29/103	46/103	0·49 (0·31–0·79)	0·0039
LDH >190 U/L	43/182	72/200	0·60 (0·41–0·87)	0·0088
Age >60 years	23/92	41/95	0·53 (0·32–0·89)	0·0150
Presence of t(4;14) with or without del(17p)	20/53	32/57	0·51 (0·29–0·88)	0·0174
Bone marrow plasma cells >50%	30/116	41/111	0·59 (0·37–0·95)	0·0301
ISS disease stage II–III	42/129	57/131	0·68 (0·46–0·99)	0·0482

Bortezomib Combos as induction regimens in patients with cytogenetic abnormalities (I)

- **VTD, PAD:** Improves the outcome as compared to *to* TD [1,4] or *VAD* [2,3,] but not completely overcome the adverse prognosis (BzD) (Avet –Loisseau ASH 2010)

		t(4;14)	No t(4,14)	*Reference*
PFS at 3 yrs	VTD	65%	61%	**Cavo et** al Blood 2012
	TD	24 m	41 m	Double Trx

GEM 2005 Trial (VTD with one Trx): Shorter PFS for High Risk vs standard risk (23.5 m vs Not Reached)
(Rosiñol et al , ASH 2010 , abstract 307)

Bortezomib Combos as induction regimens in patients with cytogenetic abnormalities (II)

		t(4;14)	No t(4,14)	*Reference*
PFS (3 yr OS)	PAD VAD	36 m (78%) 18 m (39%)	40 m (87%) 36 m (79%)	**Goldsmidt** ASH 2010 (305) Double Trx
3yr-PFS (3yr-OS)	PAD VAD	28% (66%*) 20% (44%)	48% (82%)* 40%	**Sonneveld** ASH 2010 (40) One Trx

*P=0.2

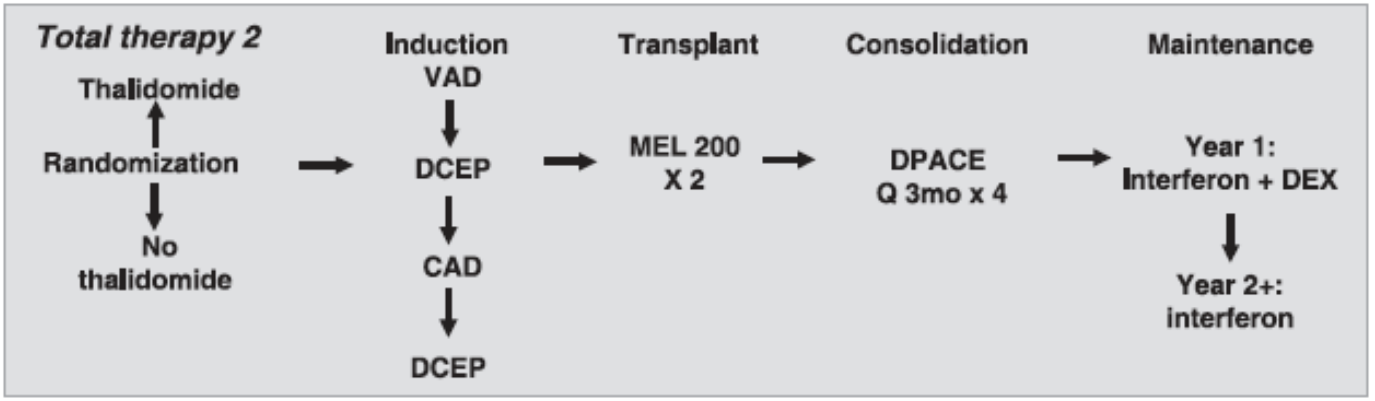
In the combined Hovon/German study, patients with **del(17p)** treated with PAD had a 3 y-OS of **69% vs 17%** for patients with del(17p) treated with VAD

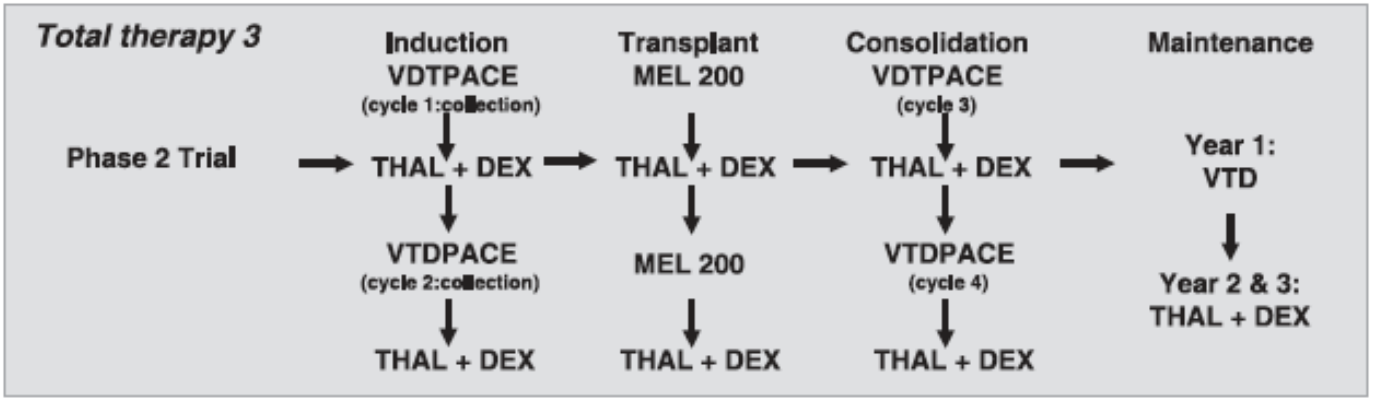
However, PAD+ASCT+bz doesn't overcome the adverse prognosis, since patients not having this abnormality had a **3-yr OS of 85%** ***(Neben, Blood 2011)***

bjh short report

TP53 deletion is not an adverse feature in multiple myeloma treated with total therapy 3

Shaughnesy et al. Br J Haematol 2009; 147:347-351



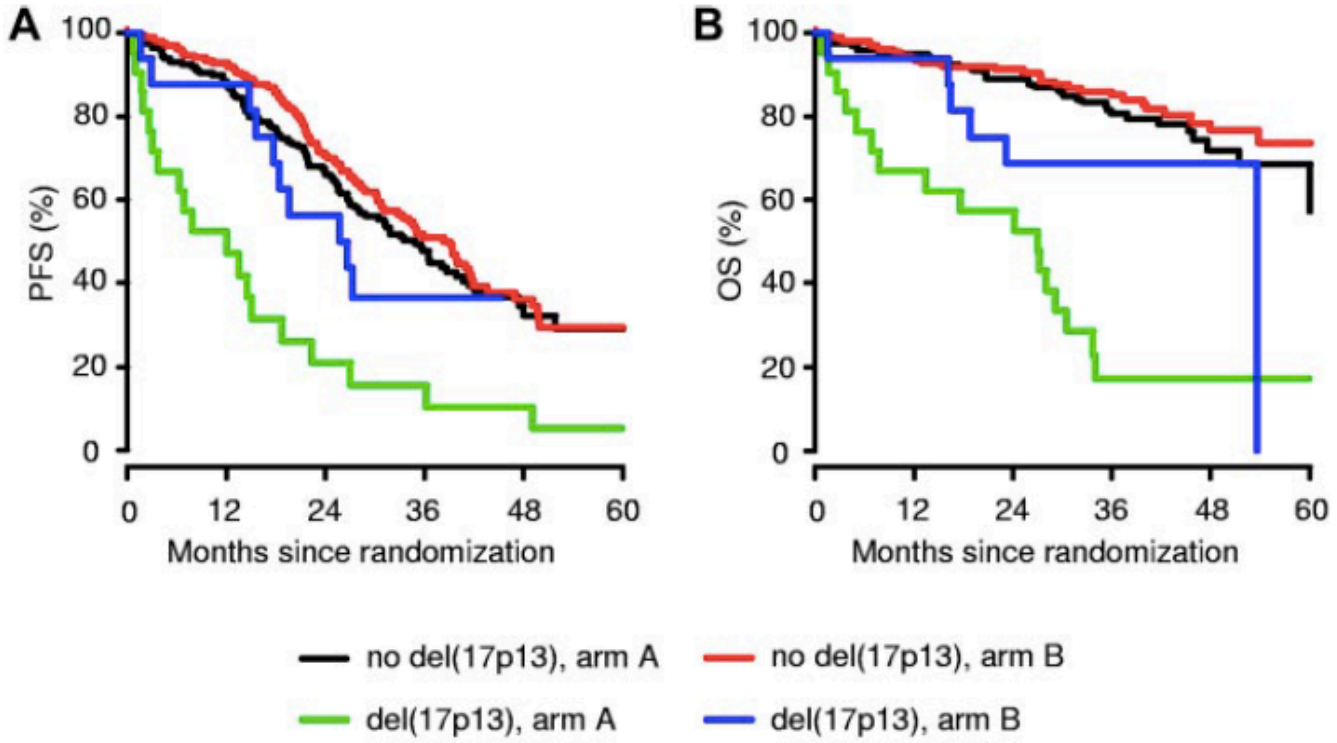


blood

2012 119: 940-948
Prepublished online December 8, 2011;
doi:10.1182/blood-2011-09-379164

Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p

Kai Neben, Henk M. Lokhorst, Anna Jauch, Uta Bertsch, Thomas Hielscher, Bronno van der Holt, Hans Salwender, Igor W. Blau, Katja Weisel, Michael Pfreundschuh, Christof Scheid, Ulrich Dührsen, Walter Lindemann, Ingo G. H. Schmidt-Wolf, Norma Peter, Christian Teschendorf, Hans Martin, Mathias Haenel, Hans G. Derigs, Marc S. Raab, Anthony D. Ho, Helgi van de Velde, Dirk Hose, Pieter Sonneveld and Hartmut Goldschmidt



Risk Stratification

	High Risk	Intermediate Risk	Standard Risk	Good Risk
Genetic Abn	▪ FISH ▪ Del 17p ▪ t(14;16) ▪ t(14;20)	▪ FISH ▪ t(4;14) ▪ Cytogenetic Deletion 13 or hypodiploidy	▪ All others including ▪ Hyperdiploid ▪ t(11;14) ▪ t(6;14)	▪ Absence of following: ▪ Del 17p ▪ t(4;14) ▪ Gain 1q21
Median OS	2 years	5 years	7-8 years	>10 years
% Patients	15%	20%	45%	20%

What have we learn

- Velcade especially benefit t(4;14) patients
- Inclusion of Velcade (and hence prolonged use) in different phases of treatment is important in high-risk disease
- The use of double autologous transplant seem to also be an important factor.
- Revlimid seem to have a more moderate and less consistent effect on high-risk disease
- Thalidomide maintenance contra-indicated in 17p13 deletion

How do I apply Risk Stratification in Clinic for transplant eligible patients?

- Induction
  - Velcade triplet for everyone if can afford
  - If cannot afford
    - Velcade triplet for intermediate and high-risk disease
    - CTD for standard and low-risk disease. If not VGPR by 4 cycles, to then change to velcade triplet

How do I apply Risk Stratification in Clinic for transplant eligible patients?

- ASCT Consolidation
  - Double (Mel200) autologous SCT for intermediate and high-risk disease
  - Single transplant (Mel200) for others
  - If did not have Velcade at induction, consider incorporating velcade to Mel200 conditioning

How do I apply Risk Stratification in Clinic for transplant eligible patients?

- Post-ASCT Consolidation
  - If low or standard-risk, no consolidation if achieve VGPR
  - If intermediate or high-risk, 2 cycle of Velcade triplet consolidation regardless of response
- Maintenance
  - If low-risk, no maintenance if achieve VGPR
  - If standard-risk, Rev maintenance
  - If intermediate or high-risk, Velcade maintenance

Risk Stratification - Questions

	High Risk	Intermediate Risk	Standard Risk	Good Risk
Genetic Abn	▪ FISH ▪ Del 17p ▪ t(14;16) ▪ t(14;20)	▪ FISH ▪ t(4;14) ▪ Cytogenetic Deletion 13 or hypodiploidy	▪ All others including ▪ Hyperdiploid ▪ t(11;14) ▪ t(6;14)	▪ Absence of following: ▪ Del 17p ▪ t(4;14) ▪ Gain 1q21
Median OS	2 years	5 years	7-8 years	>10 years
% Patients	15%	20%	45%	20%
Therapeutic Implications / Questions	Need Novel Approaches. ? AlloSCT or immune therapy approaches	Velcade based treatment at induction and maintenance	? Is VGPR a good enough response in these patients i.e. can maintain a MGUS state long-term	? Do these patients benefit from maintenance

National University
Cancer Institute, Singapore

NUHS
National University
Health System

Thank you
for your attention

NUH National University Hospital

NUS National University of Singapore