

Practical Strategies for Novel Agents in Multiple Myeloma

Collegium Medicum Jagiellonian University

Cracow, Poland

March 15, 2010

Robert A. Kyle, MD



 **Scottsdale, Arizona**



Rochester, Minnesota



Jacksonville, Florida

Disclosures for Robert A. Kyle

Johnson & Johnson

Disease Monitoring Committee

Celgene

Disease Monitoring Committee

Bristol-Myers Squibb

Independent Review Committee

Novartis

Disease Monitoring Board

Millennium

Consultant

Merck

Data Monitoring Committee

Multiple Myeloma Epidemiology

- **1% of all malignancies**
- **10% of hematologic malignancies**
- **Incidence**
 - 4/100,000 in Caucasians**
 - 8/100,000 in African-Americans**

Multiple Myeloma

Criteria for Diagnosis

Bone marrow with $\geq 10\%$ plasma cells or plasmacytoma + 1 of the following

- M-protein in serum (usually ≥ 3.0 g/dL)
- M-protein in urine
- Lytic bone lesions

End-organ damage: CRAB (hypercalcemia, renal insufficiency, anemia, bone lesions)

Smoldering Multiple Myeloma (SMM)

M-protein in serum
and/or ≥ 3 g/dL

Plasma cells in marrow $\geq 10\%$

Anemia None

Calcium Normal

Creatinine Normal

Lytic lesions None

Plasma cell labeling index Low

No end organ damage

mSMART: Classification of Active MM

High-Risk (25%)

FISH

- Del 17p
- t(4;14)*
- t(14;16) or t(14:20)

Cytogenetic Deletion 13

Cytogenetic Hypodiploidy

PCLI $\geq 3\%$

Standard-Risk (75%)*

All others including:

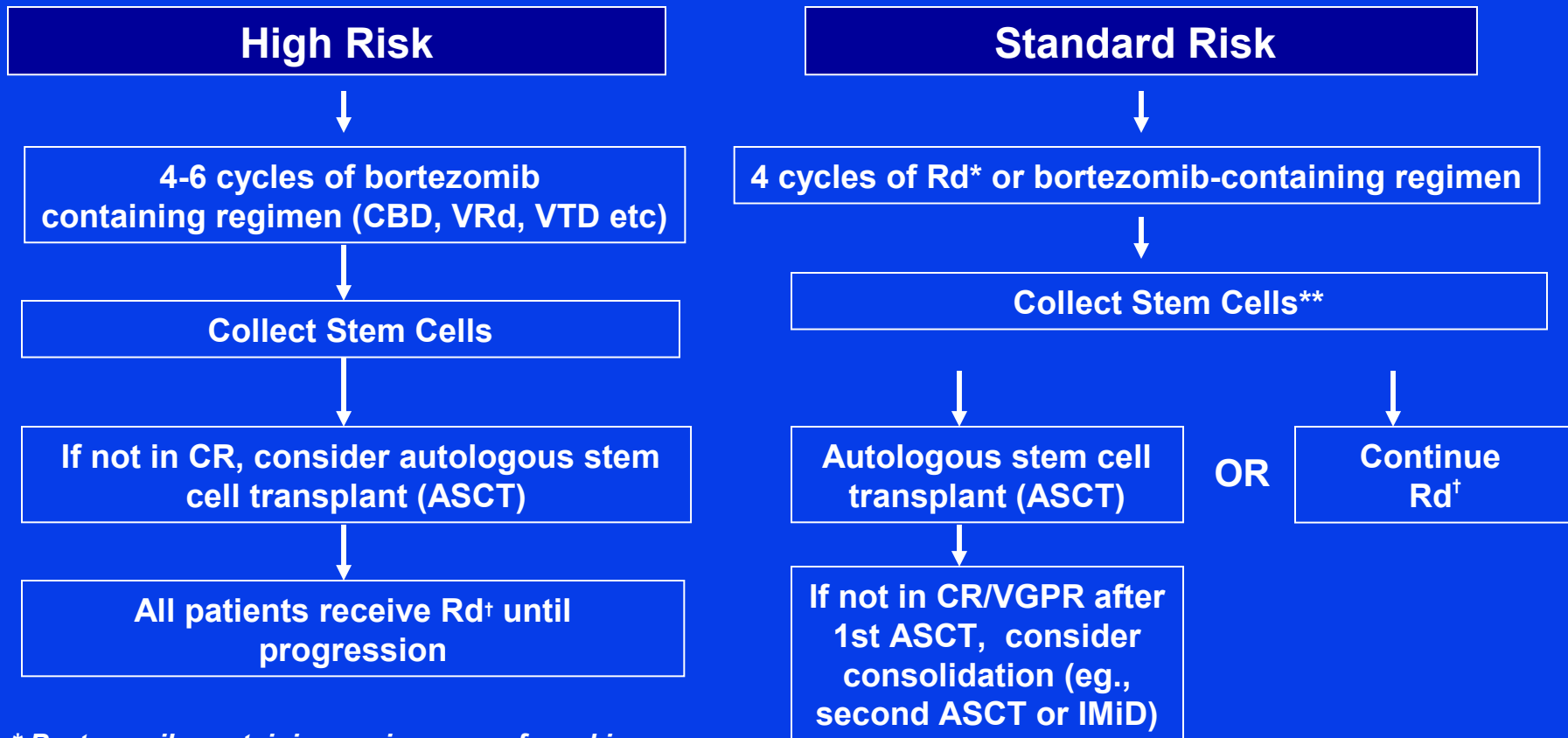
- Hyperdiploid
- t(11;14)
- t(6;14)

*Patients with t(4;14), b2M < 4 mg/l and Hb ≥ 10 g/dl may have intermediate risk disease

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; v4 Revised and updated: January 2008

Kumar et al, Mayo Clin Proc 2009; 84:1096

mSMART – Off-Study Transplant Eligible

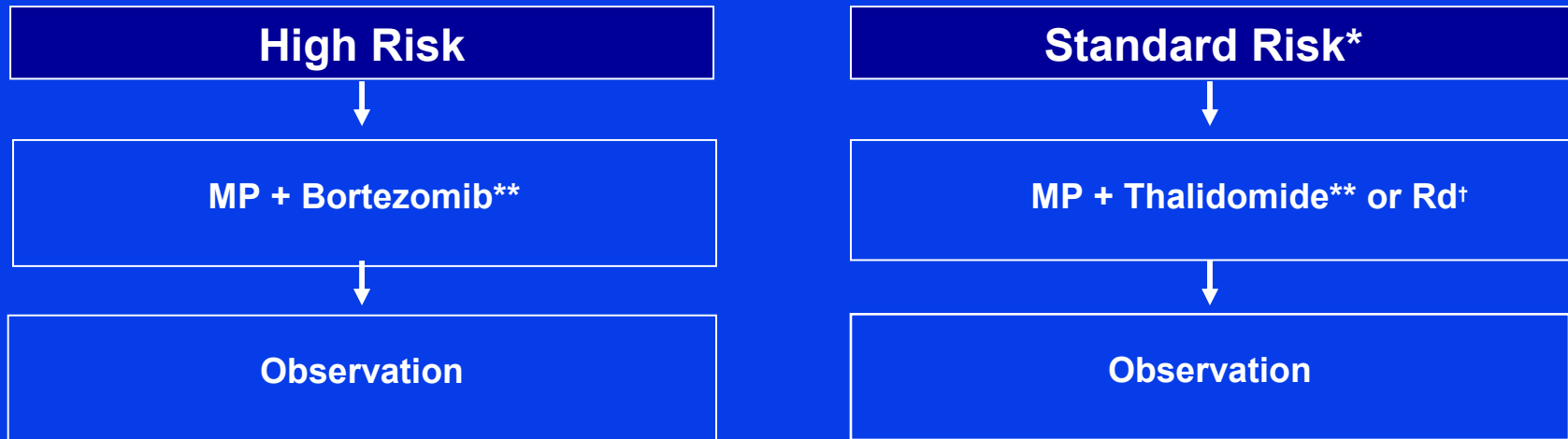


* Bortezomib containing regimens preferred in renal failure or if rapid response needed

(**If age >65 or > 4 cycles of Rd
Consider G-CSF plus cytoxan or plerixafor)

† Continuing Rd is an option for patients responding well to induction with low toxicities; Dex is usually discontinued after first year

mSMART – Off-Study *Transplant Ineligible*



**Bortezomib containing regimens preferred in renal failure or if rapid response needed*

*** In patients in whom administration of thalidomide or bortezomib is of concern, consider MP or Rd*

† Continuing Rd is an option for patients responding well to induction with low toxicities; Dex is usually discontinued after first year

Multiple Myeloma Untreated

Initial Therapy

Transplant eligible

Multiple Myeloma Untreated

N = 470

	Resp CR/PR %	TTP mos (med)	DVT %
Thal 50-200 mg/day + Dex 40mg(day 1-4, 9-12, 17-20)	63	22.6	12
vs.			
Placebo + Dex 40mg (day 1-4, 9-12, 17-20)	46	6.5	2

Survival Rate

Year	N	Survival Probability	
		One-Year %	Two- %
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	223	88	78
vs.			
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1, 8, 15, 22	222	96	88

Multiple Myeloma Untreated

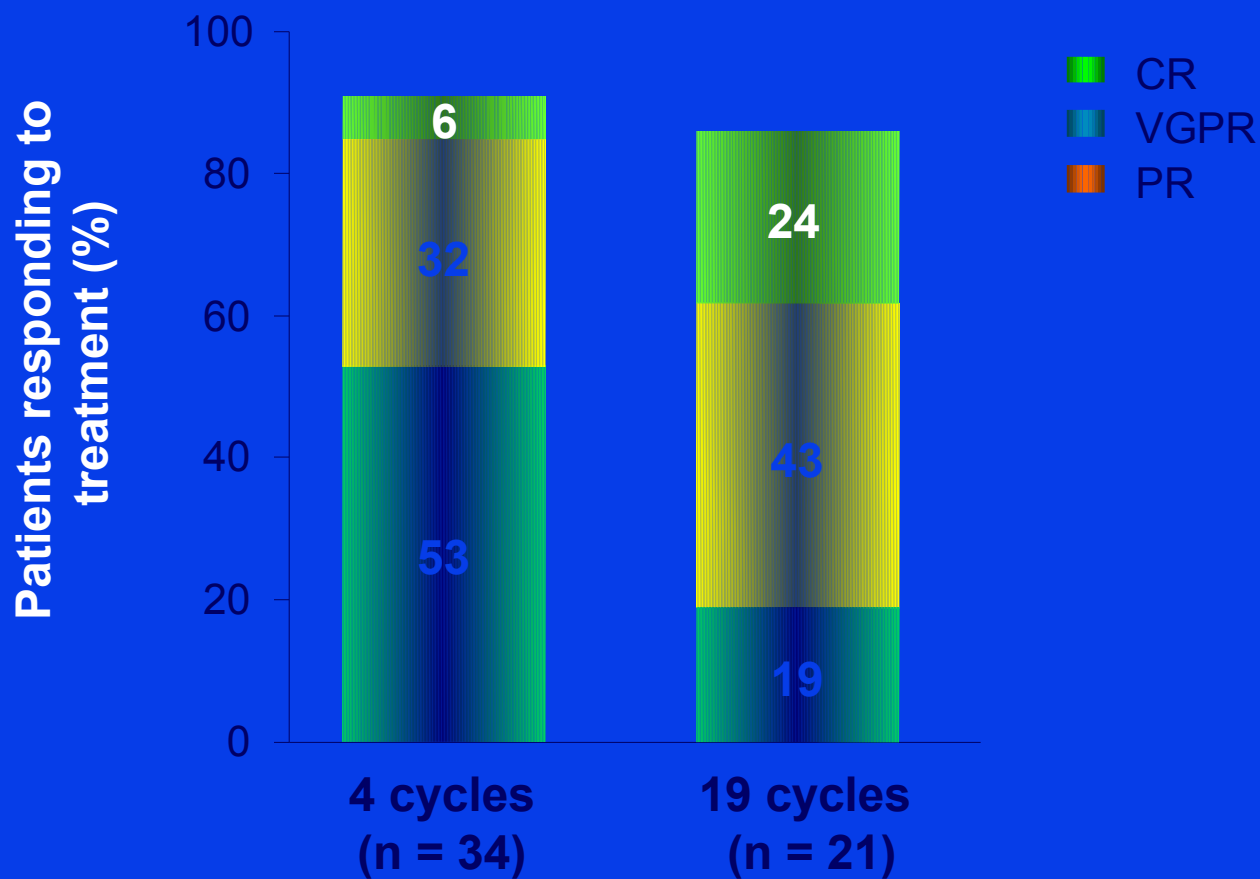
N = 445

	DVT %	Infection %
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20		25
14		
vs.		
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1, 8, 15, 22	6	7

Rajkumar, et al., Blood 2007, 110:31a

Depth of response improves over time with lenalidomide

Mayo clinic phase II



Multiple Myeloma

BiRD Trial

N = 72

	CR %	≥ PR %
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg weekly + Clarithromycin 500 mg b.i.d.	39	90

Multiple Myeloma

Untreated
N = 48

Response

Bortezomib 1.3 mg/M2		%
2/wk x 2 q3 wks	CR/NCR	19
+		
Dexamethasone 40 mg		
Day of and day after Bortezomib	PR	71
if no response		
	Total	90

Overall survival 67% at 4 years

Multiple Myeloma Autologous Transplant

	Standard (ABCM) n=200	Intensive (Tx) n=201
Complete response (%)	8	44
Prog-free survival (mo)	20	32
Overall survival (mo)	42	54

Child JA et al: NEJM 348:1875, 2003

Multiple Myeloma Autologous Peripheral Blood Transplantation

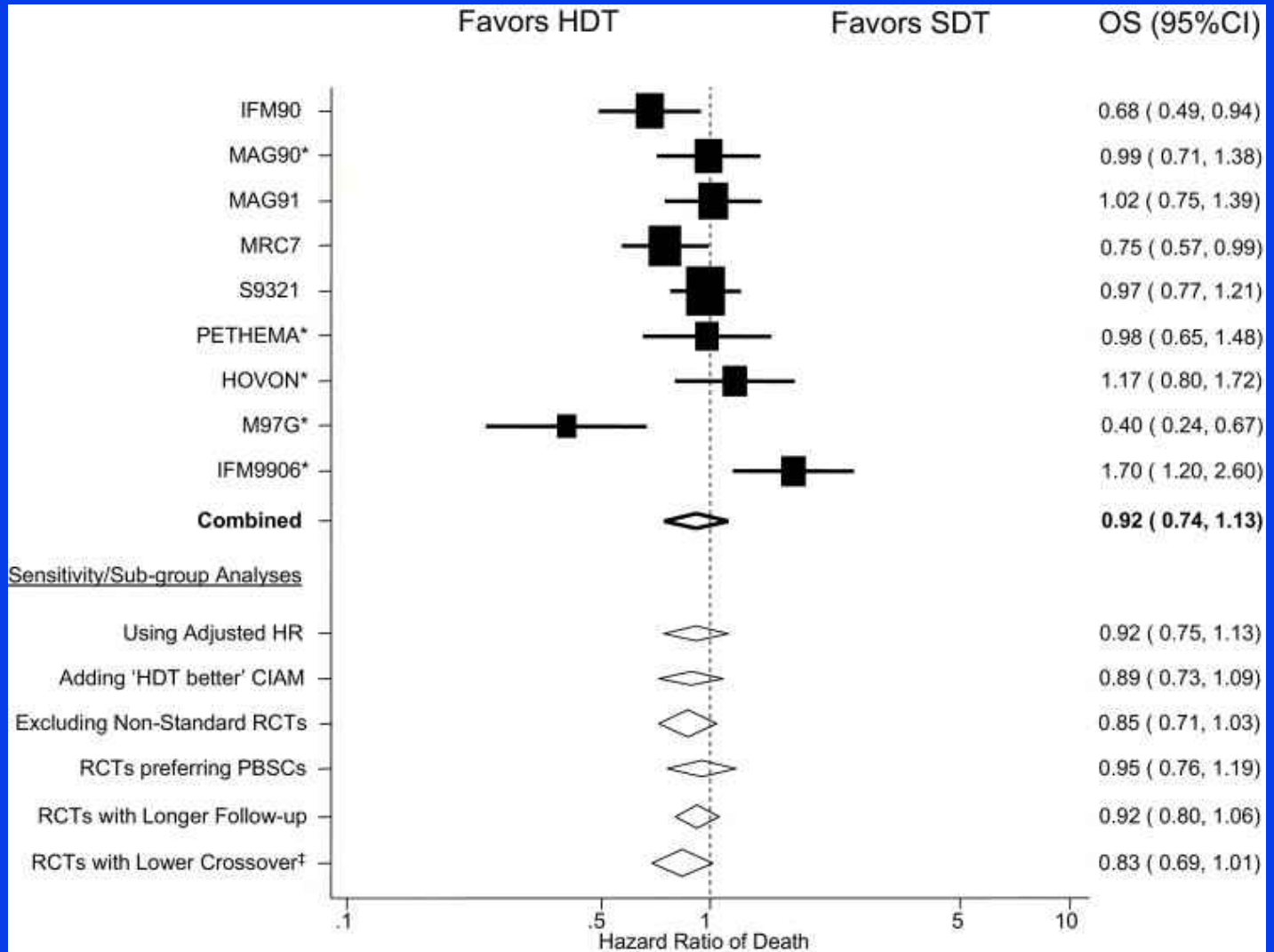
Pro

- **Low mortality (circa 1%)**
- **Available for up to 50% of myeloma**

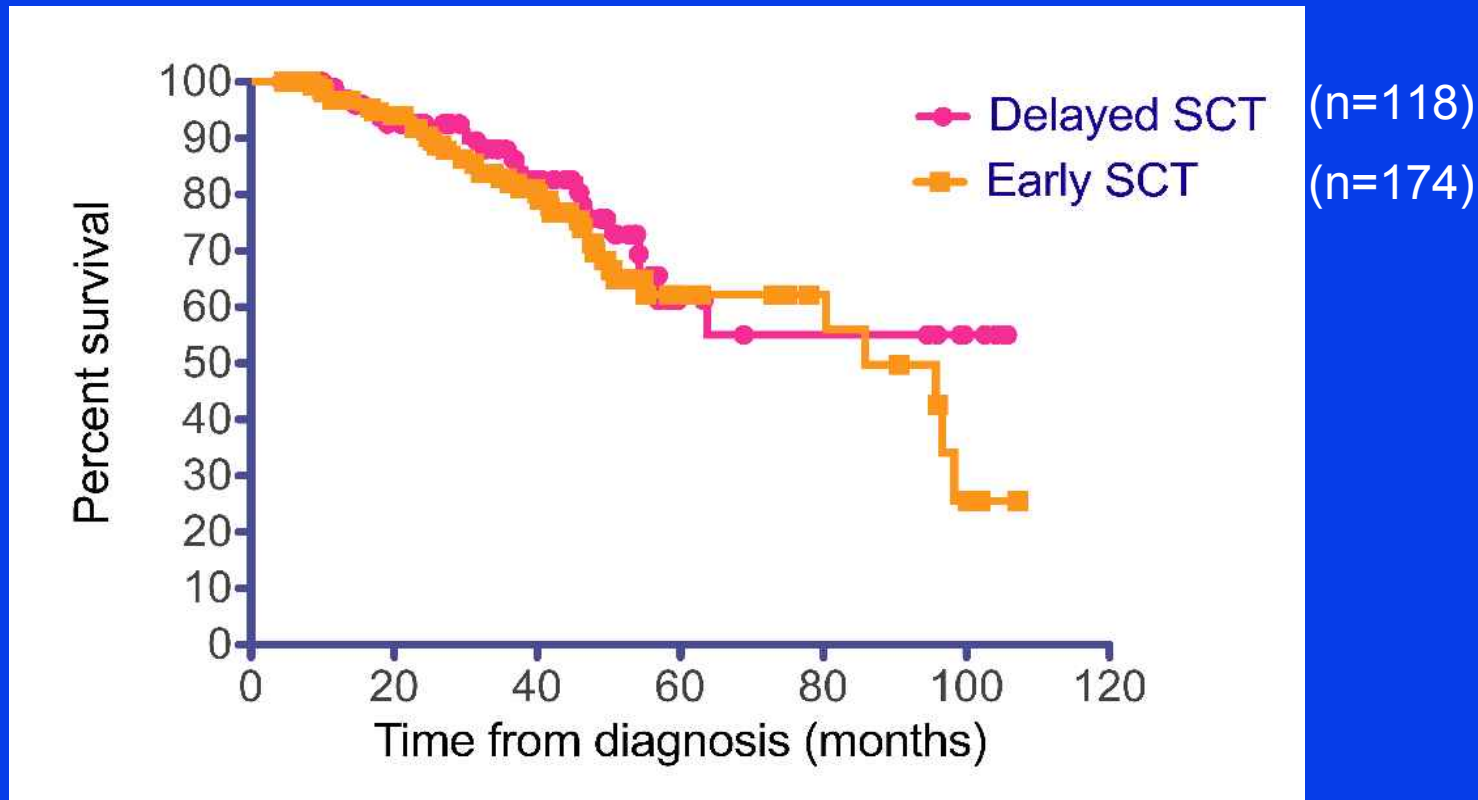
Con

- **Contamination by tumor cells**
- **Lack of cure**

Overall survival: Meta-analysis



Overall Survival From Diagnosis



Median OS for early group was 86 mos (95% CI; 80,98) vs. NR (95% CI; 54, NR) for delayed group (P = 0.3)

Multiple Myeloma Peripheral Stem Cell Autologous Transplantation

Challenges

- Eradication of multiple myeloma
- Removal of myeloma cells and precursors from peripheral blood

Allogeneic Bone Marrow Transplantation

Pro

- No contamination by tumor cells

Con

- 90-95% ineligible
- Early mortality
- Graft vs host disease
- Lack of cure

Non-Myeloablative (“Mini”) Allograft

Study	Conditioning regimen	Pt (no.)	TRM (%)	CR (%)	PR (%)	Chronic GVHD	PFS	OS
Kroger et al	PBSCT + Mel/Flu/ATG	17	18	72	20	40	56% at 2 yr	74%
Badros et al	Mel or Mel/TBI/Flu	31	20	61	10	32	86% at 1 yr	86%
Maloney et al	PBSCT + TBI/MMF/cyc	54	4	57	26	46	–	78% at 552 d
Bruno et al	PBSCT + TBI/200	58	10	55	31	32	43 mos	not reached

Maloney, et al., Blood, 2003, 102:3447; Bruno, et al., NEJM, 2007, 356:1110

Multiple Myeloma Untreated

Initial therapy

Transplant ineligible

Multiple Myeloma Chemotherapy

- Melphalan (Alkeran) 0.15 mg/kg daily, 7 days plus prednisone 15 mg qid, 7 days
- Repeat WBC and platelet counts every 3 weeks
- Repeat cycle every 6 weeks
- Need modest cytopenia at mid-cycle

Multiple Myeloma Single (M/P) vs Combination Chemotherapy (CCT)

n=4,930 (20 trials)

Therapy	Response (%)
M/P	53
CCT	60

P<0.00001

No difference in survival

No subsets with benefit

Multiple Myeloma

Transplant Ineligible
Untreated
N = 255

	Resp > 50%	CR	2 yr. EFS %	3 yr. survival %
MPT (100 mg) x 6	76	16	54	80
MP x 6	48	2	27	64

Palumbo, et al., Lancet 367:825, 2006.

Multiple Myeloma

Transplant Ineligible Untreated N = 255

	Gr. III – IV adverse %	TE* %	Infection %	PN+ %
MPT (100 mg) x 6	48	12	10	8
MP x 6	25	2	2	0

*TE = Thromboembolism

+PN – Peripheral Neuropathy

Multiple Myeloma

Untreated – age 65-75 years

IFM 99-06

N= 447

	PFS med mos	OS med mos
MPT (400 mg) x 12	28	52
MP x 12	18	33
VAD/Mel 100x2	19	38

Facon, et al., Lancet, 2007 370:1209

Multiple Myeloma

Untreated – age > 75 years

IFM 01/01

N= 229

	PFS med mos	OS med mos
MPT (100 mg) d 1-4, q. 6 weeks x 12	24.2	45.3
M 0.2 mg/kg + P 2 mg/kg d 1-4 q. 6 weeks x 12	19	27.7

Multiple Myeloma Untreated ≥ 65 years of age

N = 54

			%
Lenalidomide 5-10 mg d 1-21	+	CR	24
Melphalan .18 - .25 mg/Kg d 1-4	+	VGPR	48
Prednisone 2 mg/Kg d 1-4		PR	9
Lenalidomide 10 mg d 1-21 q. 4 weeks x 9 cycles			
Lenalidomide maintenance			
		Total	81

MTD: Melphalan 0.18/Kg + Lenalidomide 10 mg/d

Multiple Myeloma Non-Transplant Candidates

Cycles 1-4

**Bortezomib 1.3 mg/m² IV d 1,4,8,11,22,25,29,32
+**

Melphalan 9 mg/m² and prednisone 60 mg/m² d 1-4

Cycles 5-9

**Bortezomib 1.3 mg/m² IV d 1,8,22,29
+**

Melphalan 9 mg/m² and prednisone 60 mg/m² d 1-4

vs.

**Melphalan 9 mg/m² and prednisone 60 mg/m² d 1-4
Nine 6-week cycles of both arms**

Multiple Myeloma Response to Treatment

	MPV N=337	MP N=331
CR (IF-)	30%	4%
PR \geq	71%	35%
Duration of Response (Med, Mos)	19.9	13.1

San Miguel, et al., NEJM 2008, 359:906

Multiple Myeloma

Grade 3/4 adverse events (%)

	VMP (n=340)		MP (n=337)	
	Gr 3	Gr 4	Gr 3	Gr 4
Neutropenia	30	10	23	15
Thrombocytopenia	20	17	16	14
Anemia	16	3	20	8
GI	19	1	5	<1
Peripheral Sensory Neuropathy	13	<1	0	0
Fatigue	7	1	2	0
Asthenia	6	<1	3	0
Pneumonia	5	2	4	1
Herpes Zoster	3	0	2	0

- Transfusion (26% vs 35%) and EPO support (34% vs 42%) were somewhat lower on the VMP arm
- PN resolved or improved in 75% of cases in a median of 64 days
- **DVT was low and the same on both arms (1%)**

Multiple Myeloma

Treatment

Relapsed and/or Refractory

Refractory Multiple Myeloma Therapy

- **Vcr Adria Dex (VAD)**
- **High-dose corticosteroids**
Dexamethasone 40 mg
d 1 – 4, 9 – 12, 17 – 20 q mo
- **Thalidomide**
- **Bortezomib (Velcade)**
- **Lenalidomide (Revlimid)**

Single-Agent Thalidomide in Recurrent/Refractory Multiple Myeloma

Study	Dose (mg/d)	Pt (no.)	RR (%)
Singhal, et al.	200-800	84	32*
Barlogie, et al.	200-800	169	30**
Grosbois	200-400	121 (incl minor response)	41

* >25% ↓ in paraprotein

** 2-yr event-free survival and overall survival rates of 20% and 48%, respectively

Refractory Multiple Myeloma Treatment

Bortezomib (VELCADE™) (PS-341)

n = 193

Response (CR/PR)

35%

Duration response

12 mo

Richardson et al: NEJM 2003, 348:26.

Multiple Myeloma Relapsed

	N = 669	TTP mos	Survival med mos
Bortezomib, 1.3 mg/M² d 1, 4, 8, 11 q 3wks		6.2	29.8
vs.			
Dexamethasone, 40 mg d 1-4; 9-12; 17-20		3.5	23.7

Richardson, et al., Blood, 2007, 110:3557

Multiple Myeloma Relapsed/Refractory

	N = 646	TTP mos med	Survival at 15 mos %
Bortezomib, 1.3 mg/m² IV d 1, 4, 8, 11			
vs.		6.5	65
Bortezomib, 1.3 mg/m² IV d 1, 4, 8, 11 +			
Doxil 30 mg/m² IV d 4		9.3	76

Multiple Myeloma Relapsed/Refractory

009,010
N = 704

	Response CR/PR %	TTP Mos (Med)
Lenalidomide 25 mg d1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	60.5	11.2
vs.		
Placebo d. 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	22	4.7



Multiple Myeloma Relapsed/Refractory

N = 37

VGPR

PR

Pomalidomide (CC-4047)

24%

38%

2 mg daily +

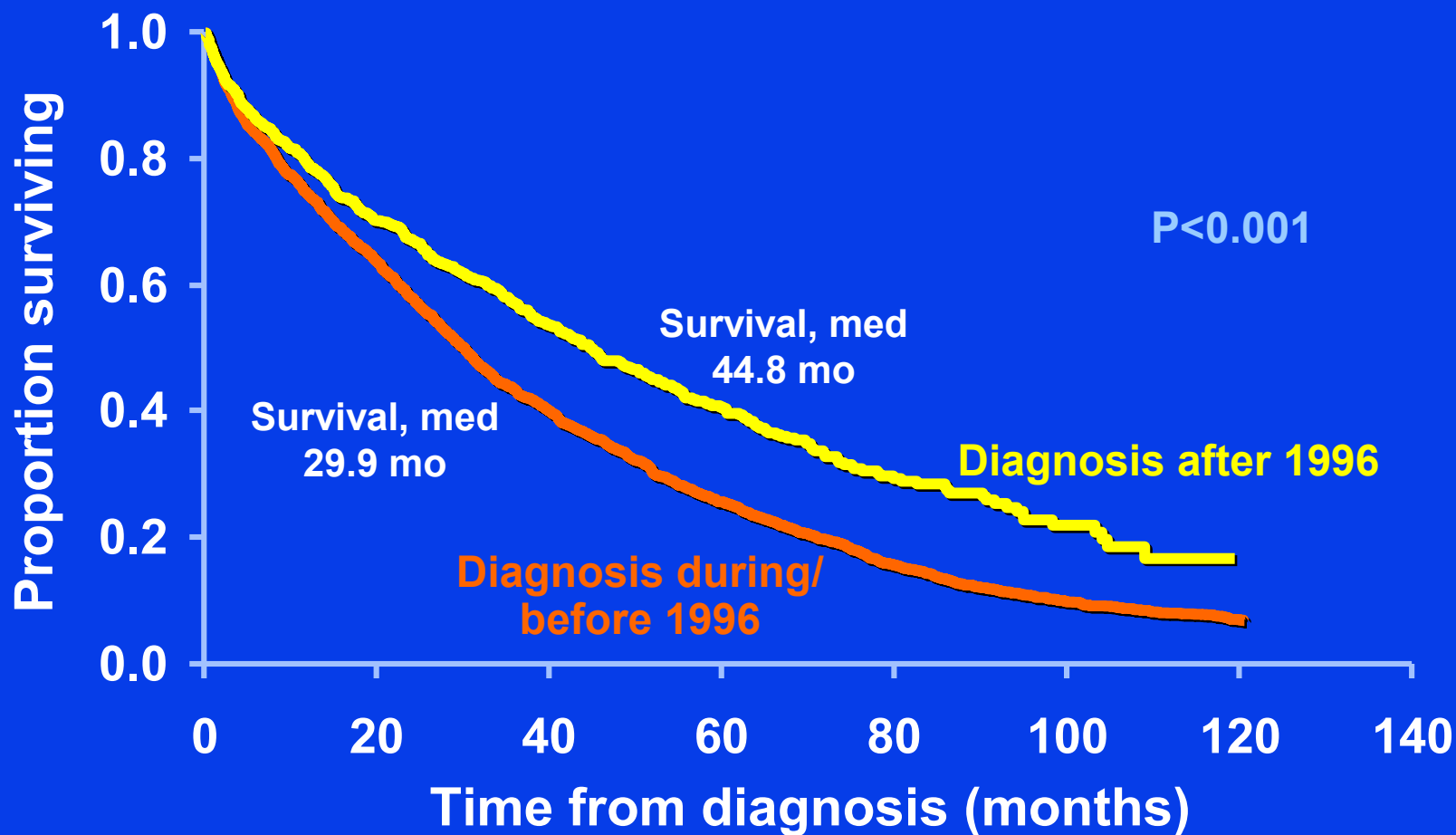
Dexamethasone

40 mg weekly



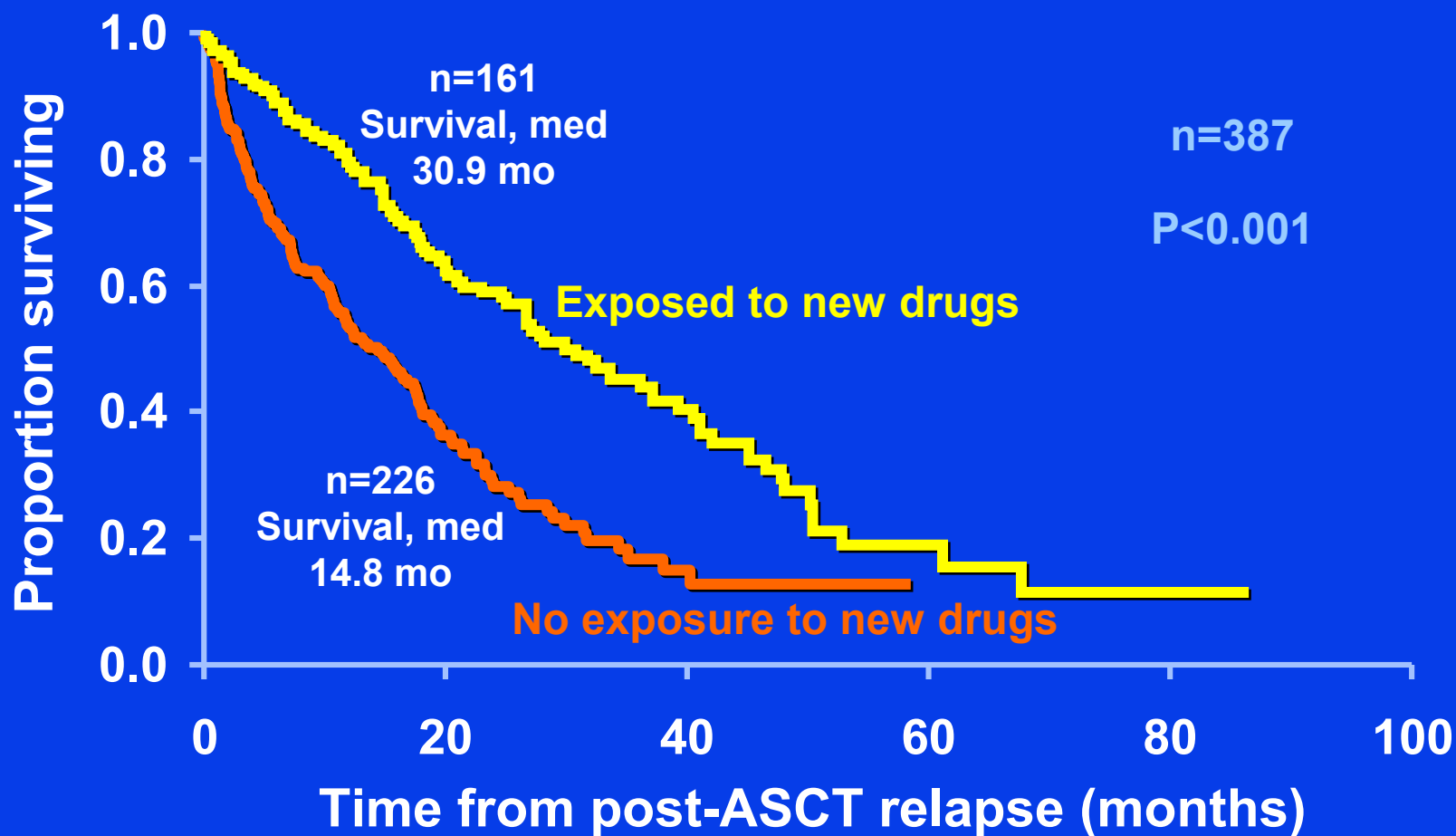
Multiple Myeloma 1971-2006

n=2,981



Kumar et al: Blood 111:2516, 2008

Relapse After Autologous Transplant for Multiple Myeloma



Kumar et al: Blood 111:2516, 2008

Multiple Myeloma Novel Agents

Histone deacetylase inhibitor	Vorinostat (SAHA)
Heat Shock protein- 90 inhibitor KOS-953	Tanespimycin
Proteasome inhibitor (oral)	NPI-0052
FGFR3 inhibitor	Chir-258
P³⁸ MAPK inhibitor	Scio-469
CARFILZOMIB	PR-171
MEK inhibitor	AZD-6244
Pomalidomide	CC-4047

