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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Hematopoietic cell transplantation for multiple myeloma

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WBMT Symposium

Cape Town, South Africa

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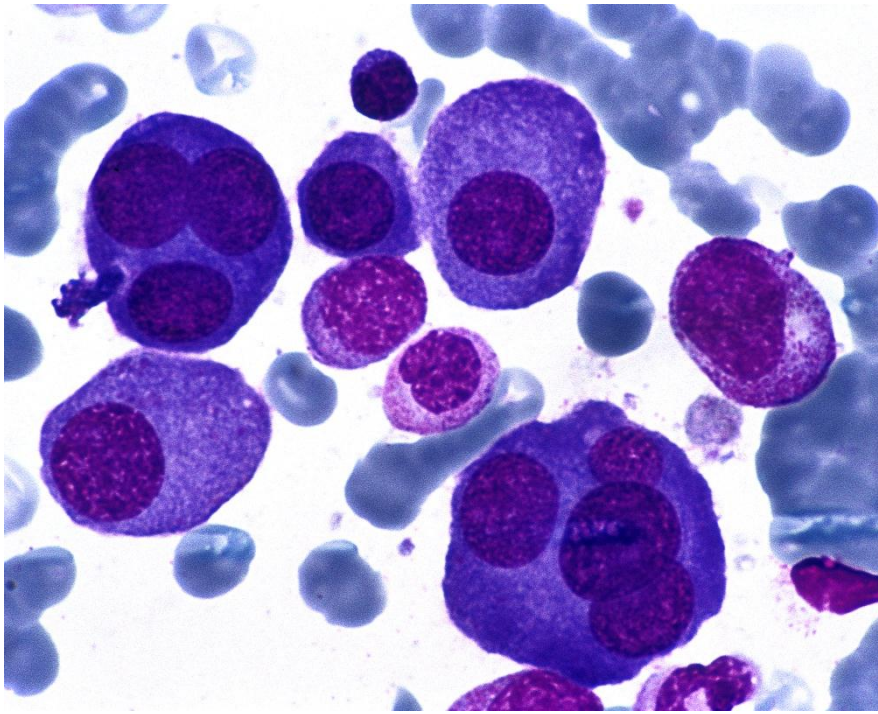
WBMT
WWW.WBMT.ORG

Froedtert & Medical College of Wisconsin

Multiple Myeloma

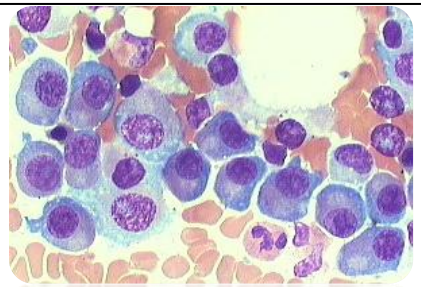
- B-cell malignancy derived from antibody-producing plasma cells in the bone marrow.
- Myeloma cells crowd out and interfere with the development and function of normal cells in the bone marrow
- The abnormal accumulation of myeloma cells in the bone marrow and production of M-protein have direct and indirect effects on the blood, skeleton, and kidneys



Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. International Myeloma Foundation. 2011/2012 edition; Multiple Myeloma Research Foundation. *Multiple Myeloma Disease Overview*. 2011.

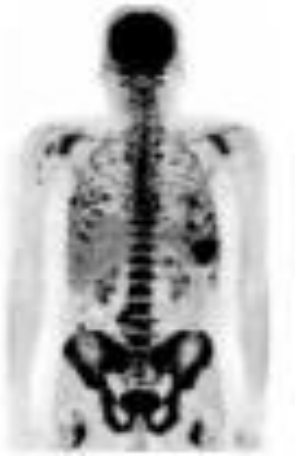
- Anemia
- Dysfunctional humoral immunity

Immune dysregulation



Proliferation

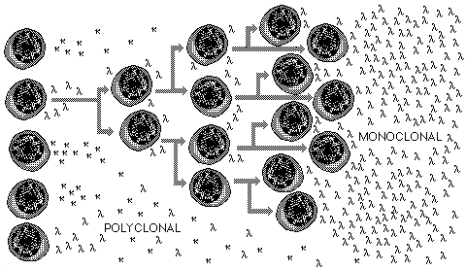
Correlation with disease burden
Assessment of disease response



Alterations in the Microenviroment

Multiple Myeloma

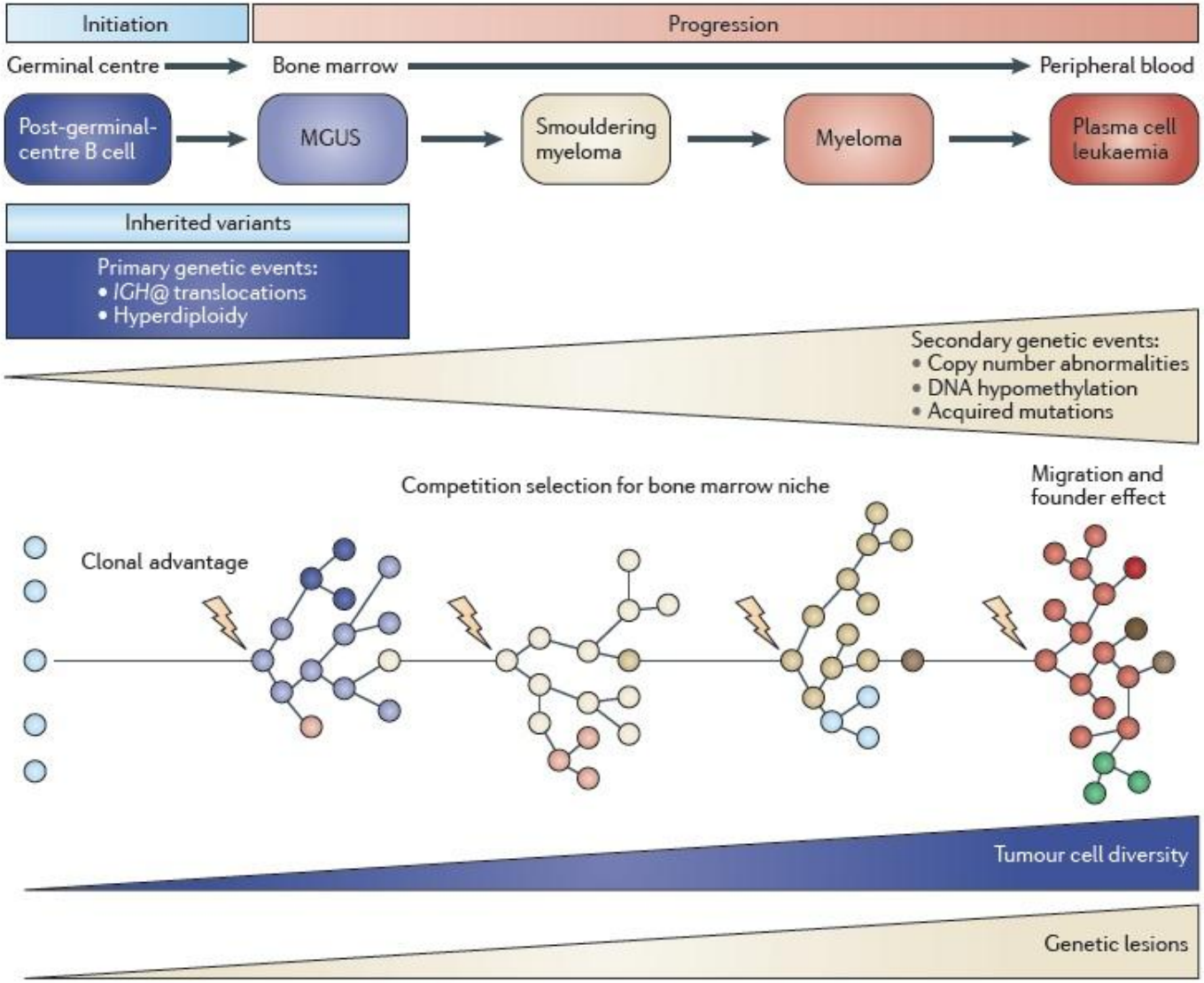
Production



- Bone destruction
- Hypercalcemia

- Dysfunctional humoral immunity
- Organ failure
- Hyperviscosity

Natural Selection of Myeloma Progression



Morgan et al. Nat Rev Cancer 2012;12:335-348

Criteria for Symptomatic Myeloma

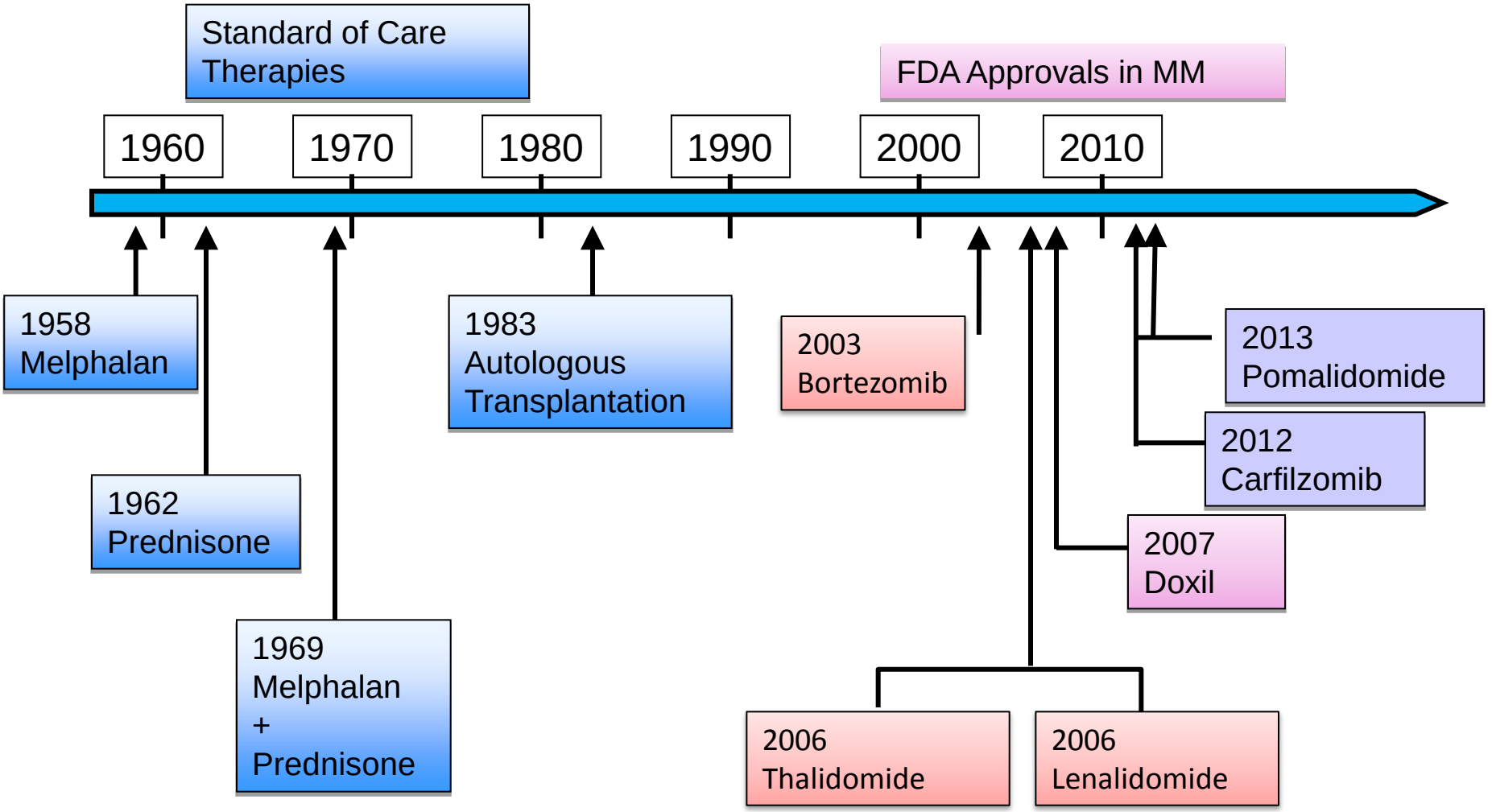
i.e Needs treatment for "cancer"

Criteria for Symptomatic MM (all 3 required)		
1	≥ 10% monoclonal plasma cells in bone marrow	
2	Monoclonal protein in serum and/or urine	
3	Presence of end-organ damage (at least one of the below)	
	Calcium	Serum calcium ≥11.5 mg/100 mL
	Renal	Serum creatinine >1.73 mmol/L
	Anemia	Hb <10 g/100 mL or >2 g/100 mL below normal
	Bone	Lytic lesions, severe osteopenia, pathologic fractures
	"**I**nfections"	Repetitive bacterial infections

Additional "soft signs" – Neuropathy, Osteoporosis, Frequent infections, Proteinuria

Modified from Palumbo. *Leukemia*. 2009;23:1716.

MM Therapy



Adapted from Kumar SK et al. *Blood*. 2008;111:2516–2520.

blood
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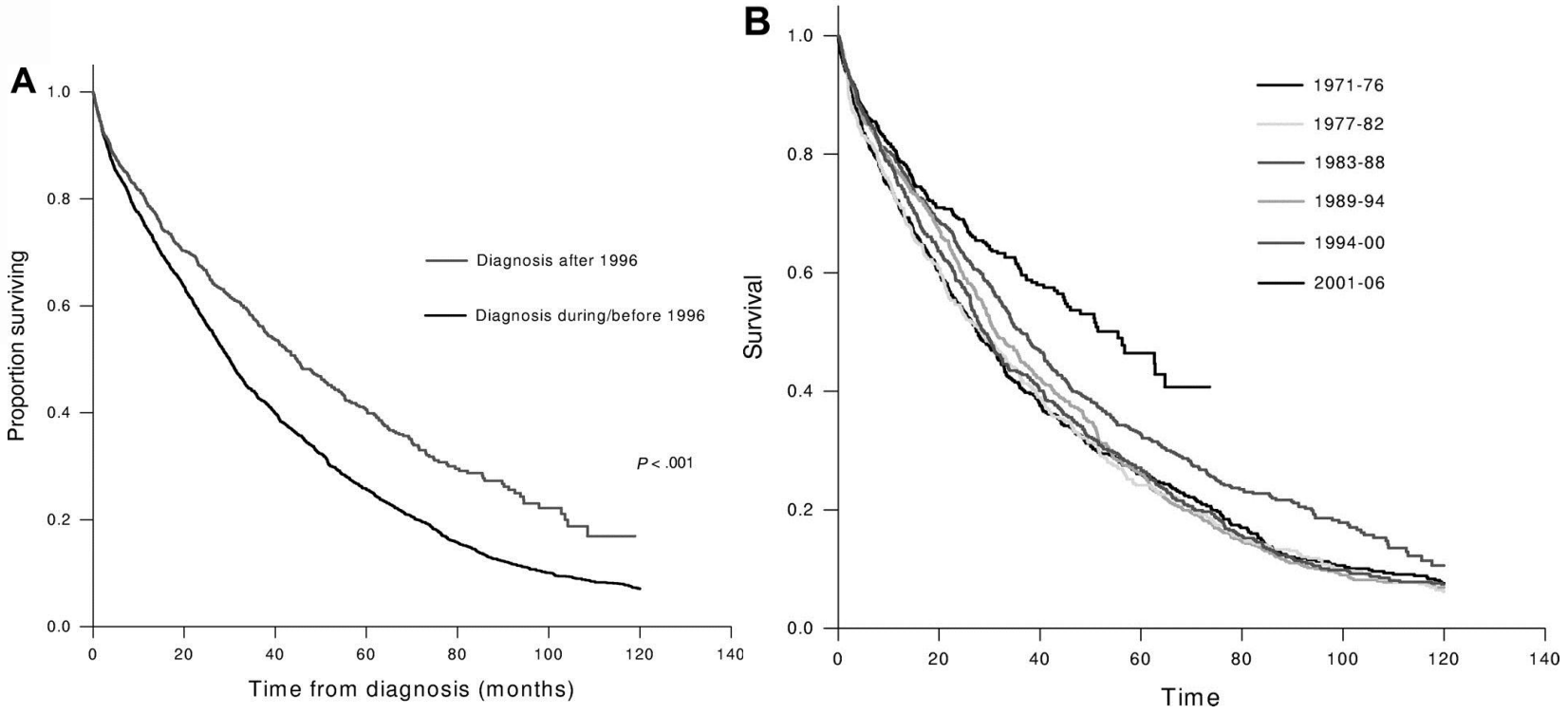
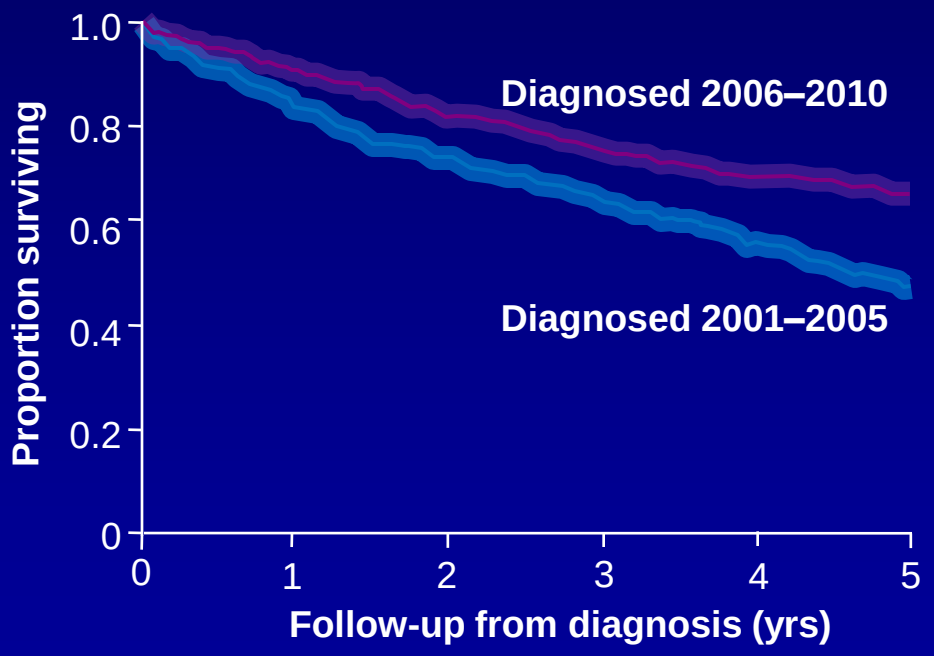
Overall survival from diagnosis of multiple myelomas.



Kumar S K et al. Blood 2008;111:2516-2520

Continued Improvement in Survival Since the Introduction of Novel Agents

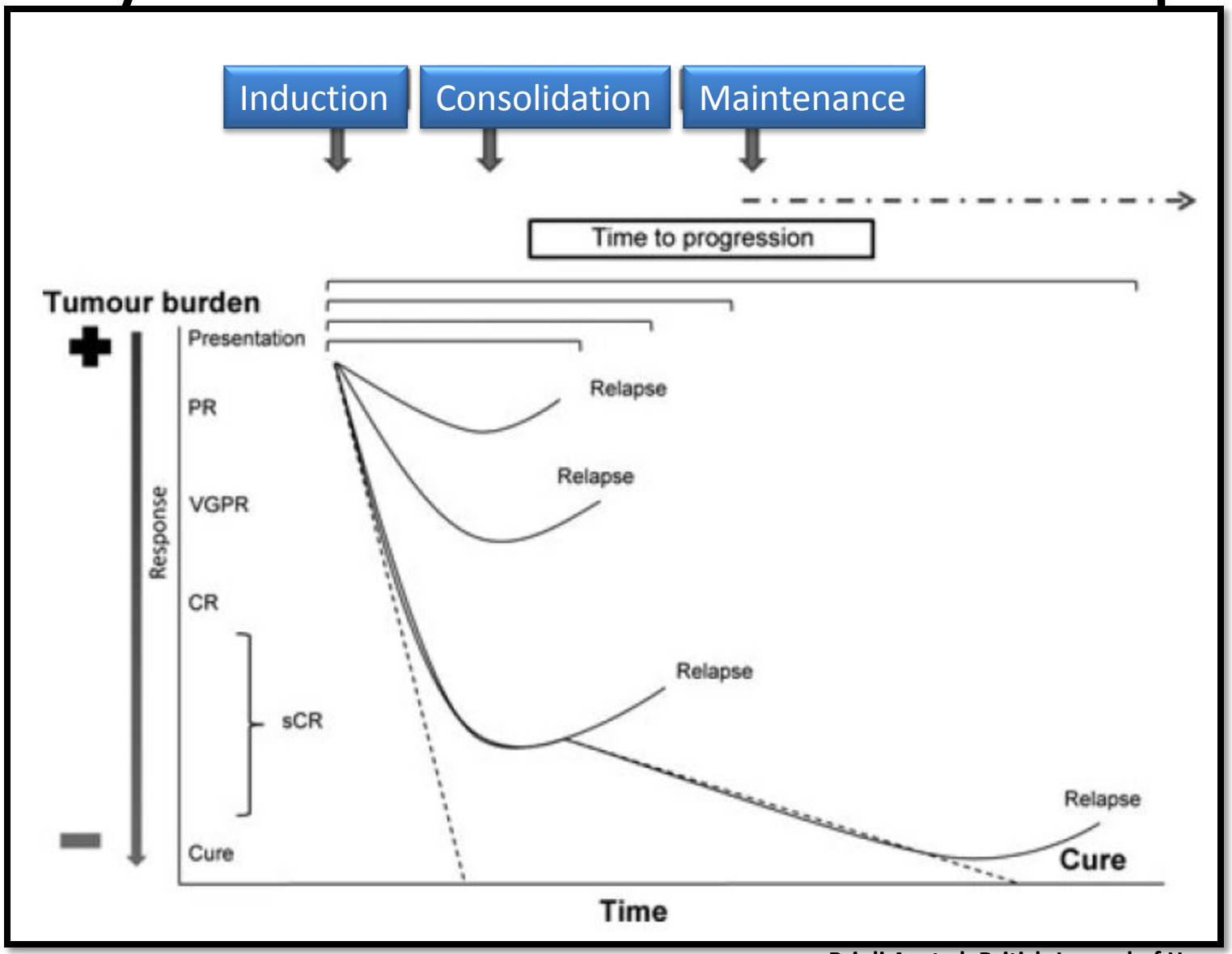
- 1,056 pts grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in pts aged > 65 years (p = 0.001)



Survival	2001–2005	2006–2010	p
Median OS, yrs	4.6	NR	0.001
1-yr survival, %	83	90	
5-yr estimated OS, %			
Overall	48	66	
> 65 yrs	31	56	0.001
< 65 yrs	63	73	NS

Kumar SK, et al. Blood. 2012;120:[abstract 3972]. Updated data presented at ASH 2012.

Myeloma Treatment Roadmap



Brioli A et al. British Journal of Haematology 2014

Classes of Drugs With Anti-MM Activity

Steroids	Immuno-modulatory Agents	Proteasome Inhibitors
Prednisone	Thalidomide	Bortezomib
Dexa-methasone	Lenalidomide	Carfilzomib
	Pomalidomide	Ixazomib
		Oprozomib
		Marizomib
		CEP-18770 (Delanzomib)

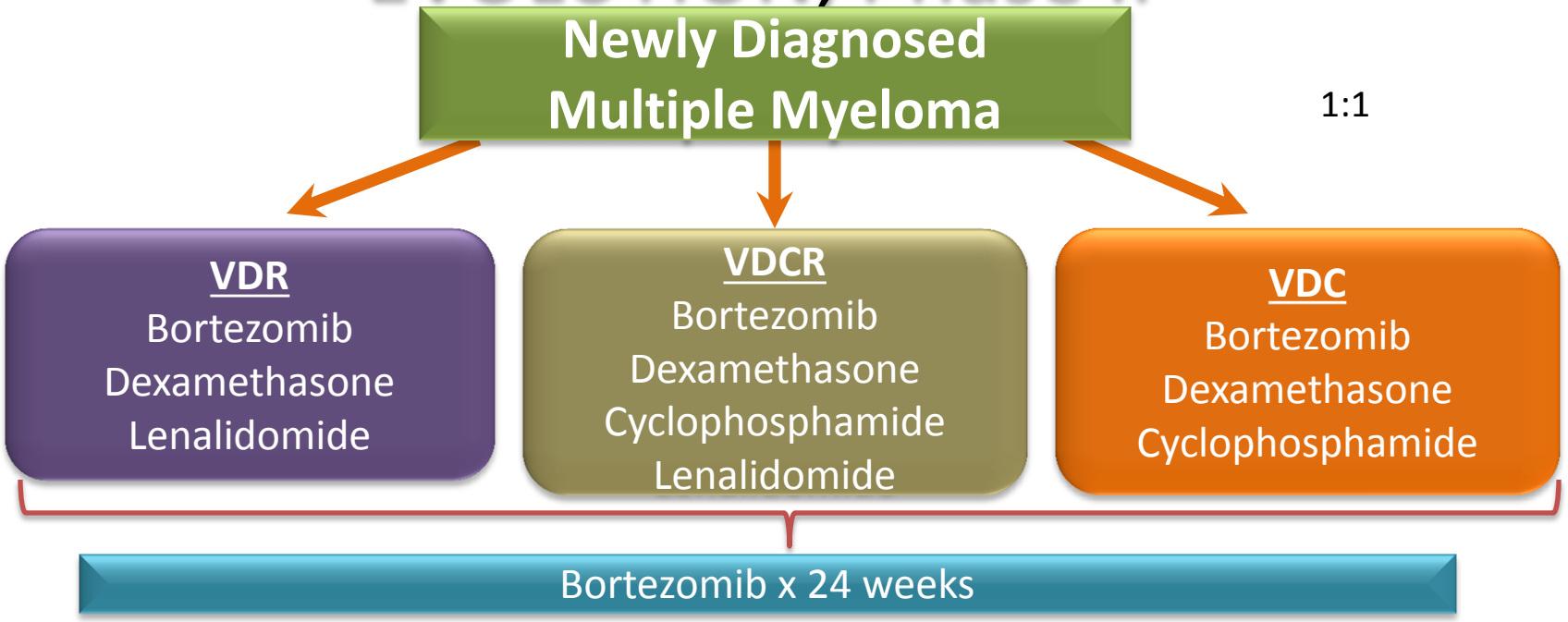
Classes of Drugs With Anti-MM Activity

Cytotoxic CT	HDAC inhibitors	mTOR inhibitors	mAbs
Melphalan Cyclophos-phamide BCNU Bendamustine Anthracyclines PACE DCEP	Vorinostat Panobinostat	Perifosine	Elotuzumab Daratumumab

Anti-myeloma Initial Therapy

- Initial disease de-bulking
- Reduction of the paraprotein
- Decreasing the intra-clonal heterogeneity

EVOLUTION, Phase II

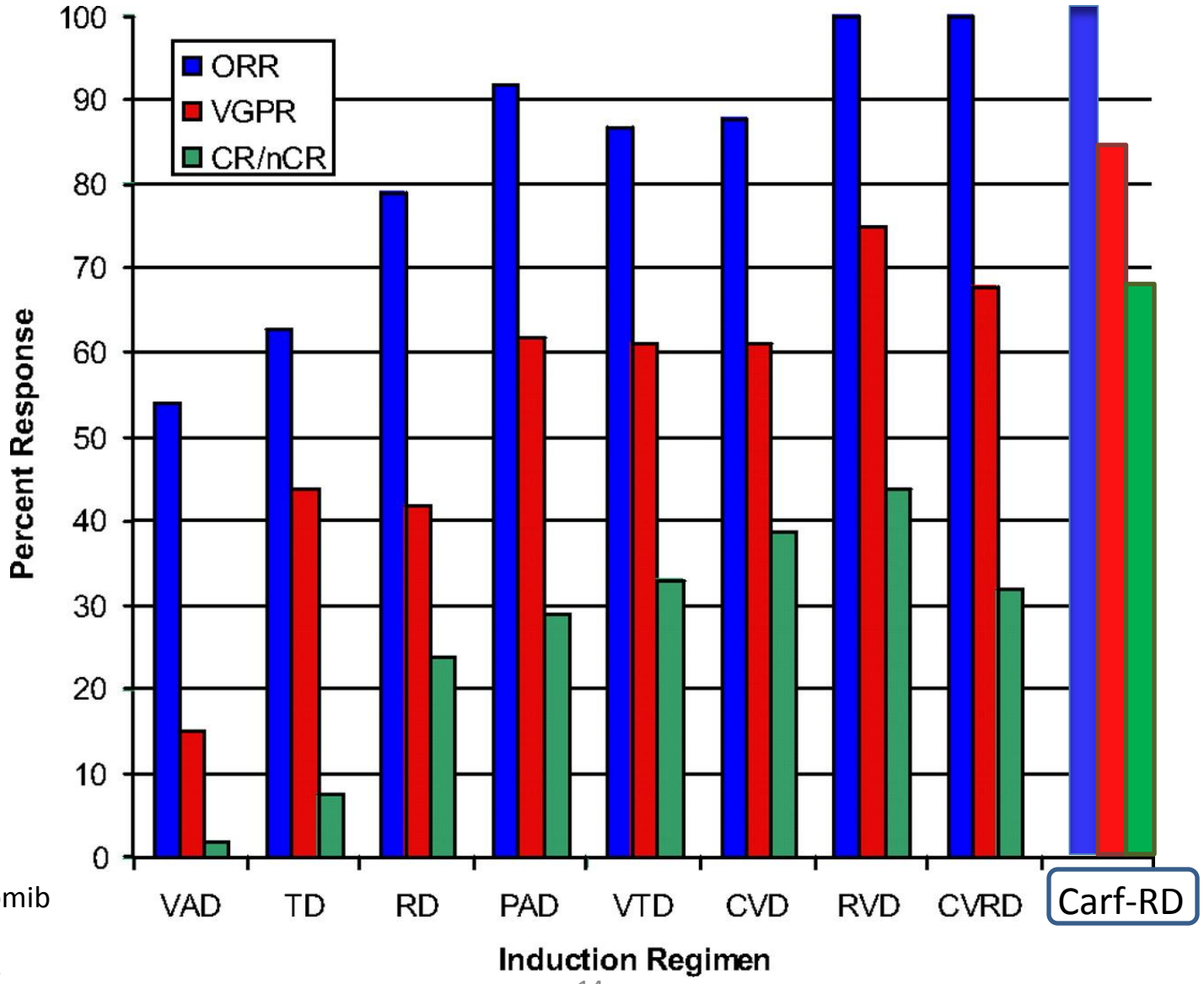


	VDCR N = 41	VDR N = 42	VDC N = 32	VDC-modified* N = 15
CR	20%	24%	22%	40%
≥ VGPR	**59%**	**55%**	**47%**	**60%**
≥ PR	93%	93%	91%	93%

Compare to RVD regimen phase II – 67-74% VGPR rate. Richardson et al JCO 2011

Kumar et al. JCO

Combinations in the Upfront Treatment of MM



V or P– Bortezomib
A - Adriamycin
T – Thalidomide
R – Revlimid ; C - Cyclophosphamide

Stewart AK, Richardson PG, San Miguel JF. *Blood.* 2009.

Induction Choices

- Transplant “eligible”
  - 3 drug combination excellent VGPR rate in phase II
  - Another 3 drug regimen PAD (Bz+Doxo+Dex)
  - Comparison to 2 drug combination unlikely to happen in US.
  - 4 drugs – CVRD or RVDD (anthracycline) – no evidence of benefit at this time
  - 4 drugs regimens maybe a role in relapsed setting / plasma cell leukemia induction

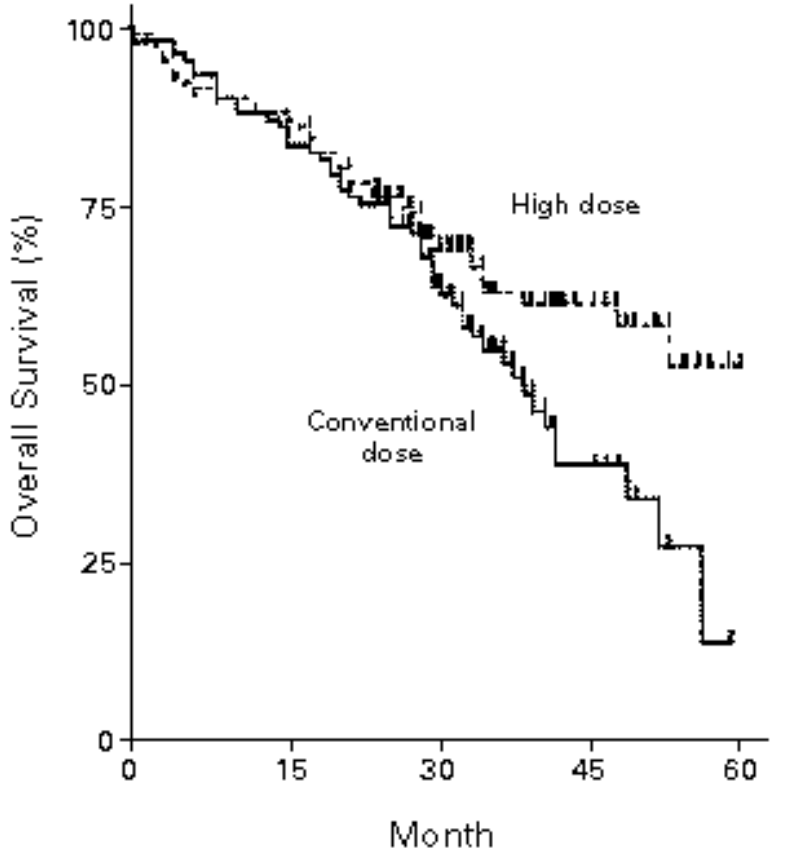
Induction Choices

- Transplant “ineligible”
  - 2 or 3 drug combination
  - Bortezomib or lenalidomide + dexamethasone
  - Melphalan/pred/bortezomib or len or thalidomide
  - Length of therapy: 2 to 12 months
  - Goal is disease control not necessary Complete Response

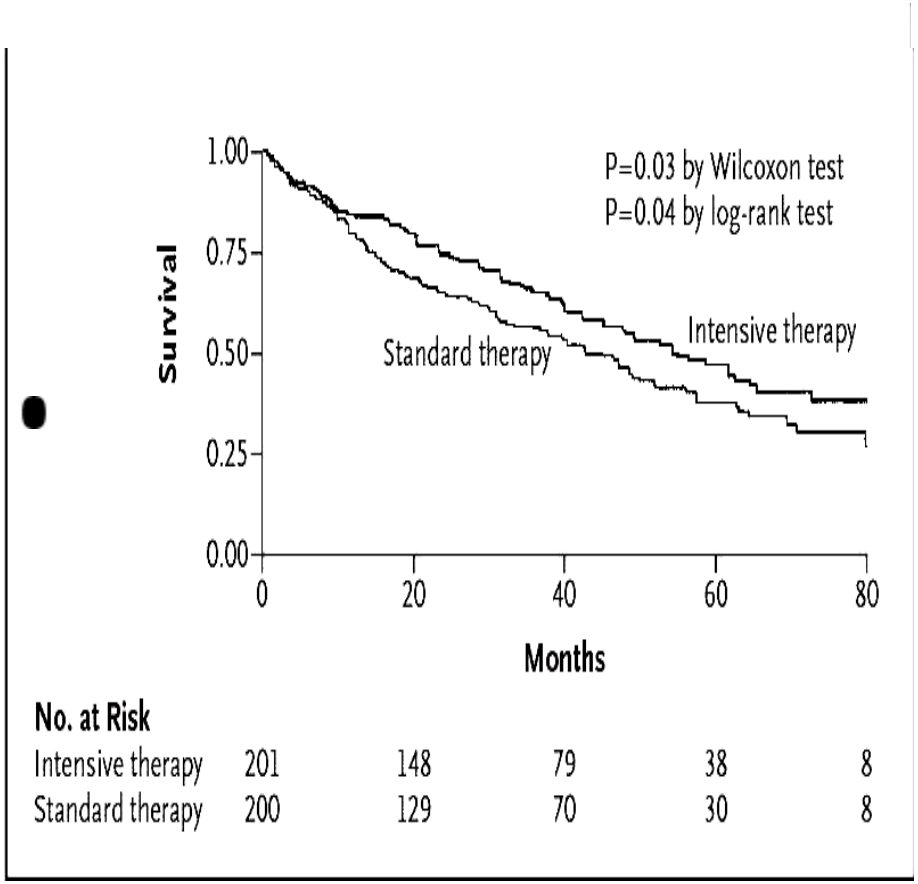
Consolidation

- Maximize disease control
- Goal: to reach complete response or better
- Further reduce inter-clonal heterogeneity

Autologous HCT vs. Chemotherapy for Newly Diagnosed Myeloma



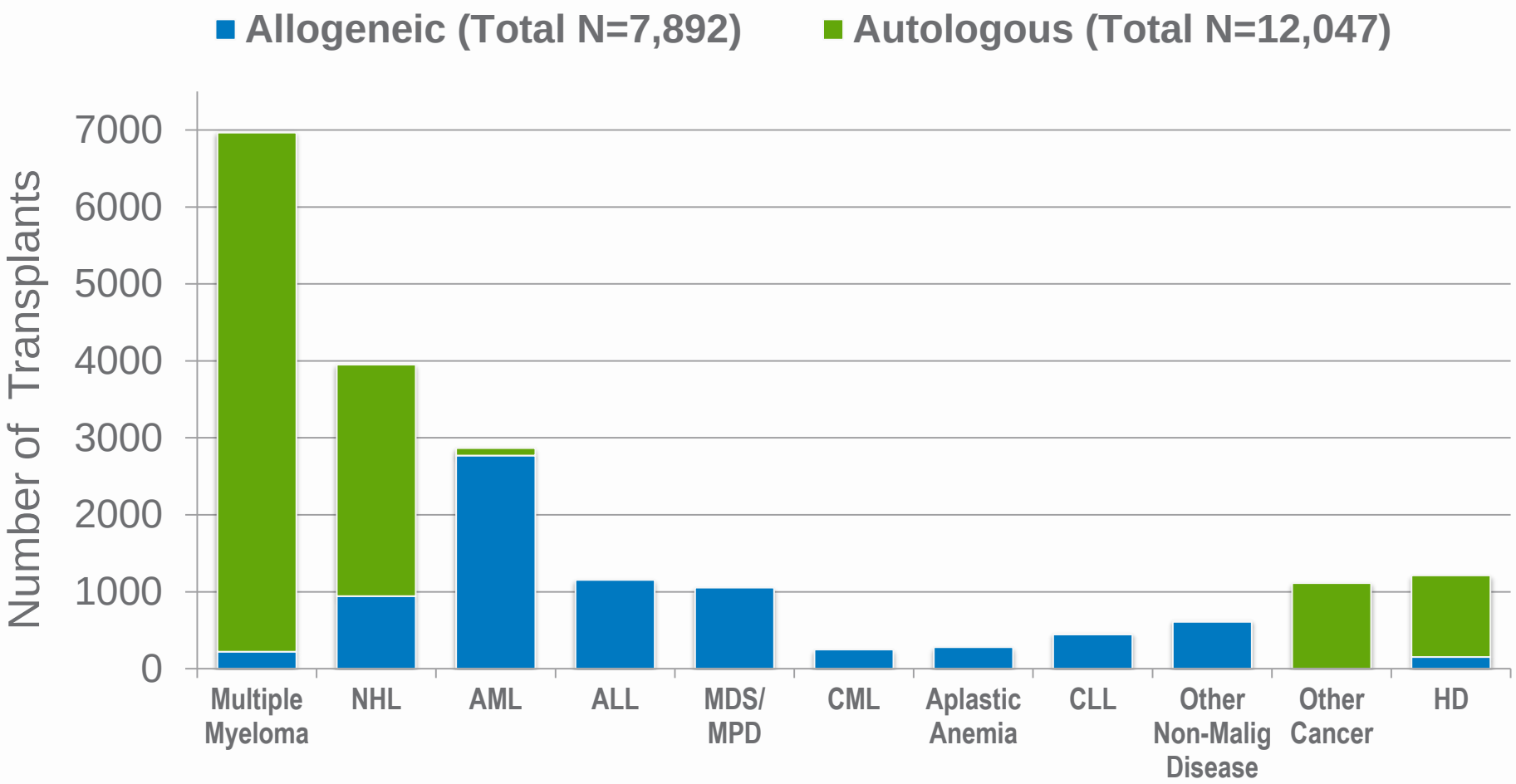
Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)	
High dose	69 (58–78)	61 (50–71)	52 (36–67)	



Attal M. N Engl J Med 1996; 335:97

Child J. N Engl J Med 2003; 348:1875

Indications for Hematopoietic Stem Cell Transplants in the US, 2011



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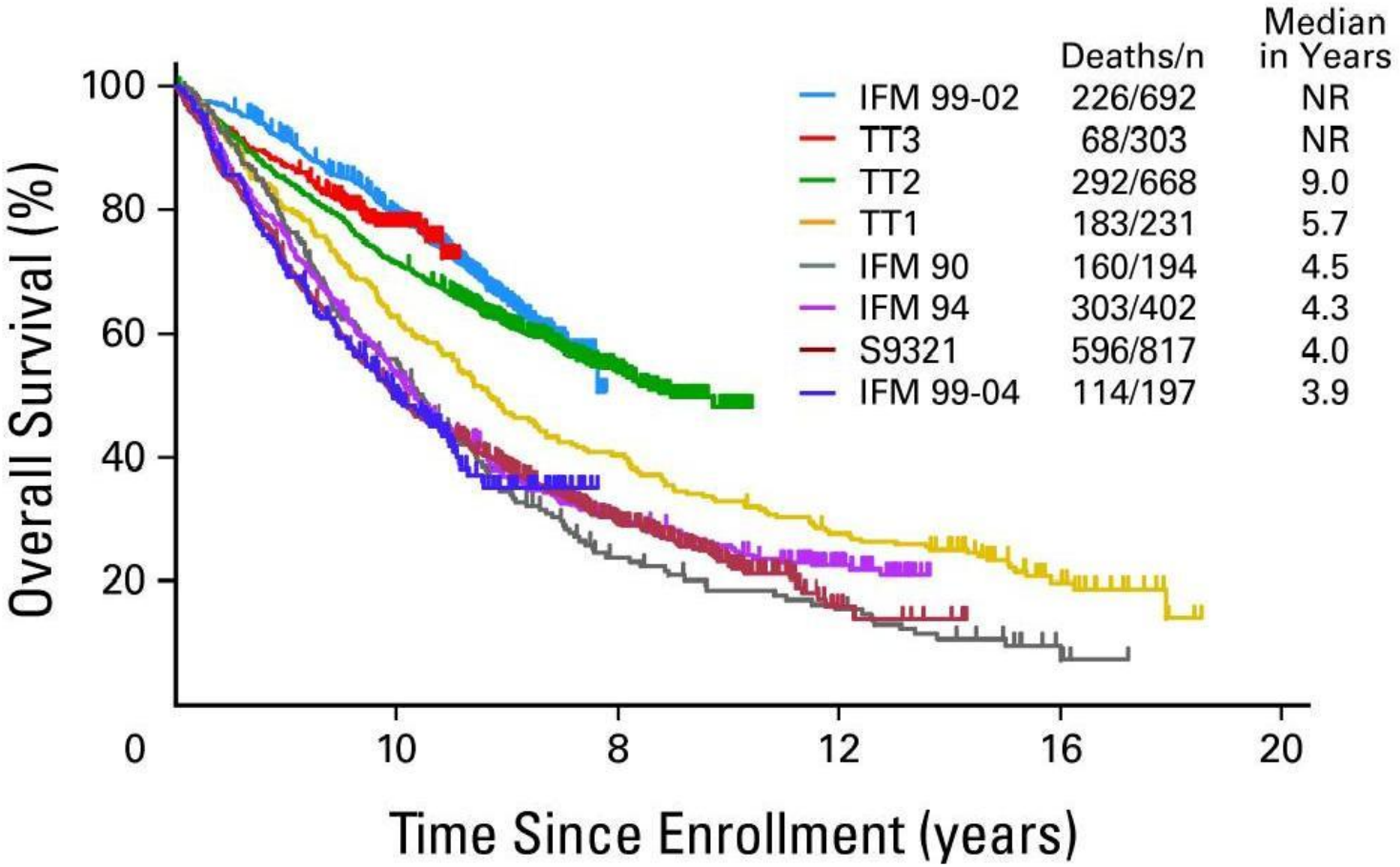
Overall Survival of Autotransplantation in MM



Barlogie B, et al. *J Clin Oncol.* 2010;28(7):1209-1214.

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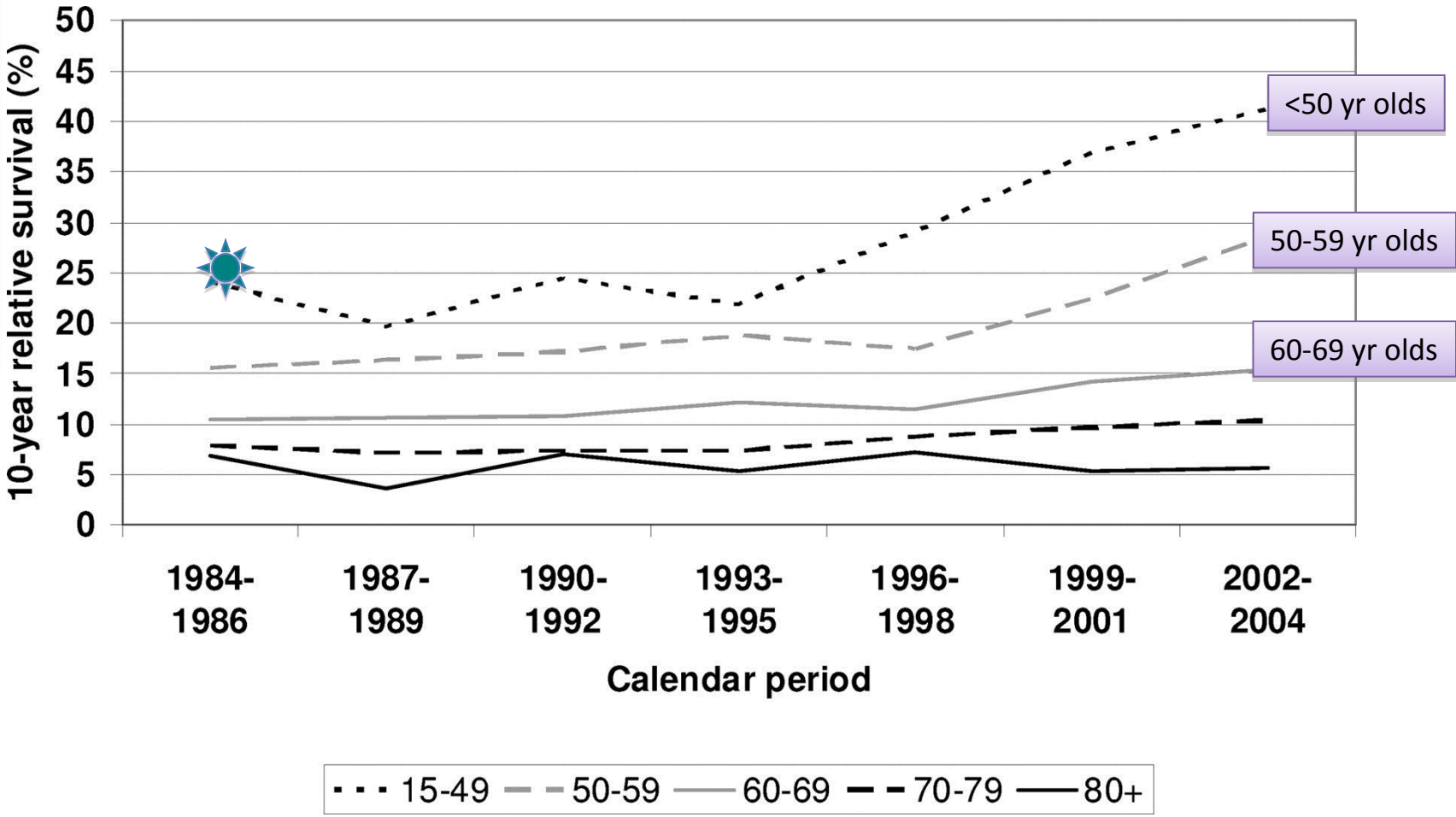
MYELOMA SURVIVAL
Over Time



Brenner, H. et al. Blood 2008;111:2521-2526

Autologous HCT for multiple myeloma in US and Canada within 12 months from diagnosis from 1995 to 2010 registered with CIBMTR

Characteristics of patients	1995-1999	2000-2004	2005-2010	P-value
Registered patients	**2226**	**6408**	**11644**	
Number of centers	189	195	174	
Median Age	54 (19-77)	57 (22-80)	58 (18-89)	
18-50 years	734 (33)	1445 (23)	2079 (18)	<0.001
50-65 years	1330 (60)	3875 (61)	6945 (60)	
65-80 years	**162 (7)**	**1088 (17)**	**2620 (23)**	

Costa L. et al

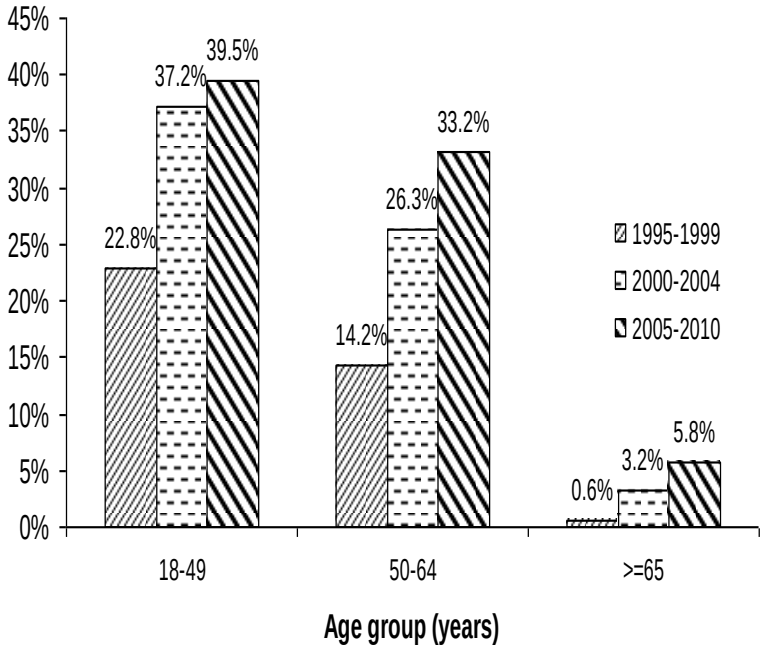
MEDICAL COLLEGE OF WISCONSIN

Subset of patients from Research CIBMTR centers

Characteristics of patients	1995-1999	2000-2004	2005-2010	P-value
Number of patients	686	1464	2223	
Cytogenetics				
Abnormal	26 (4)	57 (4)	487 (22)	
Normal	105 (15)	78 (5)	473 (21)	
Untested/Missing	555 (81)	1329 (91)	1263 (57)	
Disease status				
CR/PR	539 (79)	1273 (87)	1966 (88)	<0.001
Mobilization				
GCSF alone	167 (24)	358 (24)	921 (41)	<0.001
Conditioning regimen				
Melphalan alone	370 (54)	1363 (93)	2198 (99)	<0.001

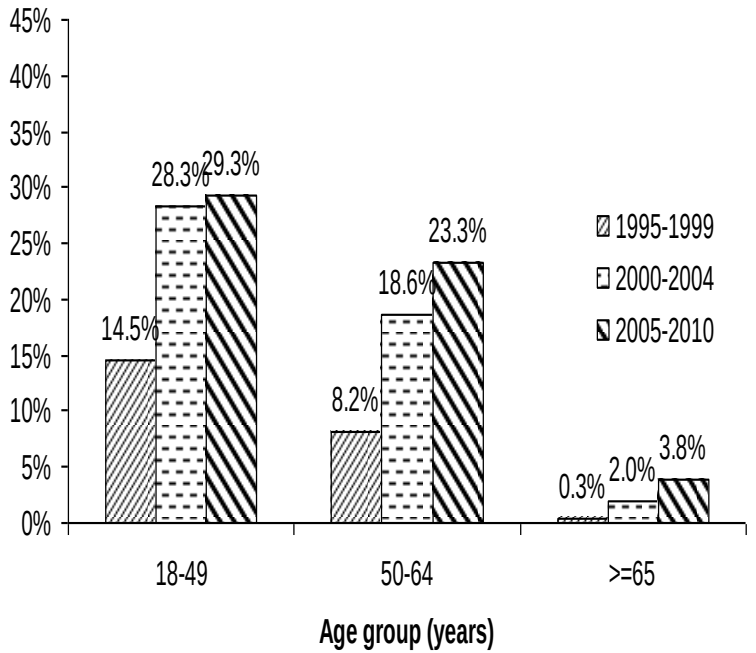
Ratio between first transplants/ newly diagnosed MM cases in U.S.A

a



Ratio between upfront transplants (<12 months)/ newly diagnosed MM cases in U.S.A.

b



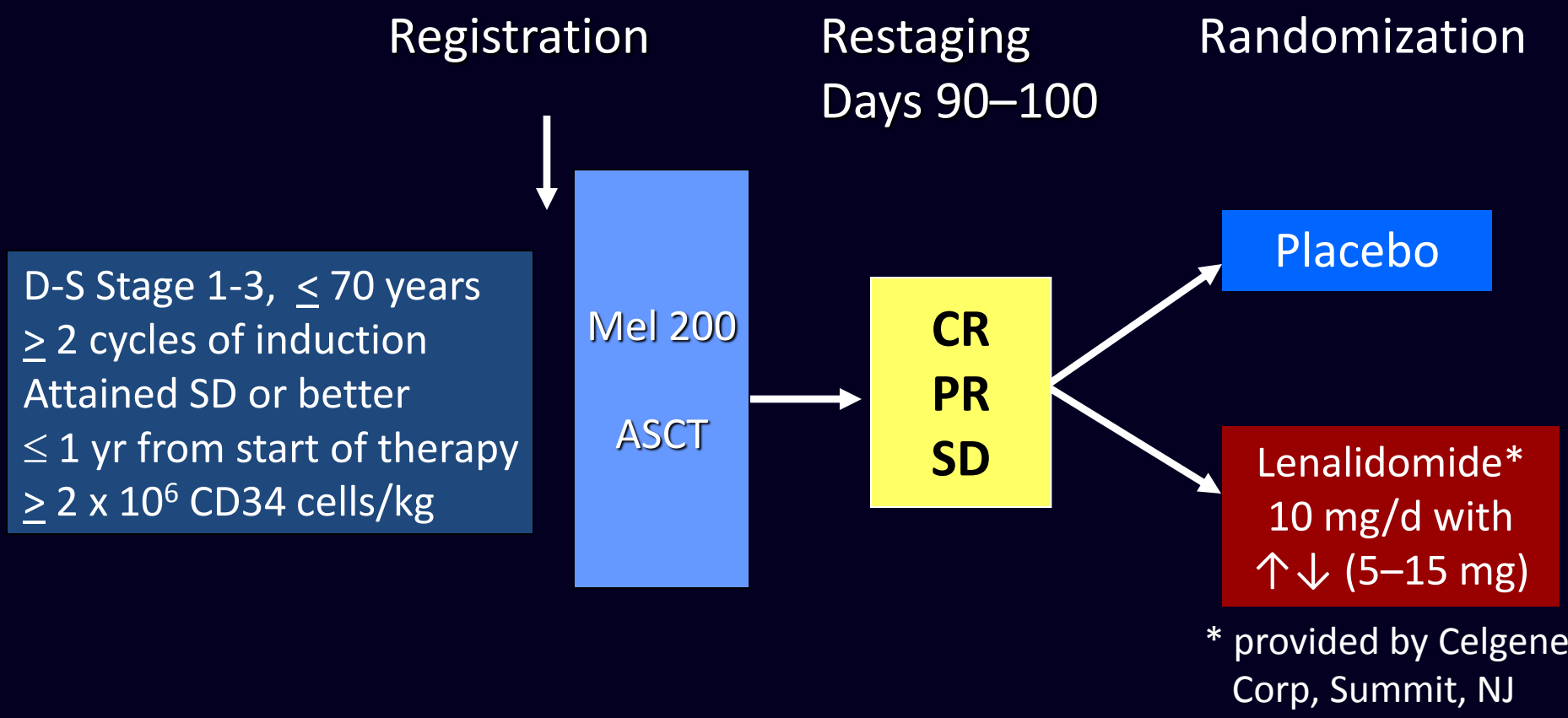
Costa L. et al

MEDICAL COLLEGE OF WISCONSIN

Maintenance

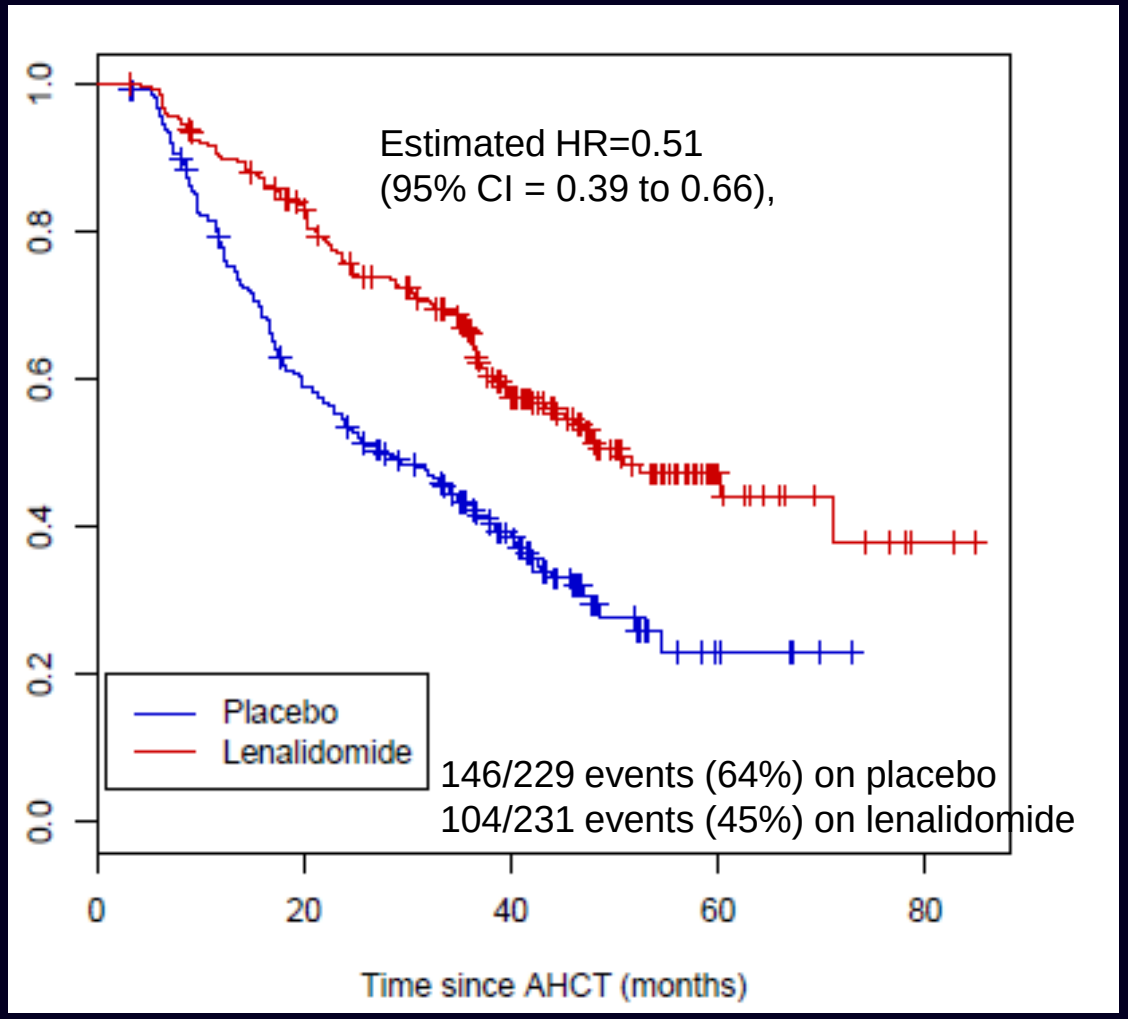
- Long term treatment with an anti-myeloma agent that is tolerable and effective
- Maximize disease control
- Prevent the inception of “new” subclones

CALGB 100104 Schema



Stratification based on registration β-2M level and prior thalidomide and lenalidomide use during Induction. Primary Endpoint: powered to determine a prolongation of TTP from 24 months to 33.6 months (9.6 months)

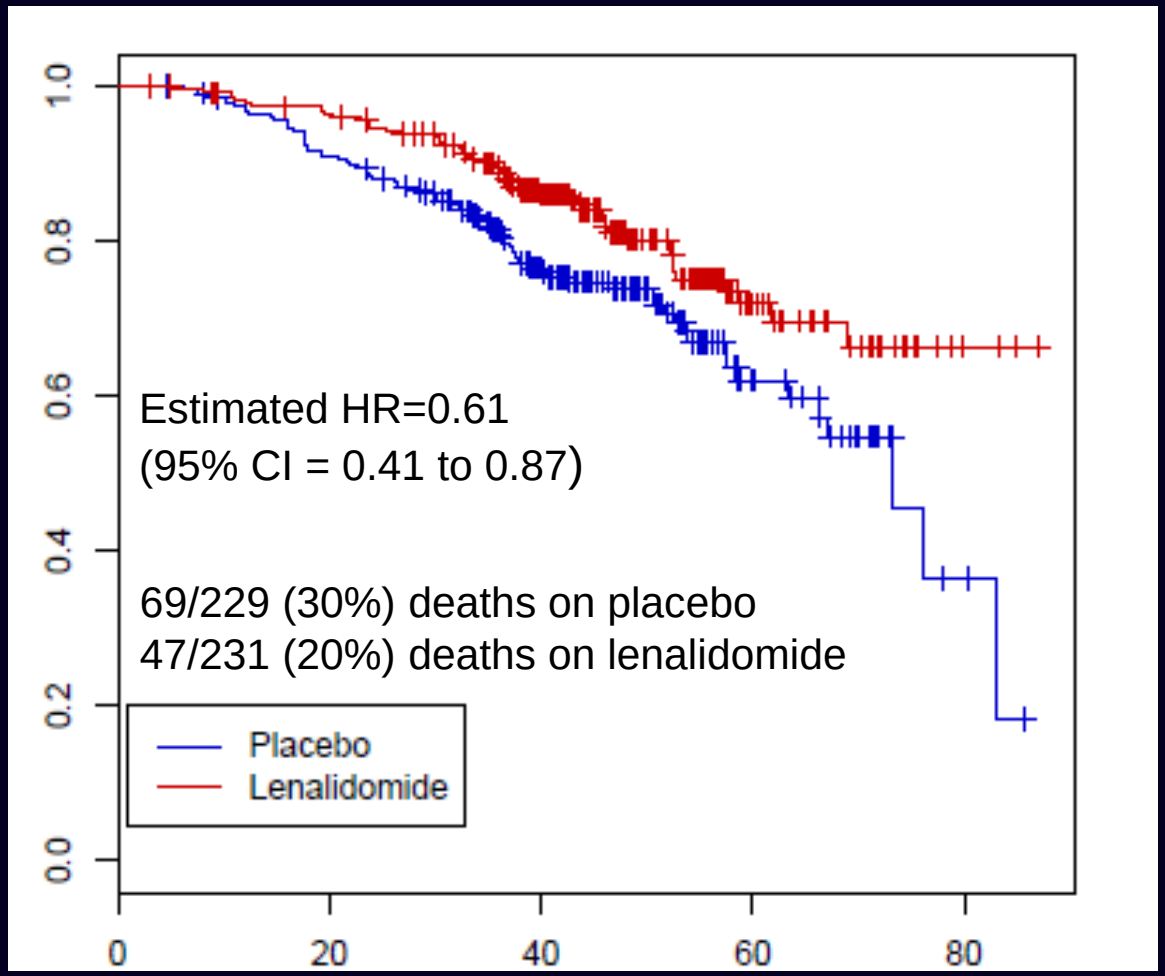
CALGB 100104: Updated TTP



CALGB 100104 IMW 2013
follow up to January 7, 2013

ITT Analysis with a median follow-up from transplant of ~48 months p<0.001 Median TTP: 50 months versus 27 months with 86 of 128 non-progressing placebo patients receiving lenalidomide at study un-blinding in Jan 2010

CALGB 100104: Updated OS



CALGB 100104 IMW 2013
follow up to January 7, 2013

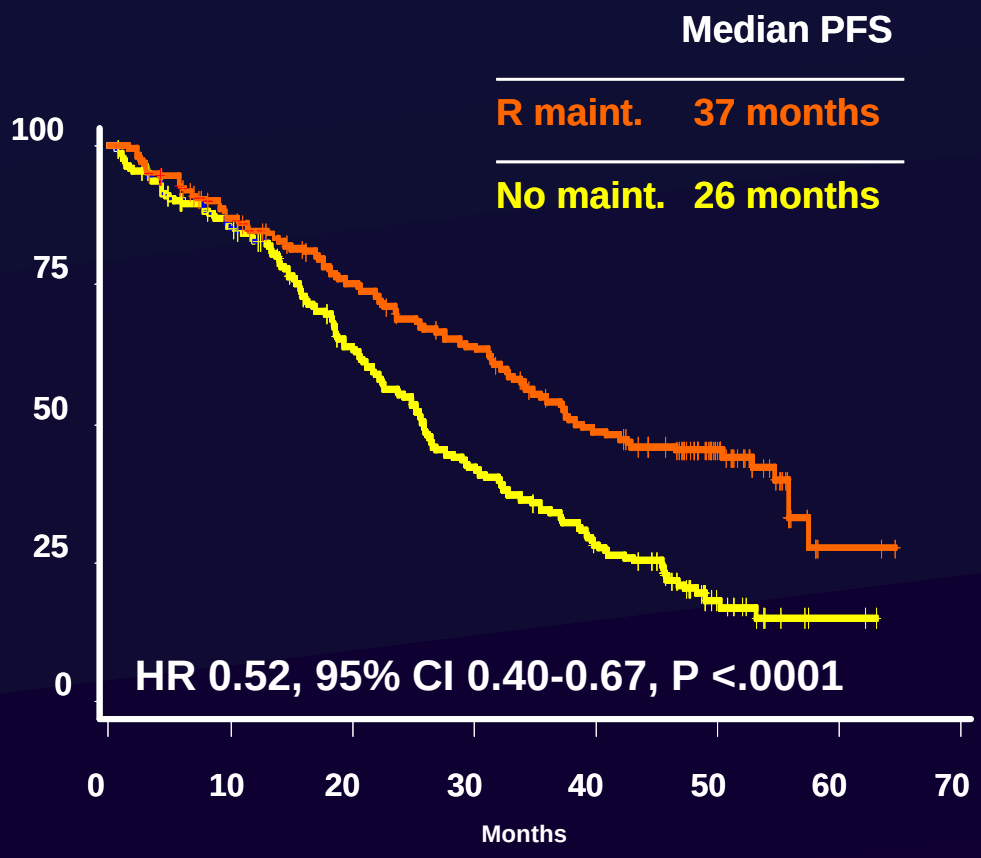
ITT Analysis with a median follow-up from transplant of ~48 months. p= 0.008, Median OS: not reached versus 73 months

Palumbo ASCO 2013

R maintenance vs No maintenance

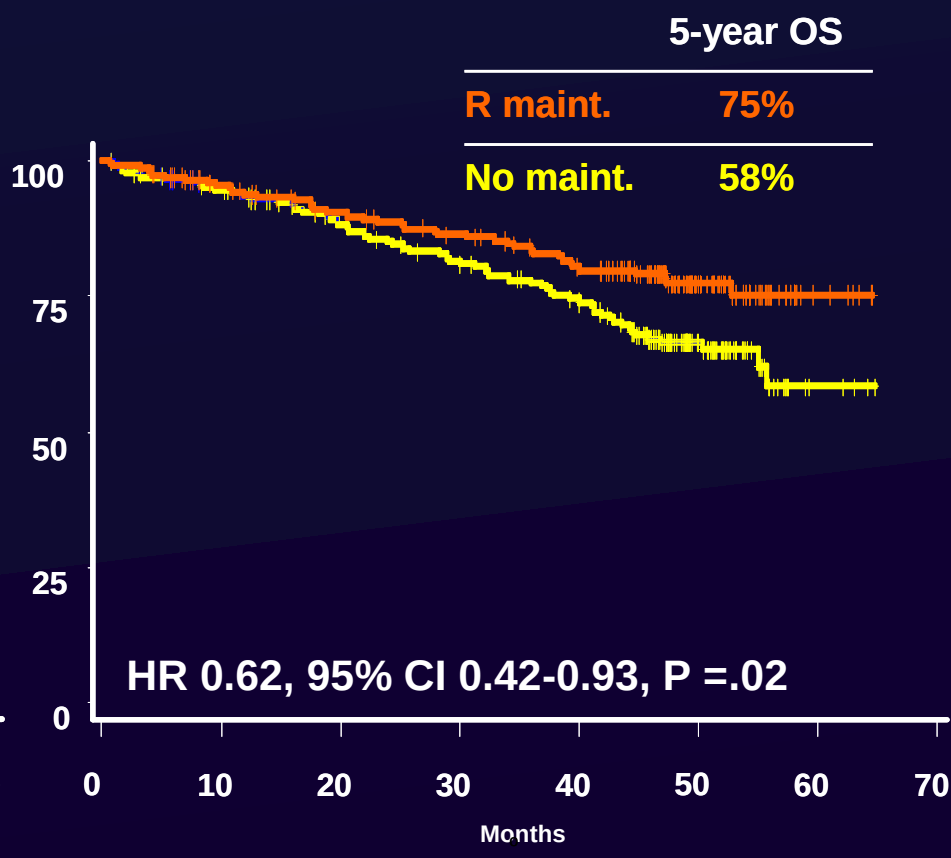
Progression-free survival

48% reduced risk of progression



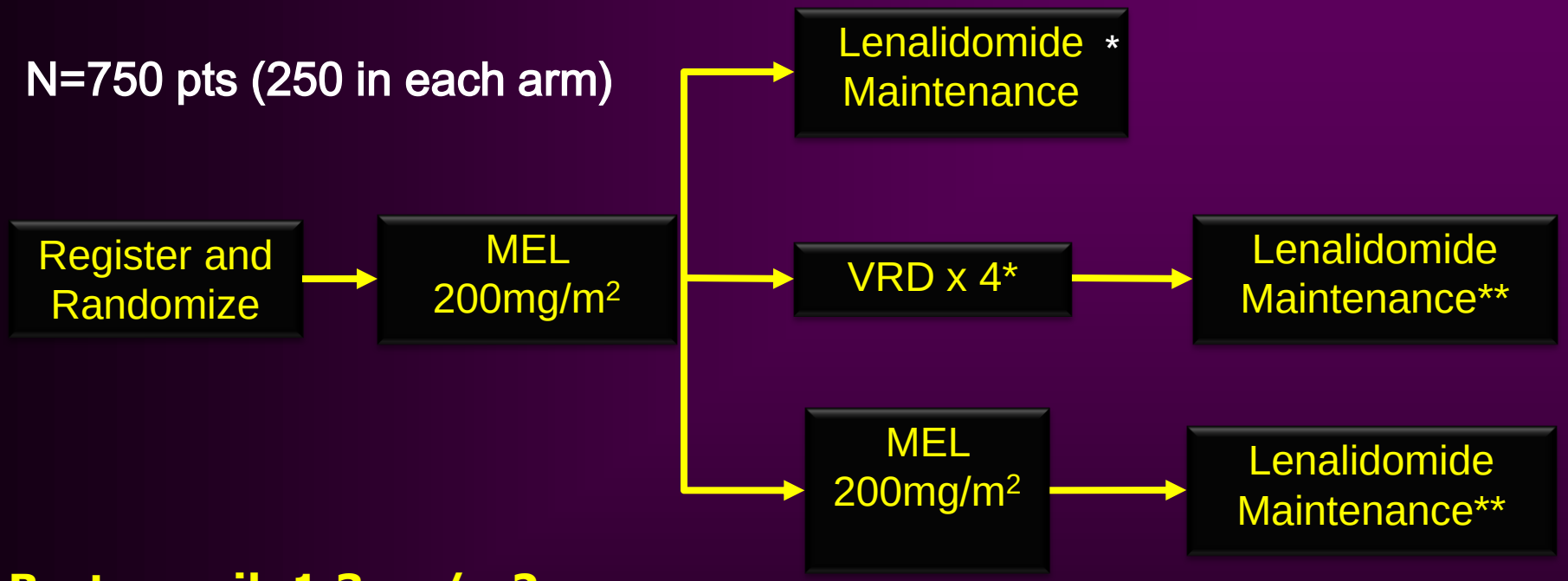
Overall survival

38% reduced risk of death



R, lenalidomide

BMT CTN 0702 - STaMINA



Bortezomib 1.3mg/m2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15

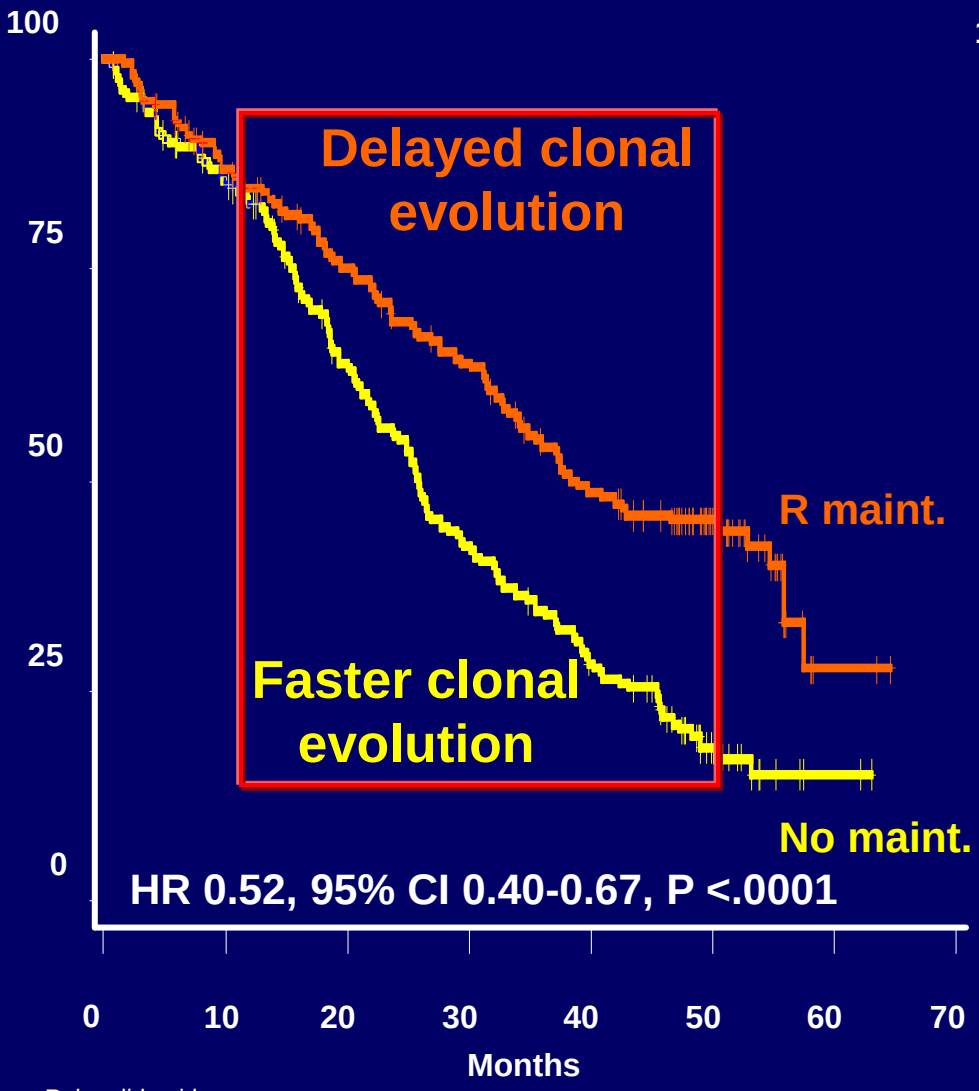
****Lenalidomide x 3years : 10mg /d for 3 cycles , then 15 mg /d**

Caveats with Continuous Treatment

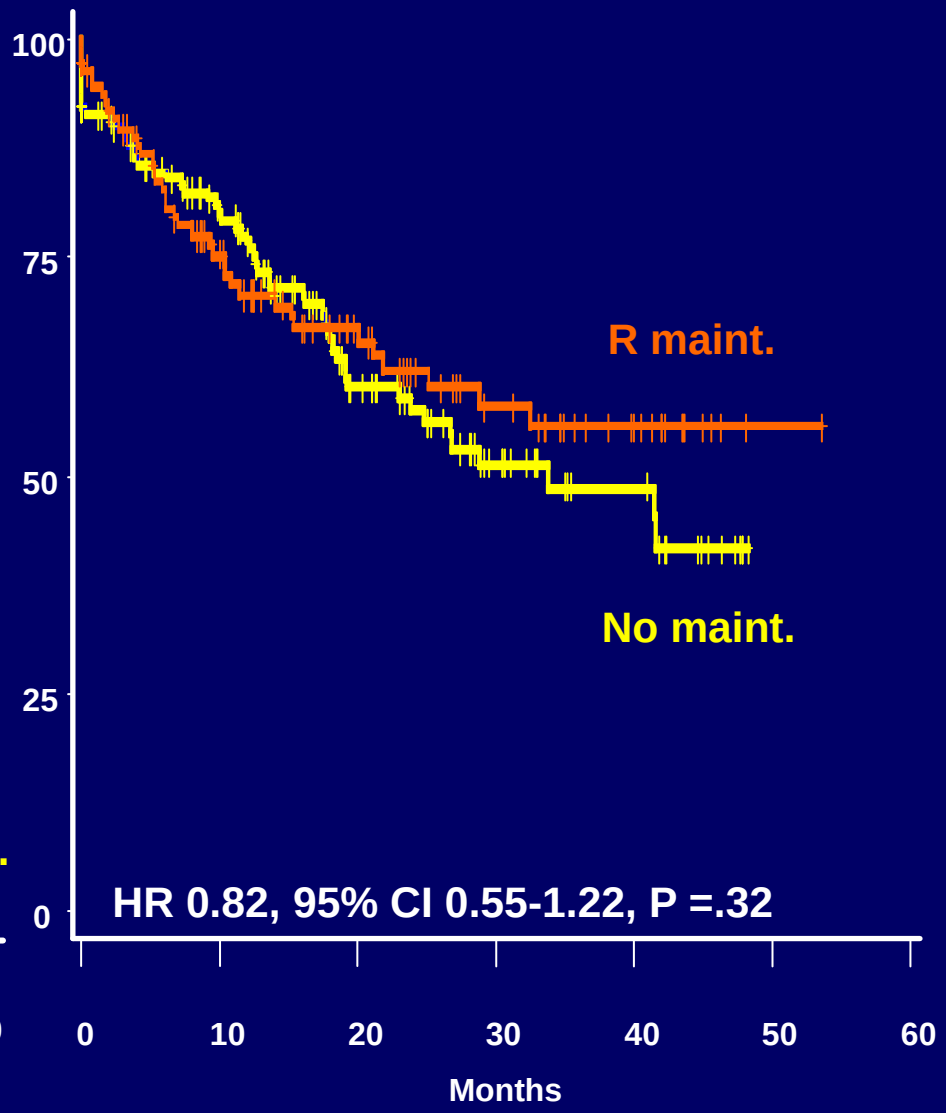
- Does using all “active” drugs at once favors the inception of resistant subclones?

R maintenance vs No maintenance

PFS from diagnosis



OS from relapse



R, lenalidomide

Caveats with Continuous Treatment

- Does using all “active” drugs at once favors the inception of resistant subclones?
- Does this treat strategy work for all patients?

High Risk Myeloma Markers

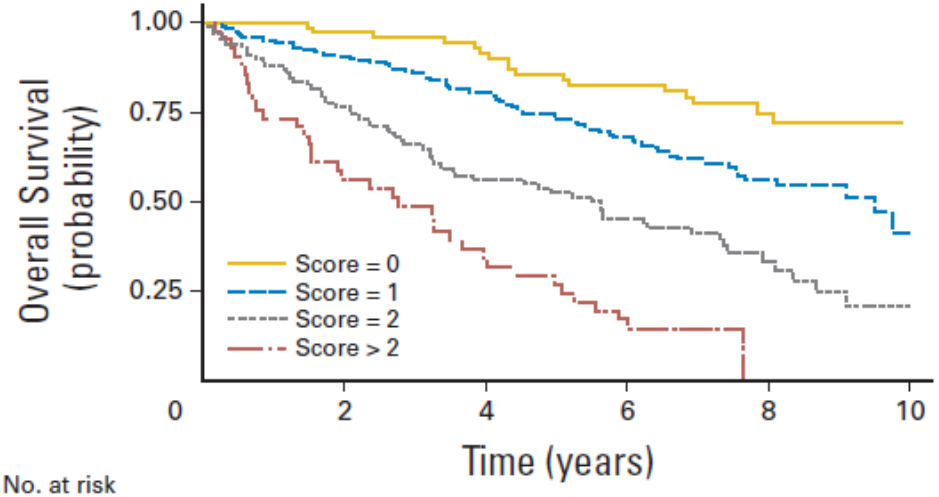
VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Parameter	Univariate Analysis HR	95% CI	P	Multivariate Analysis 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

Abbreviation: HR, hazard ratio.



Avet-Loiseau H et al JCO 2012

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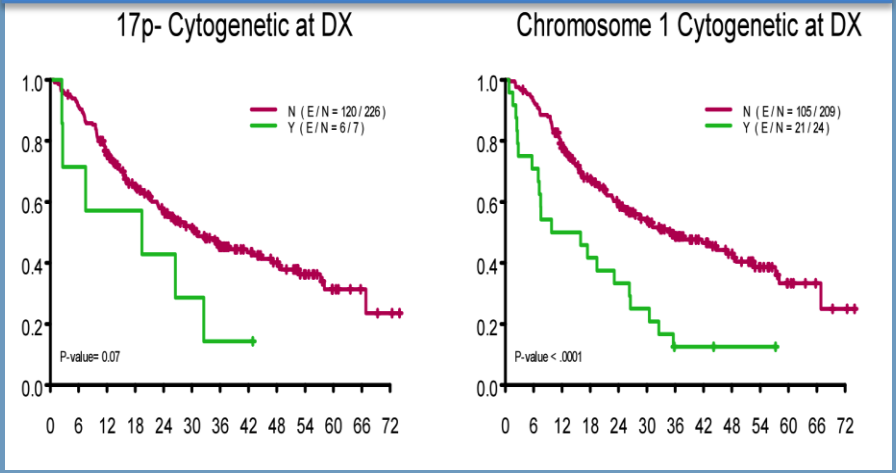
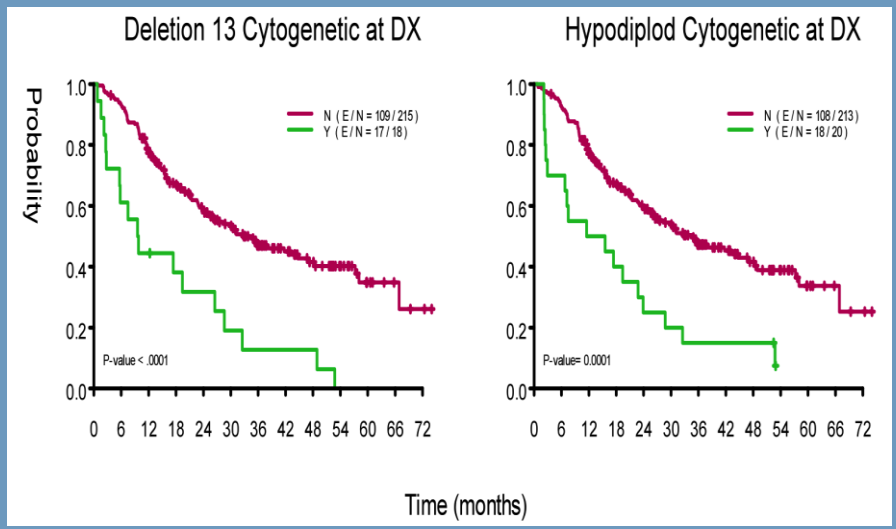
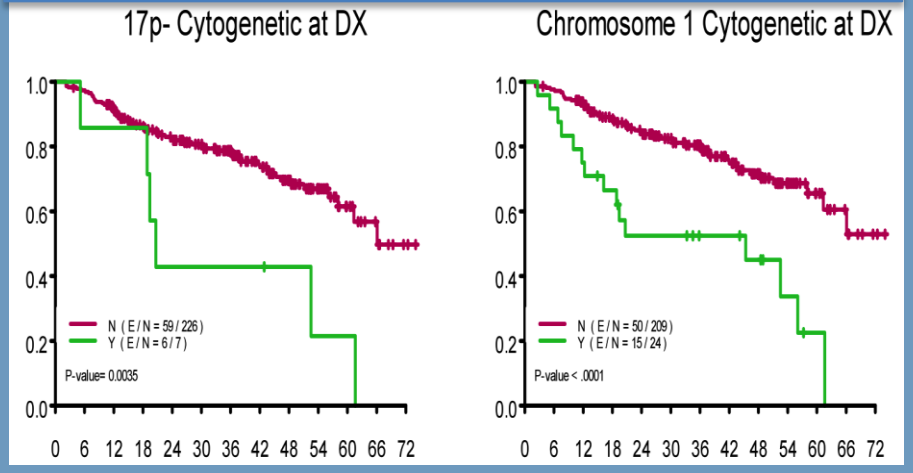
High-risk Chromosomal Abnormalities (MDACC; N=679; 2006 – 2010)

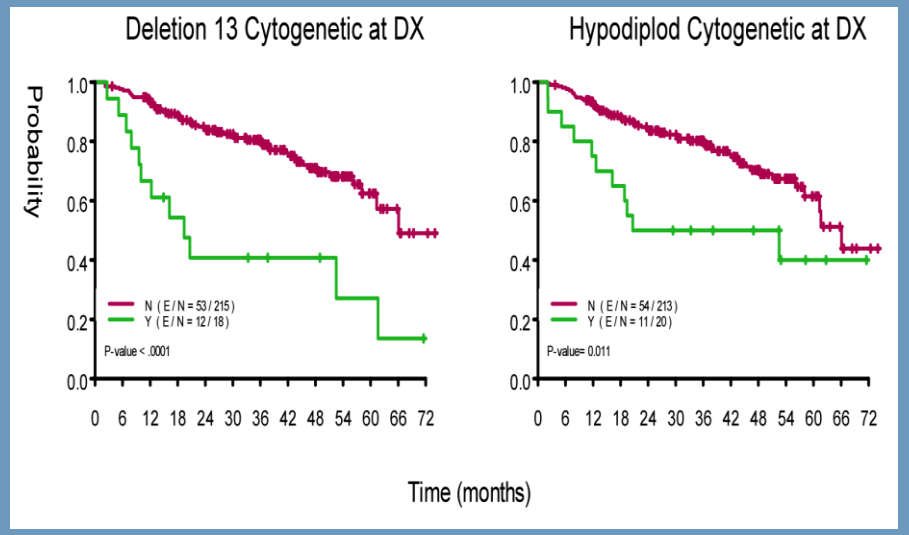
PFS





OS





High Risk FISH abnormalities

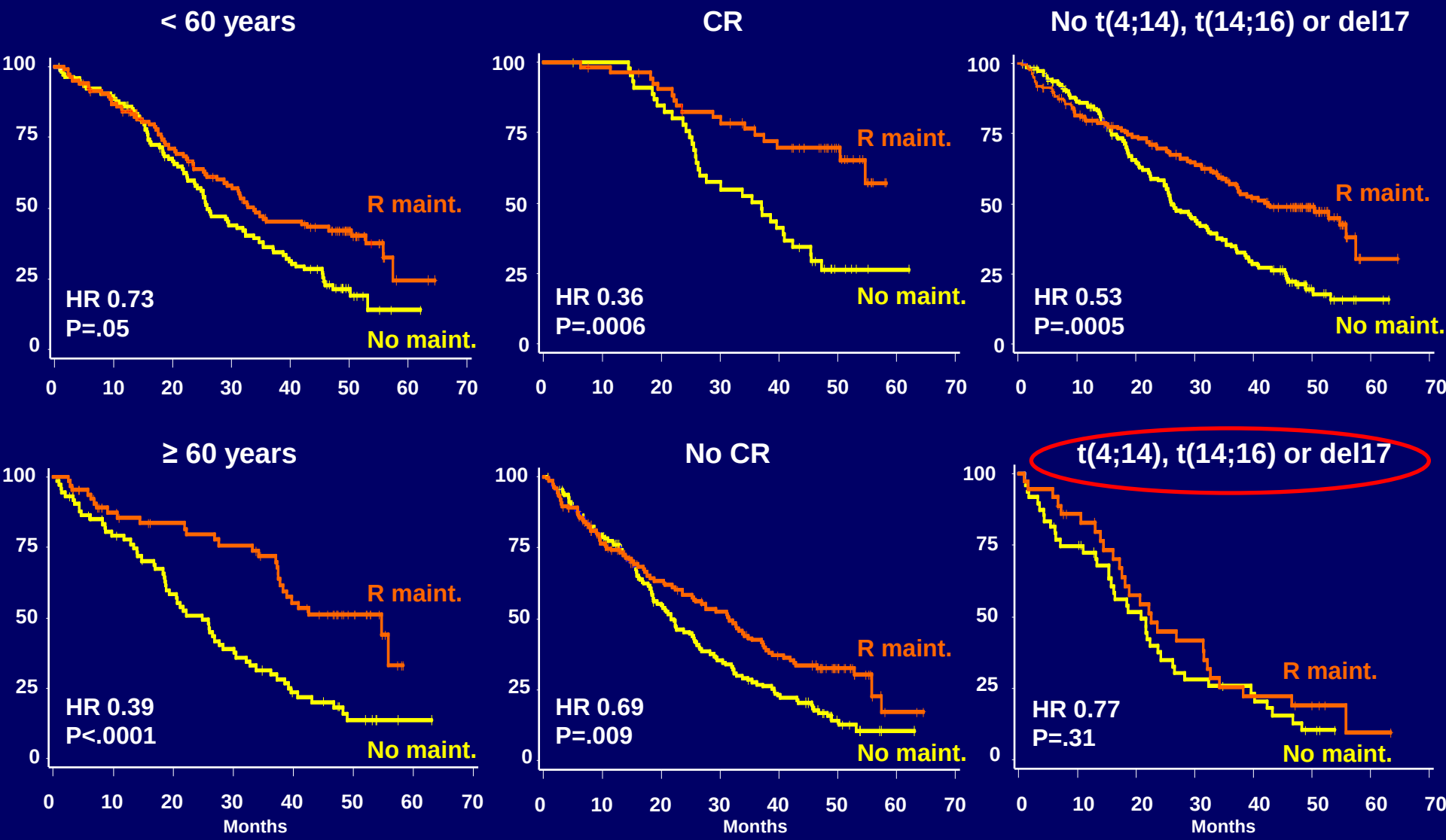
Abnormality	Frequency	Prognosis
Hyperdiploidy	50%–60%	Good/neutral
t(4;14)	15%	Poor (neutral if bortezomib therapy)
t(11;14)	20%	Neutral
t(14;16)	3%	Poor/neutral
Monosomy 13	45%	Neutral if by FISH
del(17p)	8%	Poor
1q gain	35%	Poor
del(1p)	30%	Poor
5q gain	50%	Good
del(12p)	10%	Poor

The Impact of Genomics on the Management of Myeloma
Jill Corre and Hervé Avet-Loiseau - JNCCN Mar 2012 ; 10 (3)

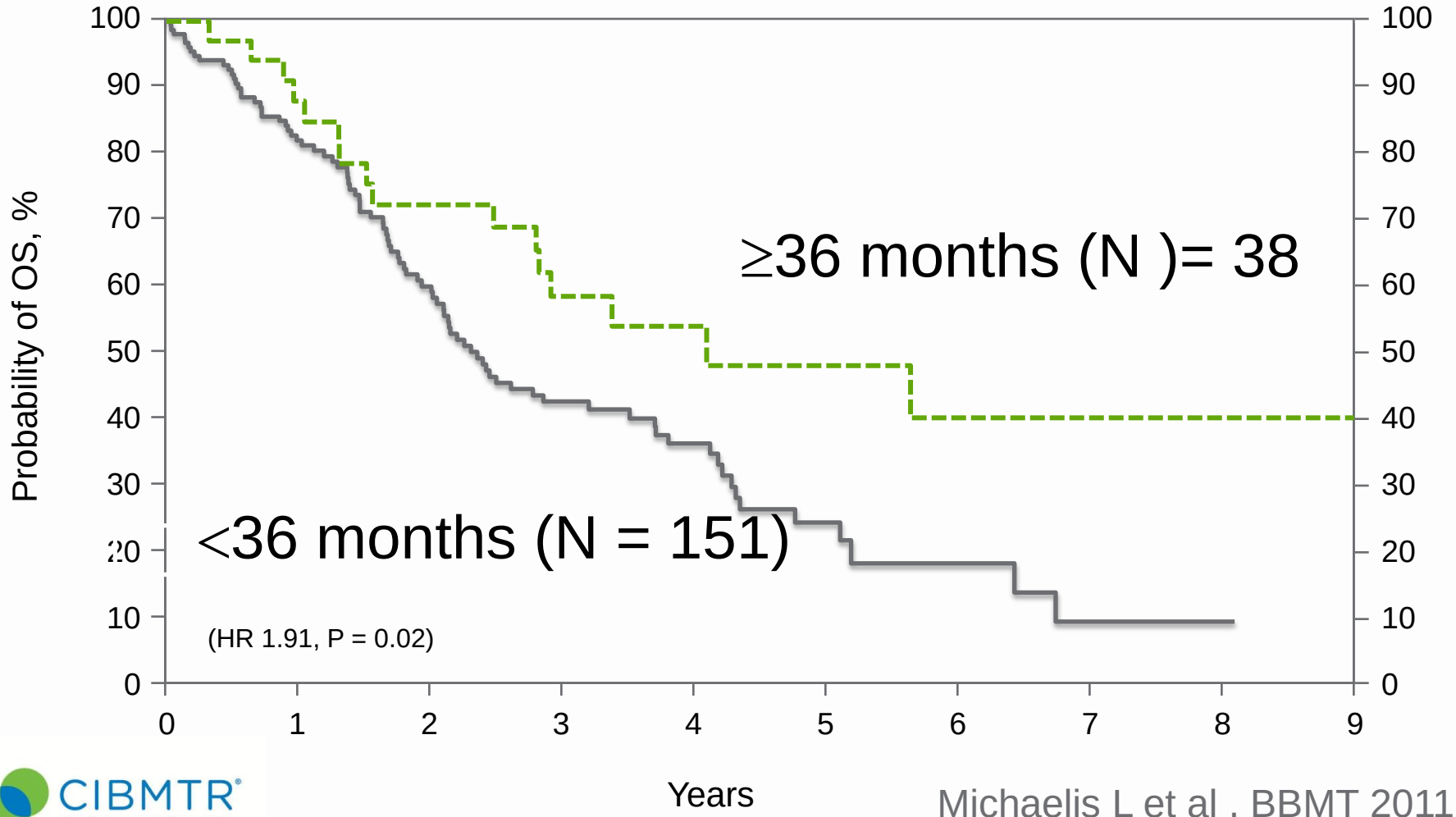
MEDICAL COLLEGE OF WISCONSIN

Progression-free survival

According to age, response, cytogenetics



Overall Survival after Second Autologous HCT, stratified by "Time from first HCT to first progression"



Michaelis L et al , BBMT 2011

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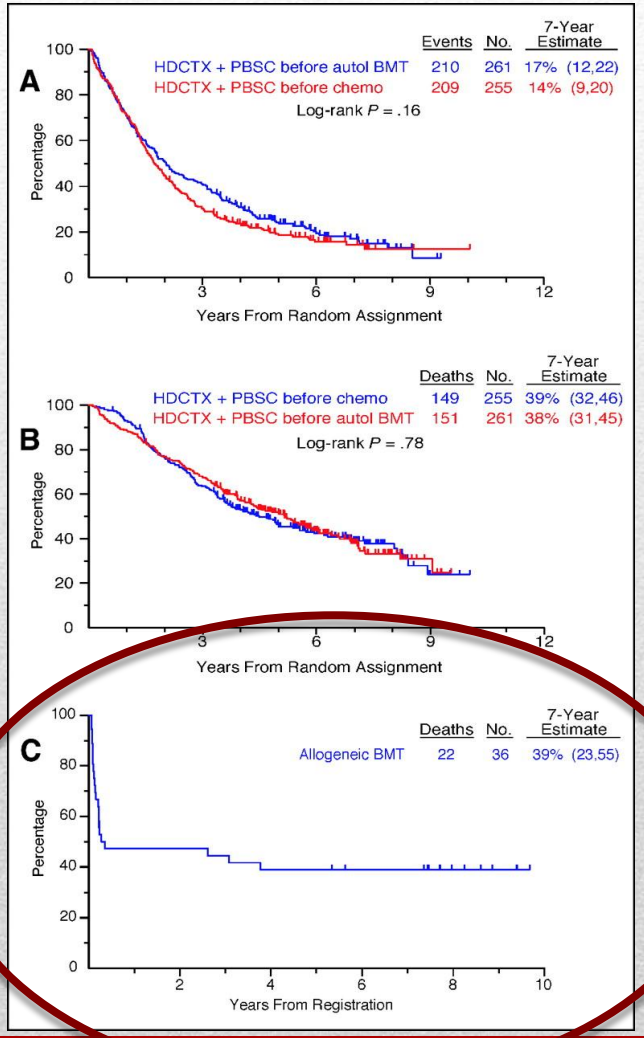
Final Results of Phase III US Intergroup Trial S9321



PFS 7 years
Auto 17%
Chemo 14%

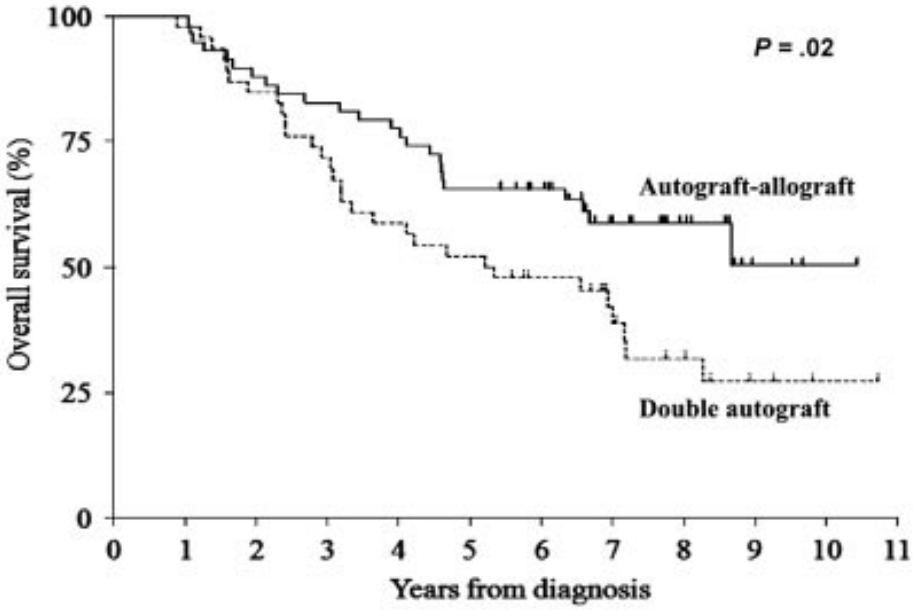
OS 7 years
Auto 39%
Chemo 38%

Allogeneic
7 years
PFS 22%
OS 39%

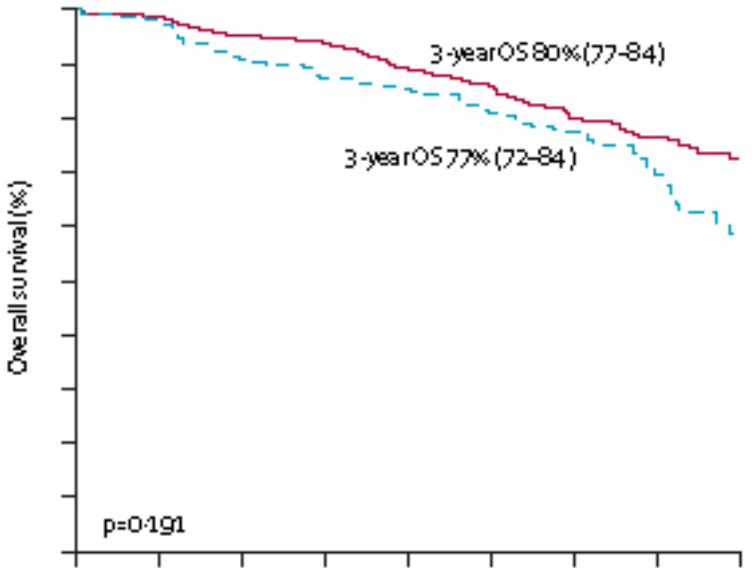
Barlogie et. Al. JCO 2006

Allogeneic Transplant

- Controversial
- US Trial – Negative (ASCT+ Allo no better than ASCTx2)
- European Trials – OS benefit esp. in high risk disease

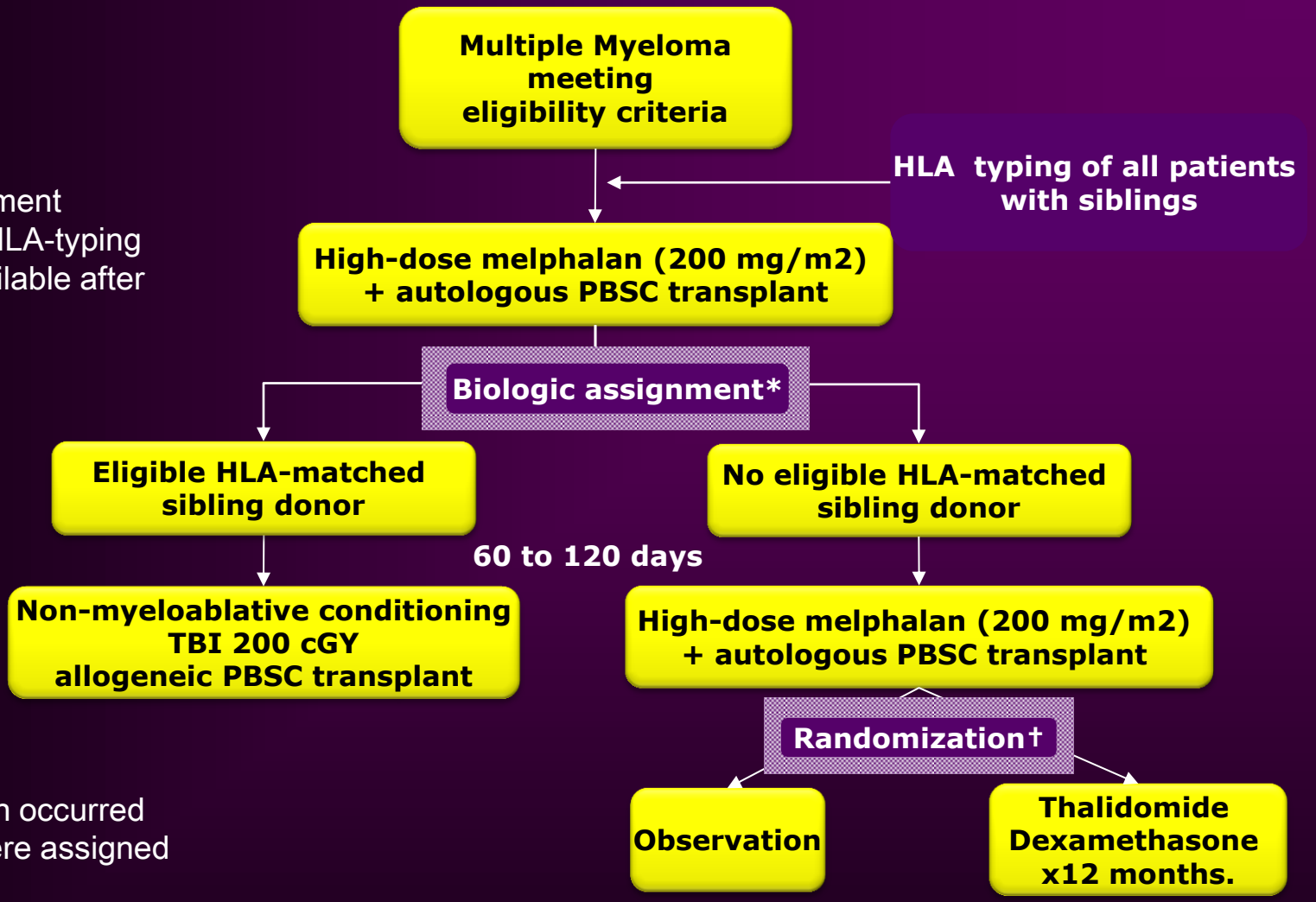


Giaccone et al 2011 117: 6721-6727



Krishnan/Pasquini et al Lancet Oncol 2011;12: 1195–203

BMT CTN 0102 Study Schema

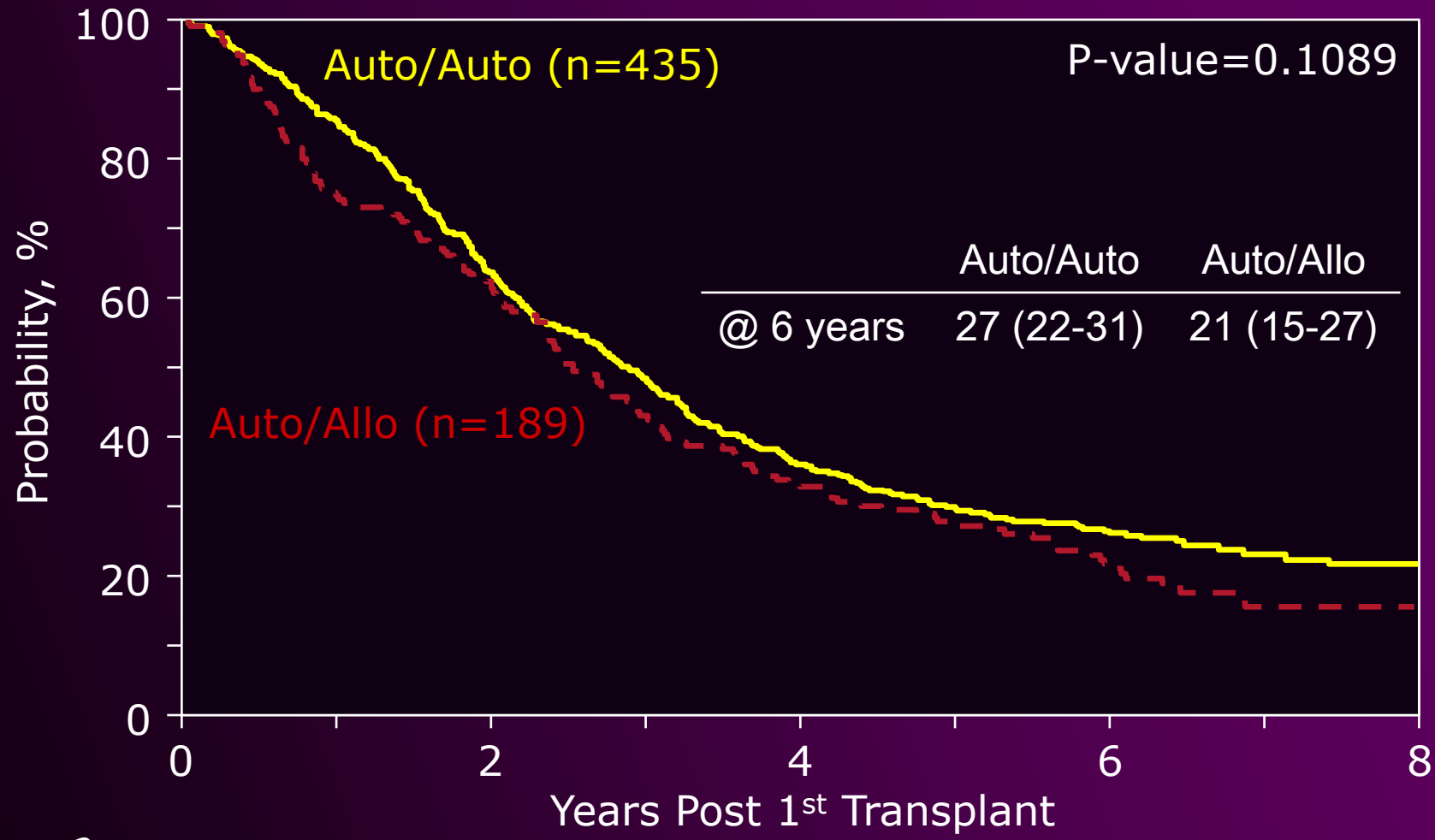


*Biologic assignment occurred when HLA-typing results were available after enrollment.

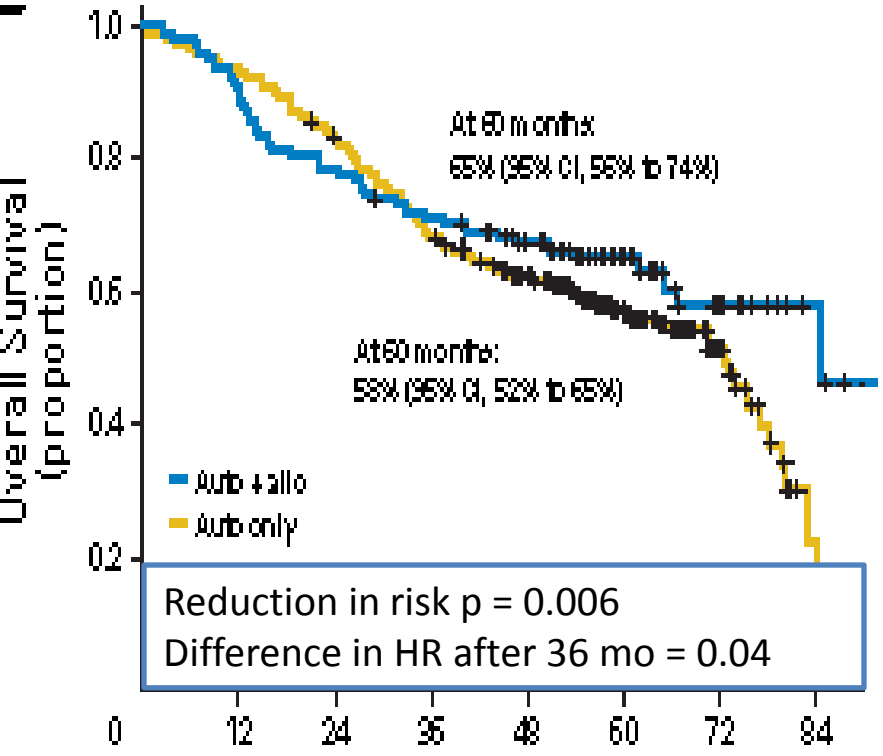
† Randomization occurred once patients were assigned to auto-auto

PRIMARY ENDPOINT : 3yr Progression Free Survival

Progression-free Survival by Treatment Arm
Standard Risk



Why not give up Allotransplant?



Bjorkstrand JCO 2011; 29: 3016 -22

- Intriguing European studies
- Longer follow up for a difference to show
- Young high risk pt – what to do?
- Low TRM - ~5% in the best centers
- Allo → Maintenance paradigm
- Backing off from “Mini” regimens

MEDICAL COLLEGE OF WISCONSIN

Leukemia (2013) 27, 780–791

www.nature.com/leu

REVIEW

Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group

C Fernández de Larrea[1], RA Kyle[2], BGM Durie[3], H Ludwig[4], S Usmani[5], DH Vesole[6], R Hajek[7], JF San Miguel[8], O Sezer[9], P Sonneveld[10], SK Kumar[2], A Mahindra[11], R Comenzo[12], A Palumbo[13], A Mazumber[14], KC Anderson[15], PG Richardson[15], AZ Badros[16], J Caers[17], M Cavo[18], X LeLeu[19], MA Dimopoulos[20], CS Chim[21], R Schots[22], A Noeul[23], D Fantl[24], U-H Melkqvist[25], O Landgren[26], A Chanan-Khan[27], P Moreau[28], R Fonseca[29], G Merlini[30], JJ Lahuerta[31], J Bladé[1], RZ Orlowski[32] and JJ Shah[32] on behalf of the International Myeloma Working Group[33]

Plasma cell leukemia (PCL) is a rare and aggressive variant of myeloma characterized by the presence of circulating plasma cells. It is classified as either primary PCL occurring at diagnosis or as secondary PCL in patients with relapsed/refractory myeloma. Primary PCL is a distinct clinic-pathological entity with different cytogenetic and molecular findings. The clinical course is aggressive with short remissions and survival duration. The diagnosis is based upon the percentage (≥20%) and absolute number ($\geq 2 \times 10^9$/l) of plasma cells in the peripheral blood. It is proposed that the thresholds for diagnosis be re-examined and consensus recommendations are made for diagnosis, as well as, response and progression criteria. Induction therapy needs to begin promptly and have high clinical activity leading to rapid disease control in an effort to minimize the risk of early death. Intensive chemotherapy regimens and bortezomib-based regimens are recommended followed by high-dose therapy with autologous stem cell transplantation if feasible. Allogeneic transplantation can be considered in younger patients. Prospective multicenter studies are required to provide revised definitions and better understanding of the pathogenesis of PCL.

Leukemia (2013) **27**, 780–791; doi:10.1038/leu.2012.336

Keywords: plasma cell leukemia; cytogenetics; bortezomib; transplantation; myeloma; prognosis

- 20% circulating plasma cells or >$2x10^9$/L absolute
- Consider plasma cell leukemia when:
  - 5% circulating plasma cells or >$0.5x10^9$/L absolute

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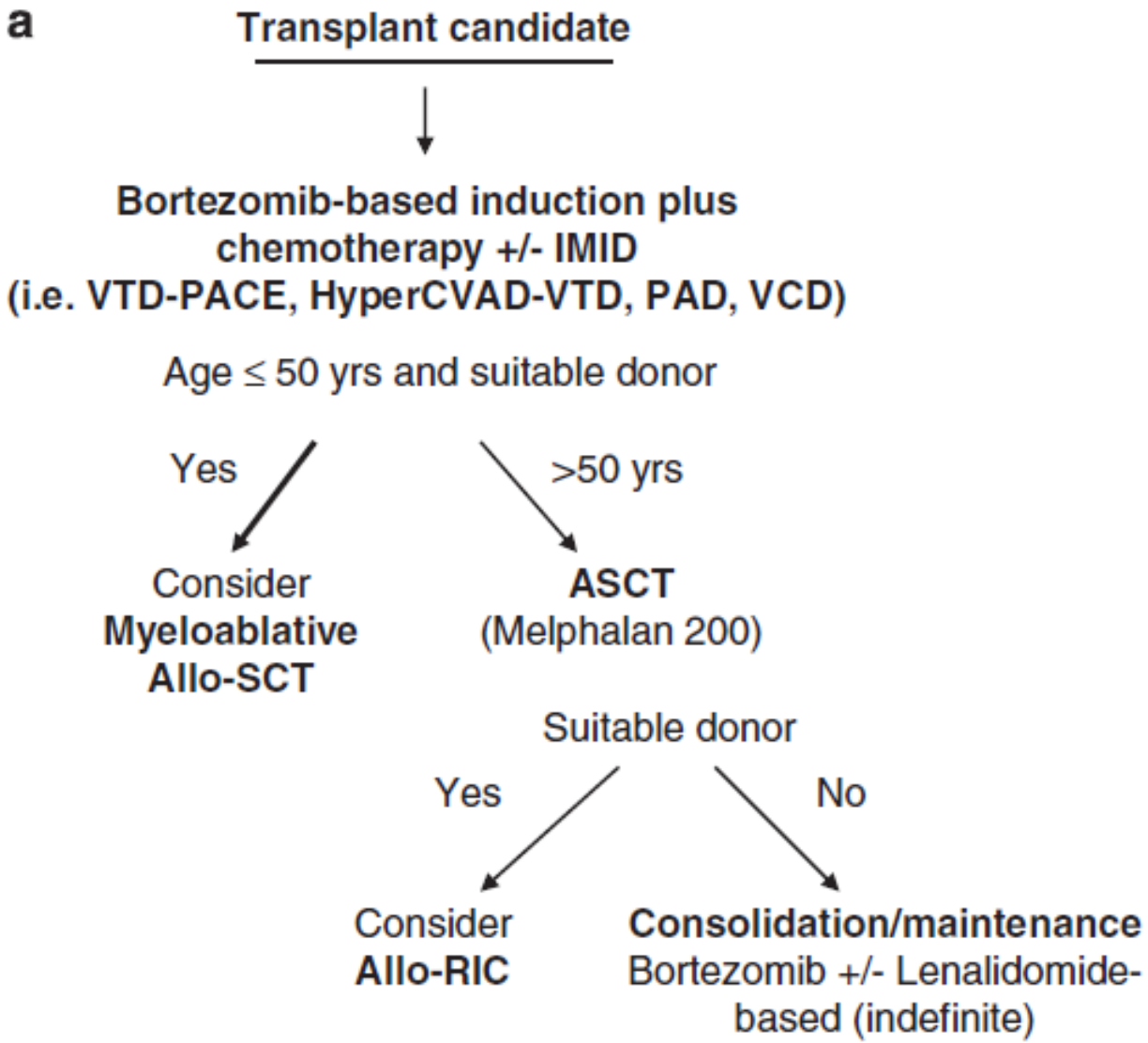
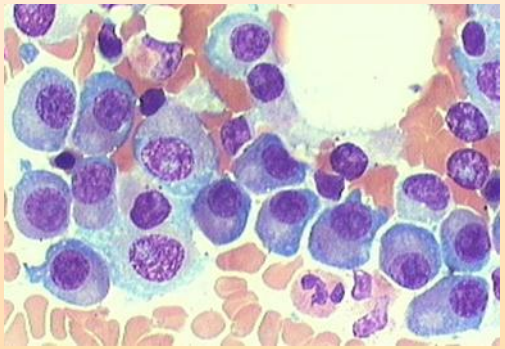


Multiple Myeloma Treatment: Future Perspective

- Myeloma now is a chronic disease
  - Patients are living longer than ever
  - Although mostly incurable
- Better stratification of patients with the highest risk
  - CRAB criteria is becoming outdated.
- Modified targeted therapy paradigm
  - Risk adapted or molecular signature adapted
  - Change from continuous to non-continuous treatment when appropriate – response adapted treatment



Conclusions

- Transplant remains the main backbone for the treatment of myeloma.
- Myeloma outcomes are now much better with combination of novel agents and transplant.
- High risk myeloma remains a challenge and novel approaches are needed.
- Allogeneic HCT remains investigational, but could be consider in patients with high risk disease.


Thank You!


Hvala


Merci


ขอบคุณ


תודה


Köszönettel


Obrigado!


Bedankt


Grazie


Gracias


Vielen
Dank


شكراً

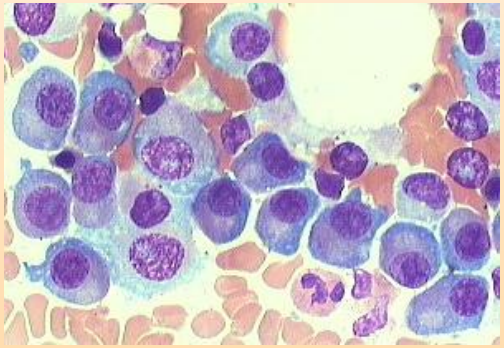

Teşekkürler


Díky


Ευχαριστώ

cảm ơn bạn

Transplants for Multiple Myeloma



- Multiple myeloma is an incurable plasma cell disorder.
- Clinical presentation includes:
  - Anemia, lytic bone lesion, kidney failure, hypercalcemia and repetitive infections
- Most common indication of autologous transplants
- Many new regimens available for disease control.