Treatment of Newly Diagnosed Myeloma: Mayo Clinic Approach

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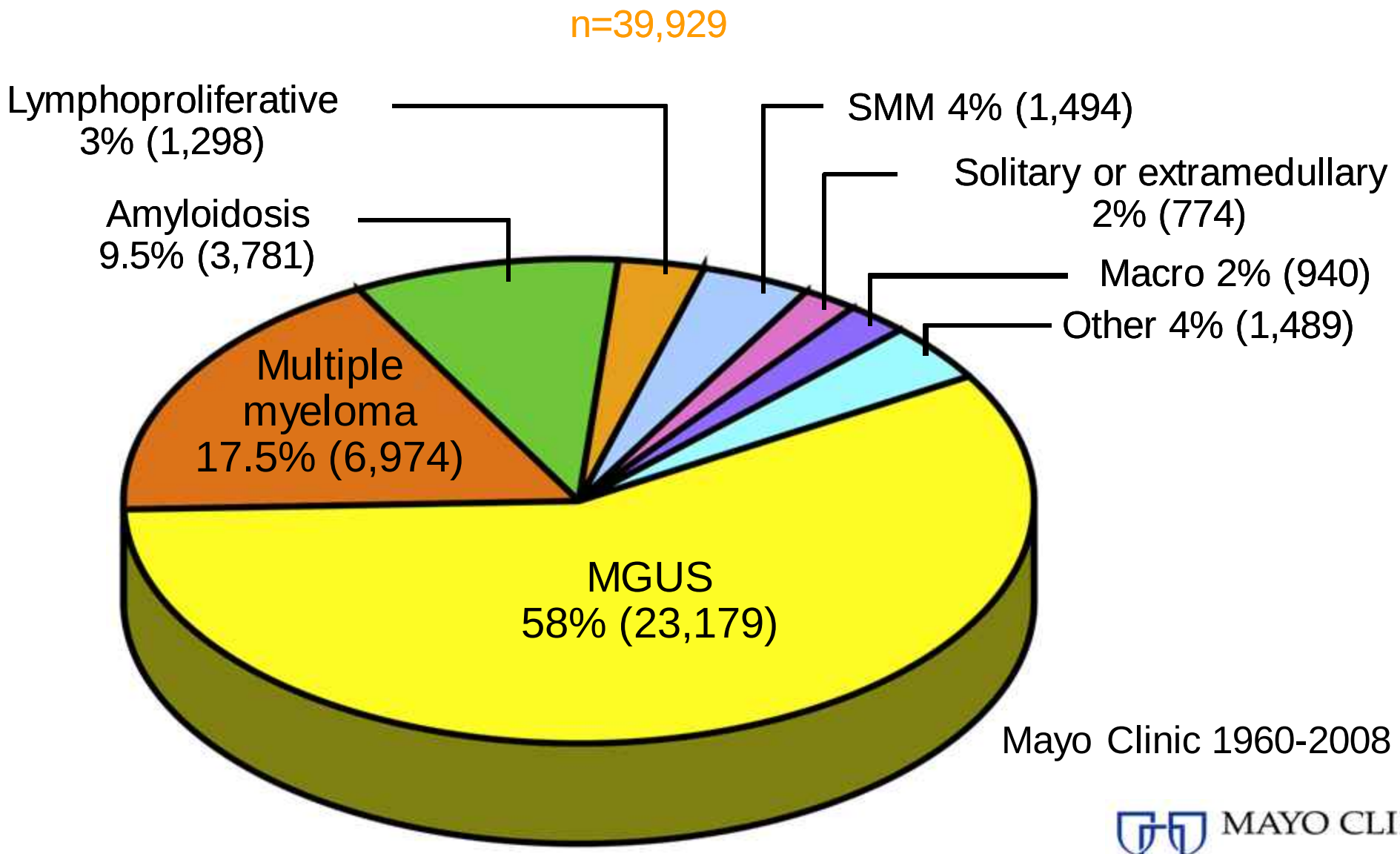
Monoclonal Gammopathies



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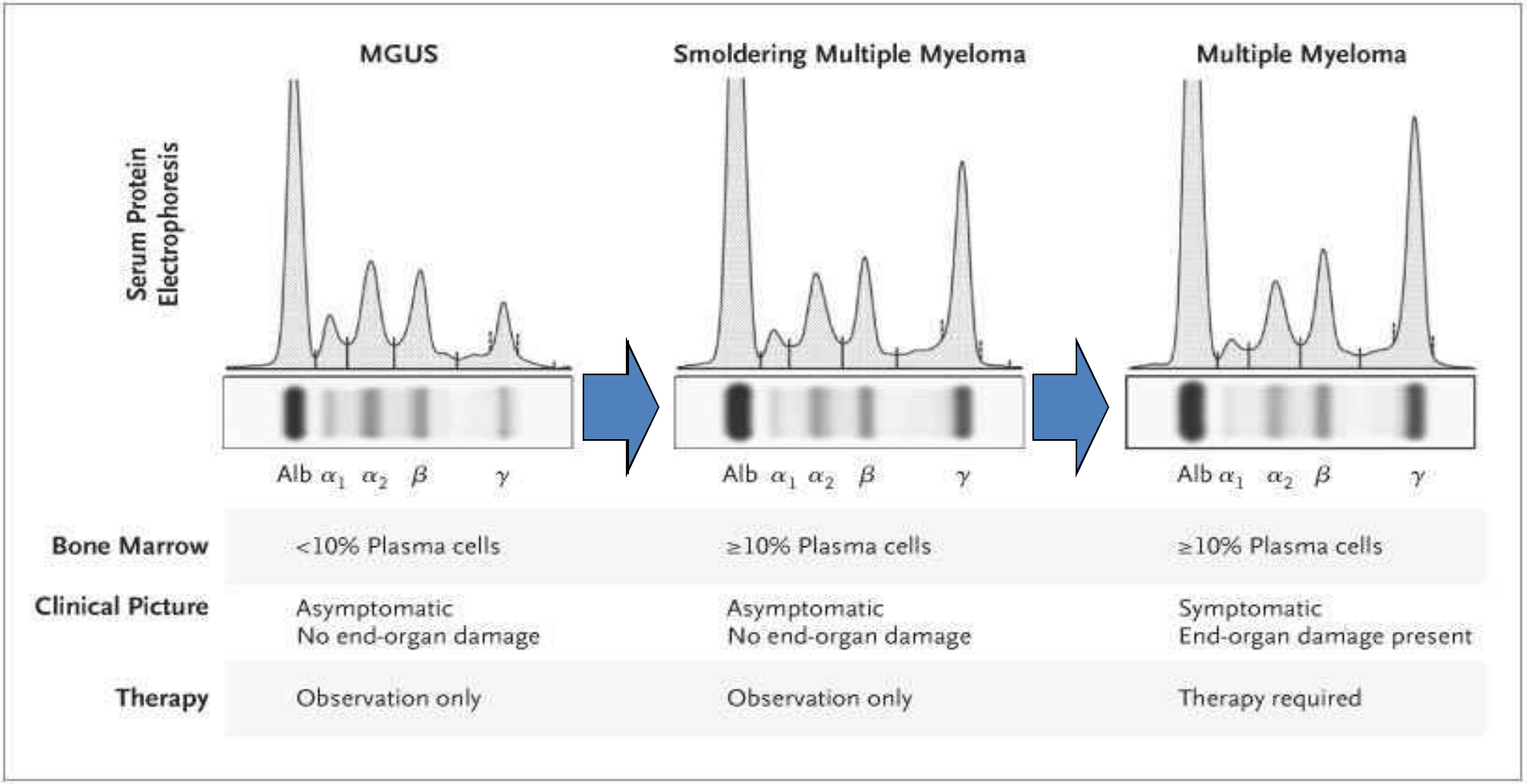
Natural History



Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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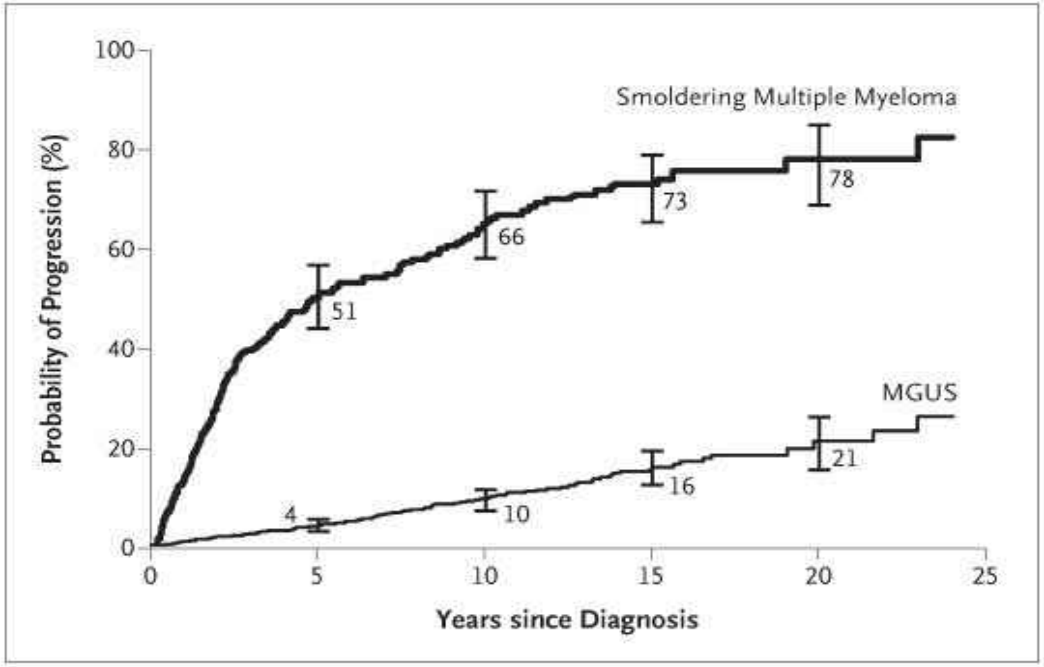
Progression to Symptomatic MM

- MGUS: up to 2 percent of persons 50 years of age or older and about 3 percent of those older than 70 years
- For SMM, maximum risk in the first 5 years
- Risk factors: Higher M spike, higher plasma cell burden, type of M protein, Abnormal free light chain ratio, circulating plasma cells



Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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Initial approach to myeloma

Diagnosis and determination of need for therapy

Risk stratification

Treatment

Diagnosis of Multiple Myeloma

- Clonal bone marrow plasma cells ≥ 10%
- Serum and/or urinary monoclonal protein and
- "End-organ Damage" or CRAB features
  - HyperCalcemia
  - Renal Insufficiency
  - Anemia
  - Bone Disease

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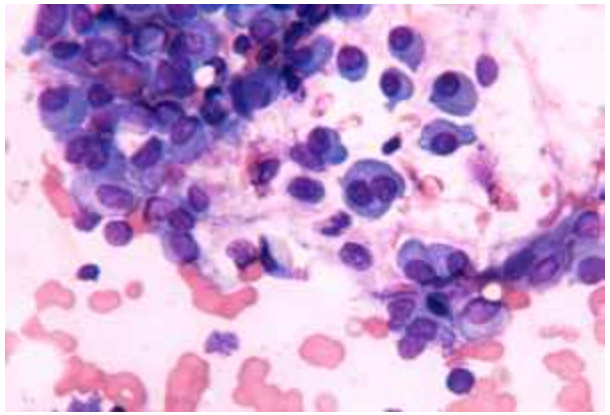
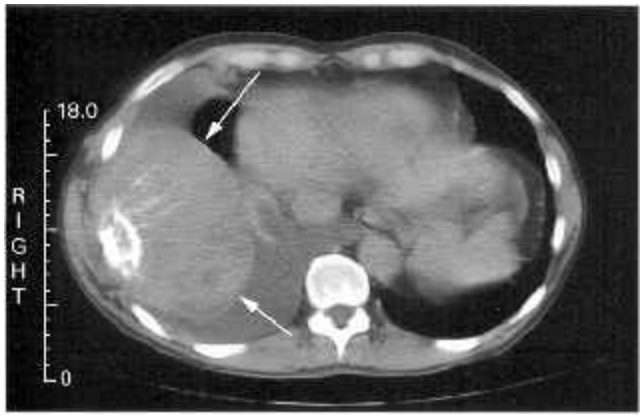
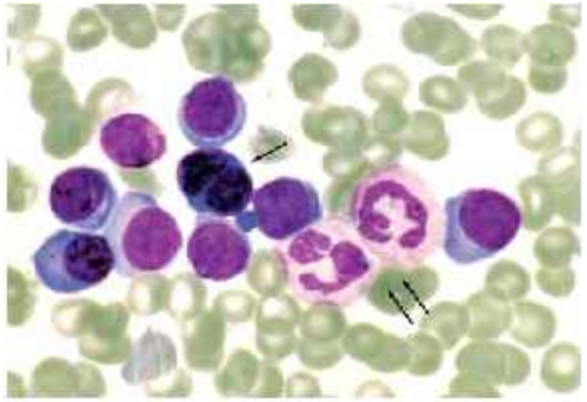
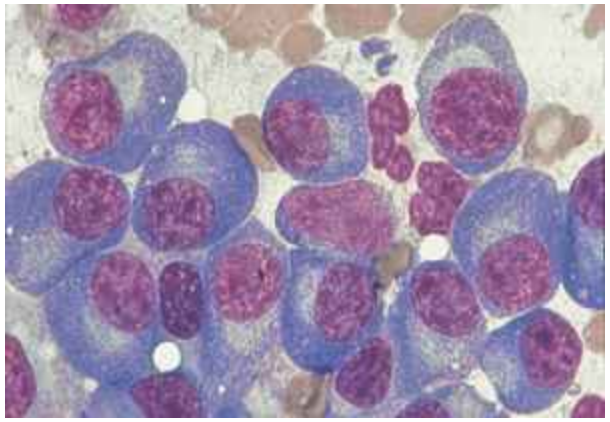
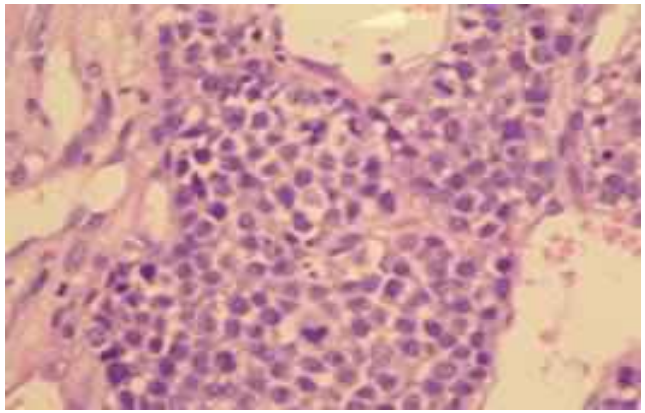
Detection of Clonal Plasma Cells

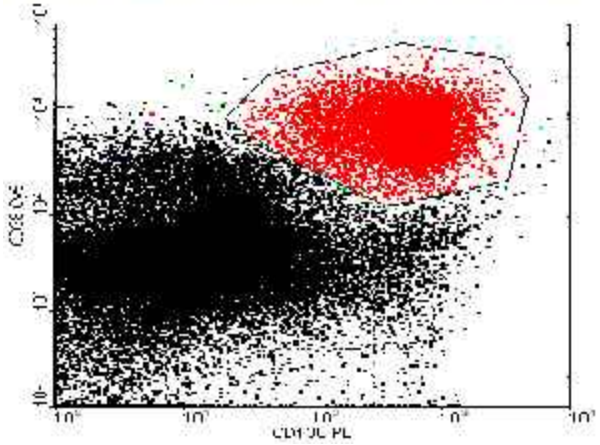












Bone marrow Plasmacytoma Peripheral blood

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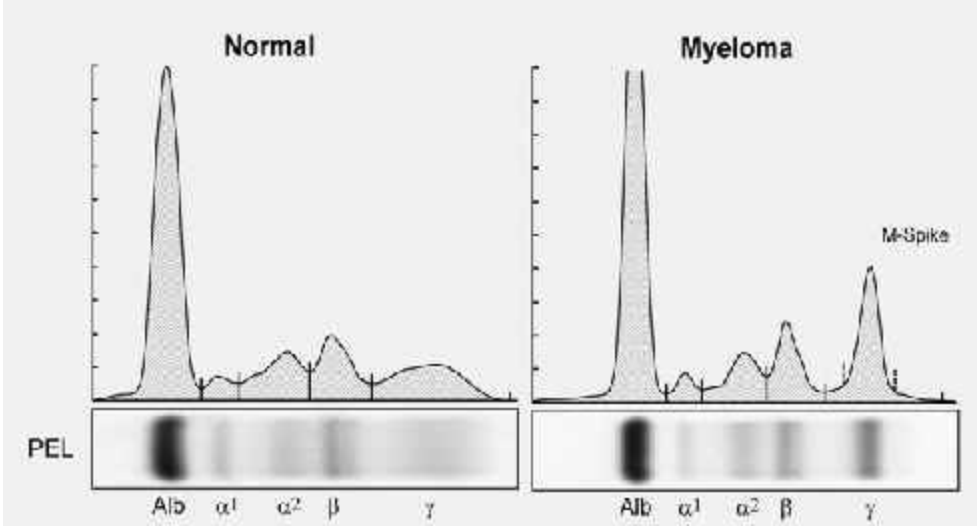
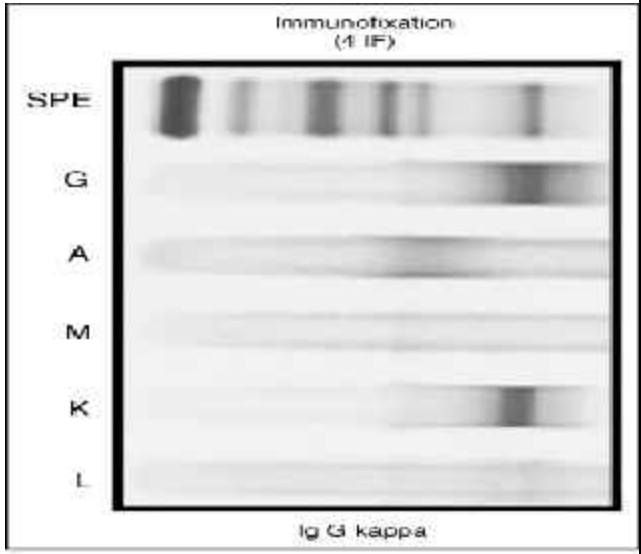
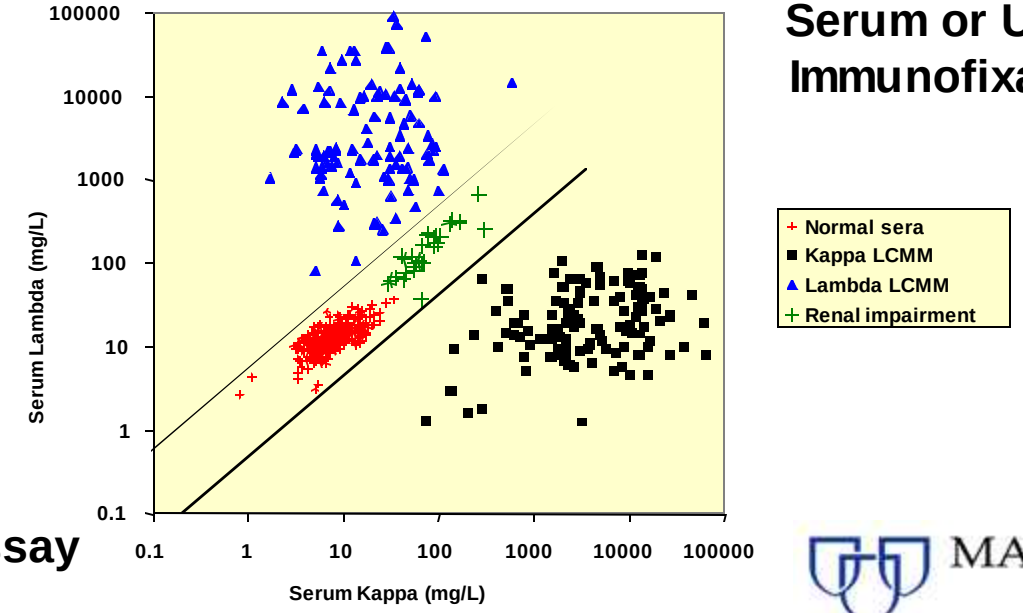
Demonstrating Monoclonal Protein



Serum or Urine Protein Electrophoresis



Serum or Urine Immunofixation



Serum Free Light Chain Assay

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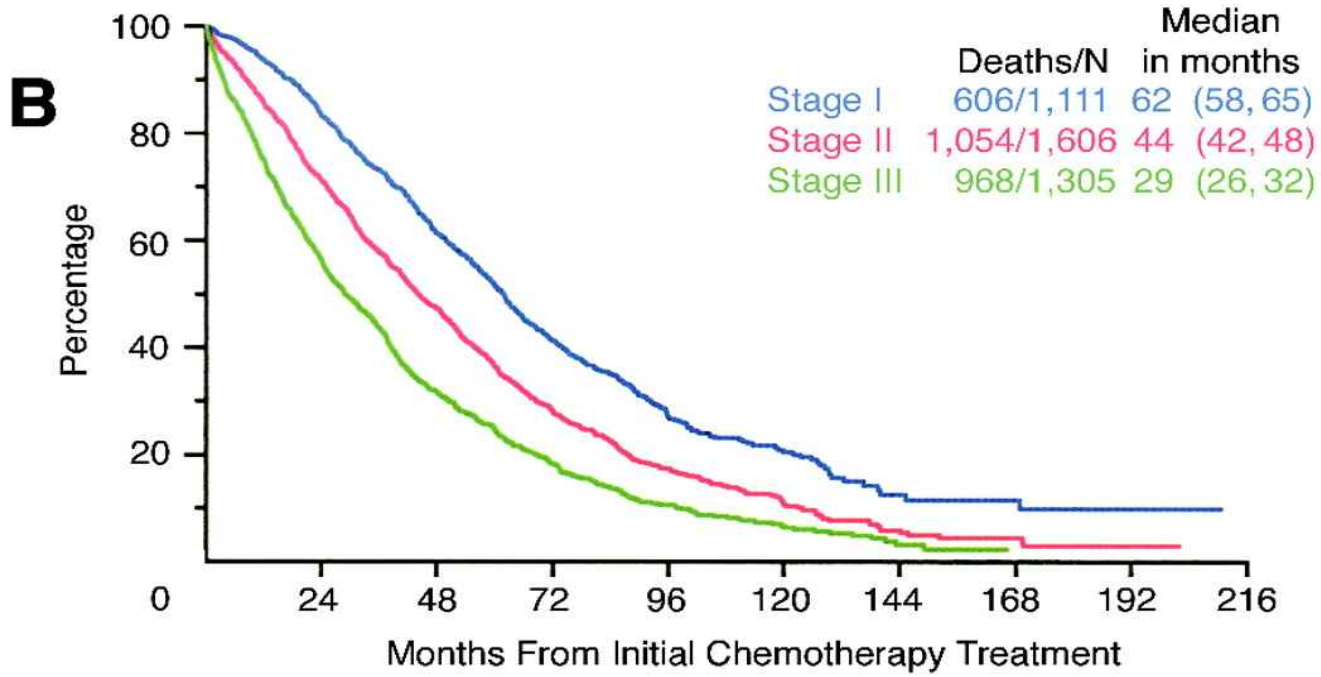
Risk assessment : Prognostic factors

- International Staging System Stage
- Cytogenetic Abnormalities
  - Deletion 13, hypodiploidy
  - (FISH) t(4;14), t(14;16), or del(17p)
- Gene expression signatures
- Plasma cell labeling index
- Poor performance status
- Abnormal free light chain ratio
- Circulating myeloma cells, Plasmablastic morphology
- High LDH, CRP levels

International Staging System (ISS)



Stage	Criteria	Median Survival (months)
I	Serum $ß_2$-microglobulin < 3.5 mg/L	62
	Serum albumin ≥ 3.5 g/dL	
II	Not stage I or III*	44
III	Serum $ß_2$-microglobulin ≥ 5.5 mg/L	29

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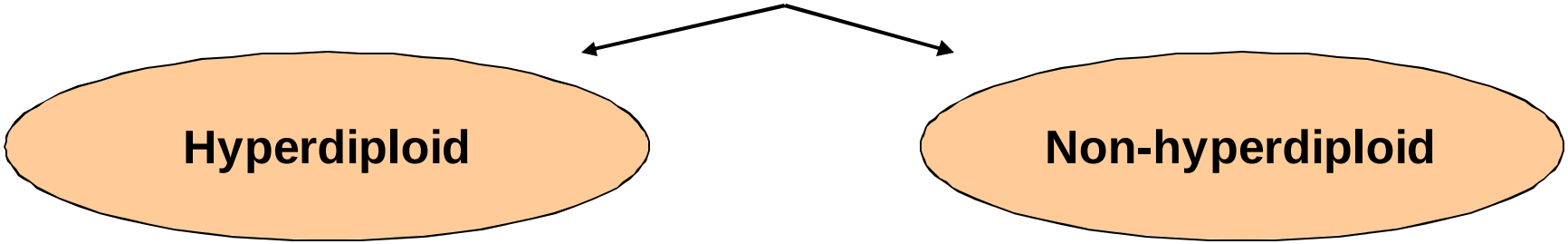
Greipp, P. R. et al. J Clin Oncol; 23:3412-3420 2005

Cytogenetic Abnormalities



Multiple trisomies

Chromosomes 3, 5, 7, 9, 11, 15, 19, and 21

Chromosome 13 abnormalities

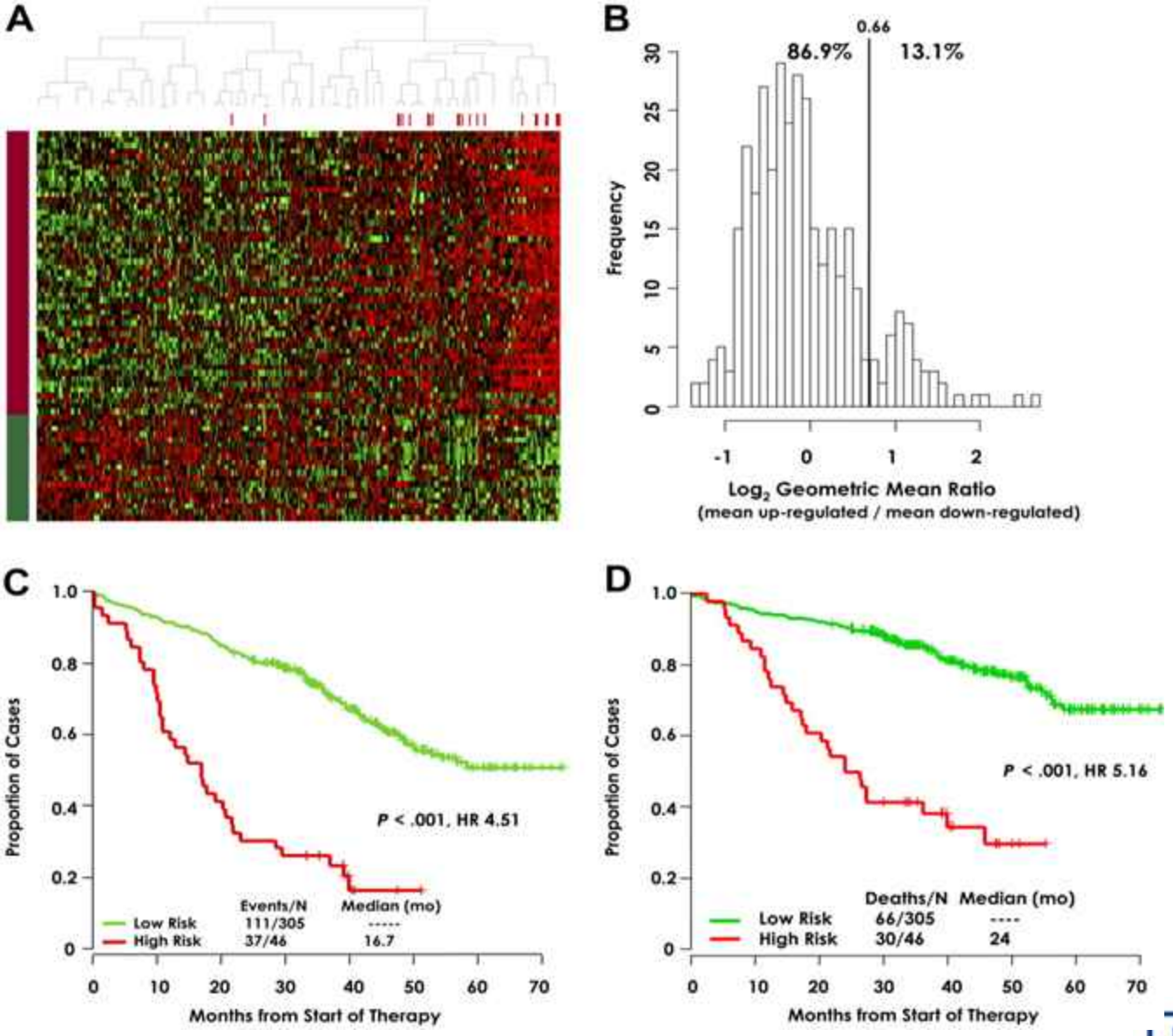
P53 mutations

Ras mutations

IgH (chr 14) translocations

1. *11q13* (*CCN D1*):16%
2. *6p21* (*CCN D3*):3%
3. *16q23* (*MAF*): 5%
4. 20q12 (*MAFB*): 2%
5. *4p16* (*FGFR3* and *MMSET*): 15%

GEP signatures



Shaughnessy et al, Blood2007, 109(6), 2276-2284

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mSMART 2.0: Classification of Active MM

High-Risk

- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk*

- FISH
  - t(4;14)‡
- Cytogenetic Deletion 13 or hypodiploidy
- PCLI ≥3%

Standard-Risk*†

All others including:

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

* Note that a subset of patients with these factors will be classified as high-risk by GEP
† LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis
‡ Prognosis is worse when associated with high beta-2 M and anemia
**t(11;14) may be associated with plasma cell leukemia

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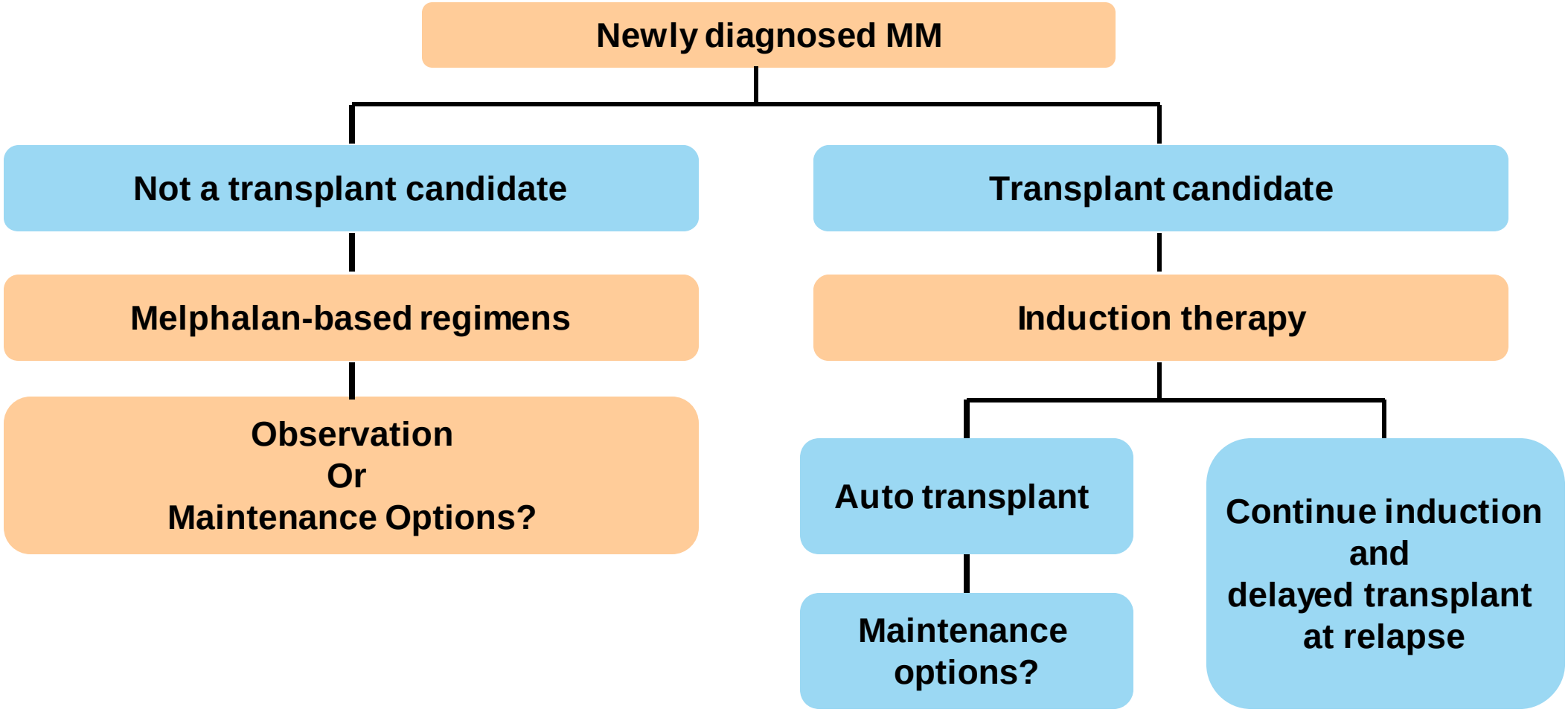
General approach to treatment



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Initial Therapy

The ideal initial therapy should:

- Rapidly and effectively control disease
- Reverse disease related complications
- Decrease the risk of early death
- Be easily tolerated with minimal/manageable toxicity
- Not interfere with the ability to collect stem cells for transplantation

The tools.....

The old

- Dexamethasone
- VAD
  - Vincristine
  - Adriamycin
  - dexamethasone

The New

- Thalidomide
- Lenalidomide
- Bortezomib

Thalidomide combinations vs VAD

	TD vs VAD[1]	TD vs VAD[2]	TAD vs VAD[3]	CTD vs CVAD[4]
	4 months	4 months	3 cycles	NA
Patients, n	200	204	402	251
Response before ASCT, %				
CR	10 vs 8	12.5	4 vs 2	20 vs 12
> VGPR	19 vs 14	35 vs 13	33 vs 15	38 vs 26
> PR	76 vs 52	–	72 vs 54	96 vs 83
Response after ASCT, %				
CR	–	–	16 vs 11	58 vs 41
> VGPR	–	44 vs 42	49 vs 32	67 vs 43
> PR	–	–	79 vs 76	99 vs 96
Deep-vein thrombosis	15 vs 2	23 vs 7.5	8 vs 4	NA

ASCT = autologous SCT; CTD = cyclophosphamide + thalidomide + dexamethasone; CVAD = cyclophosphamide + VAD; TAD = thalidomide + doxorubicin + dexamethasone; TD = thalidomide + dexamethasone.

1. Cavo M, et al. Blood. 2005;106:35-39. 2. Macro M, et al. Blood. 2006;108:[abstract 57].
3. Lokhorst HM, et al. Haematologica. 2008;93:124-7. 4. Morgan GJ, et al. Blood. 2007;110:[abstract 3593].

IFM 2005-01: bortezomib + dexamethasone vs VAD

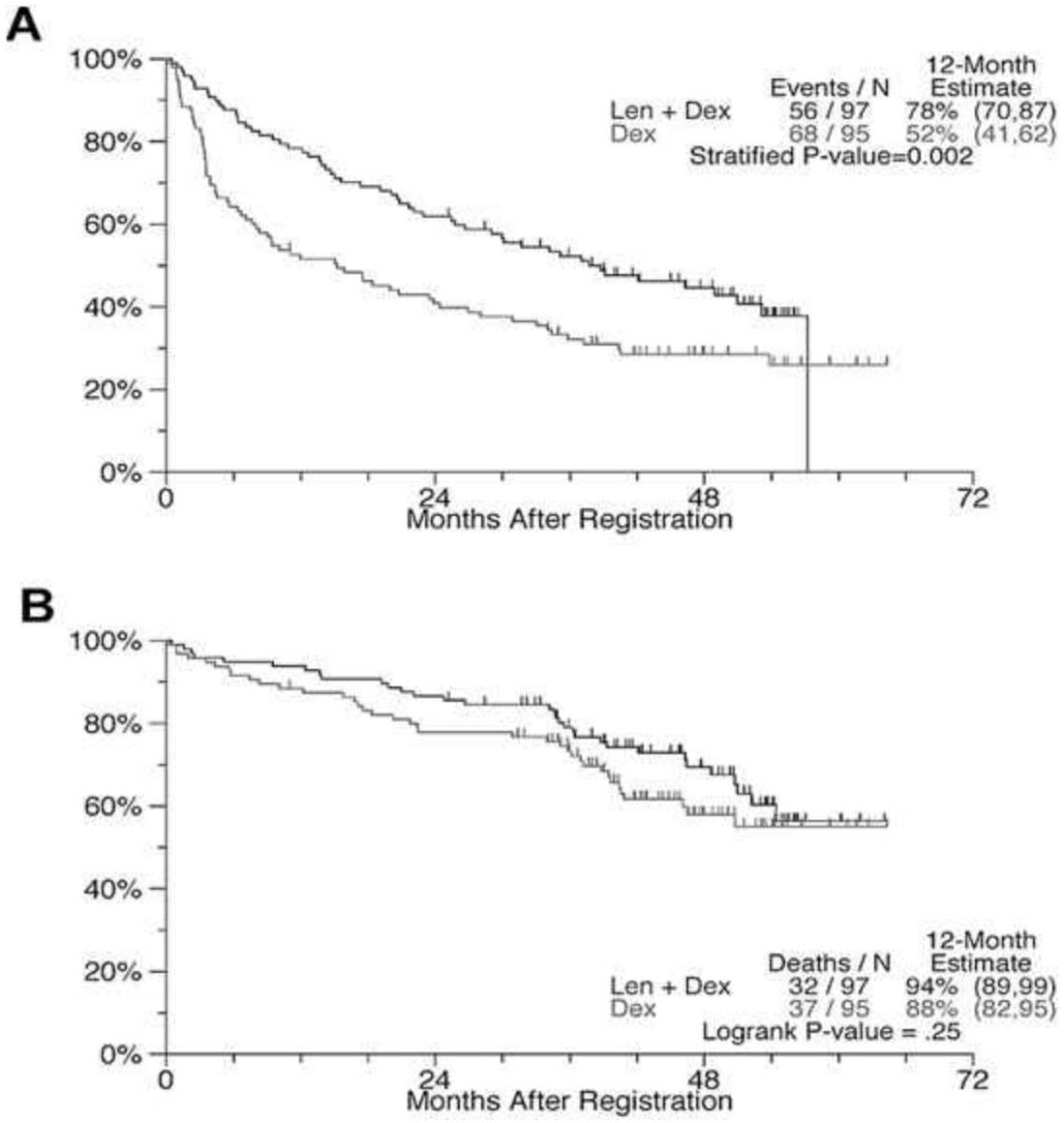
Response	VAD		Bortezomib + Dex	
	Post induction, %	Final, %*	Post induction, %	Final, %*
CR	1	NR	6	NR
CR + nCR	7	32	15	39
≥ VGPR	16	47	39	68
≥ PR	65	NR	82	NR

*Best response, including second ASCT.

NR = not reported.

Harousseau JL, et al. Presented at ASH/ASCO symposium, ASH 2008.

Len-Dex vs. Dex



- Increased response rates with Len-Dex compared to Dex

Zonder et al, Blood. 2010 Dec 23;116(26):5838-41

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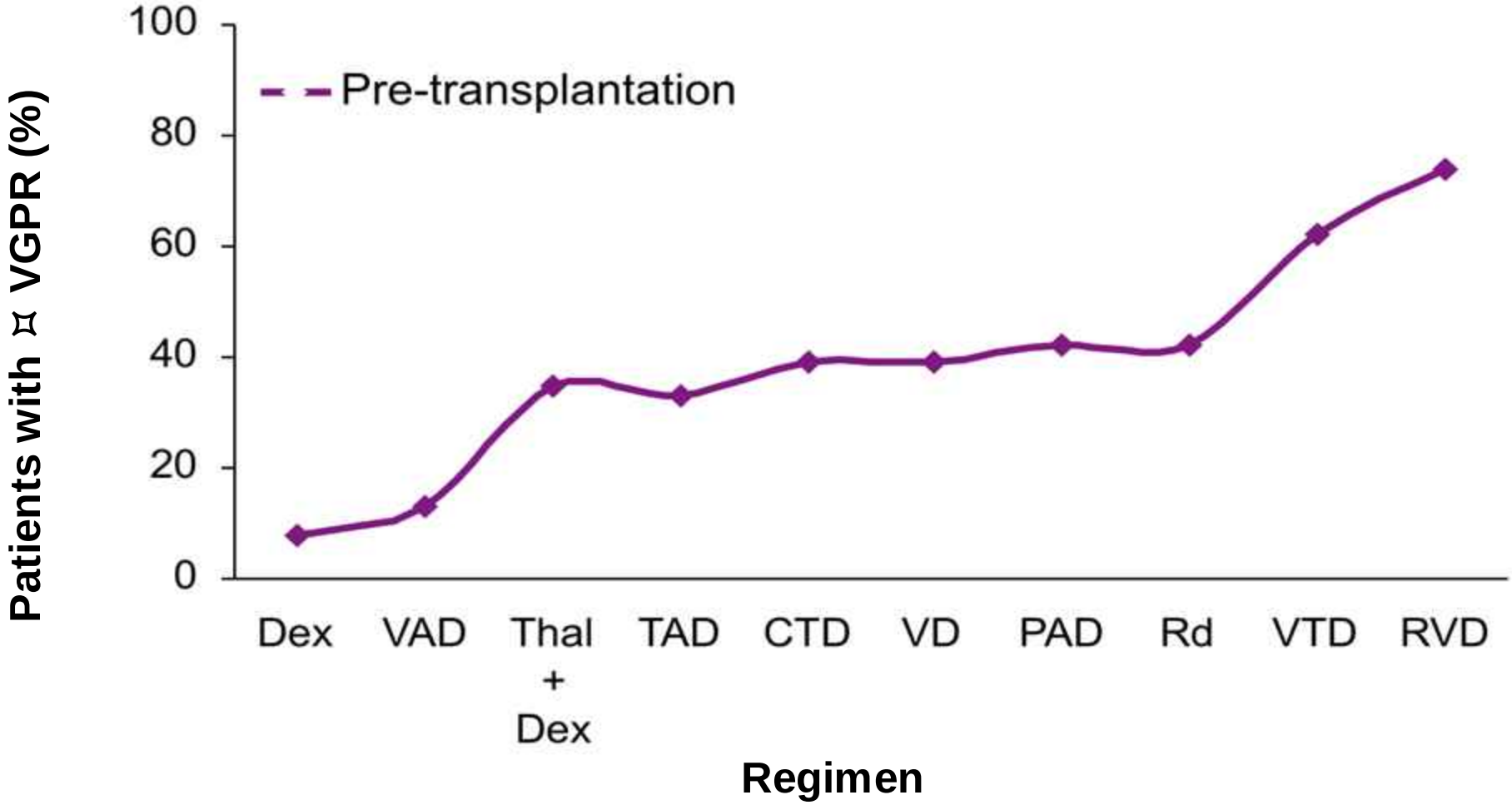
Three and four drug combinations

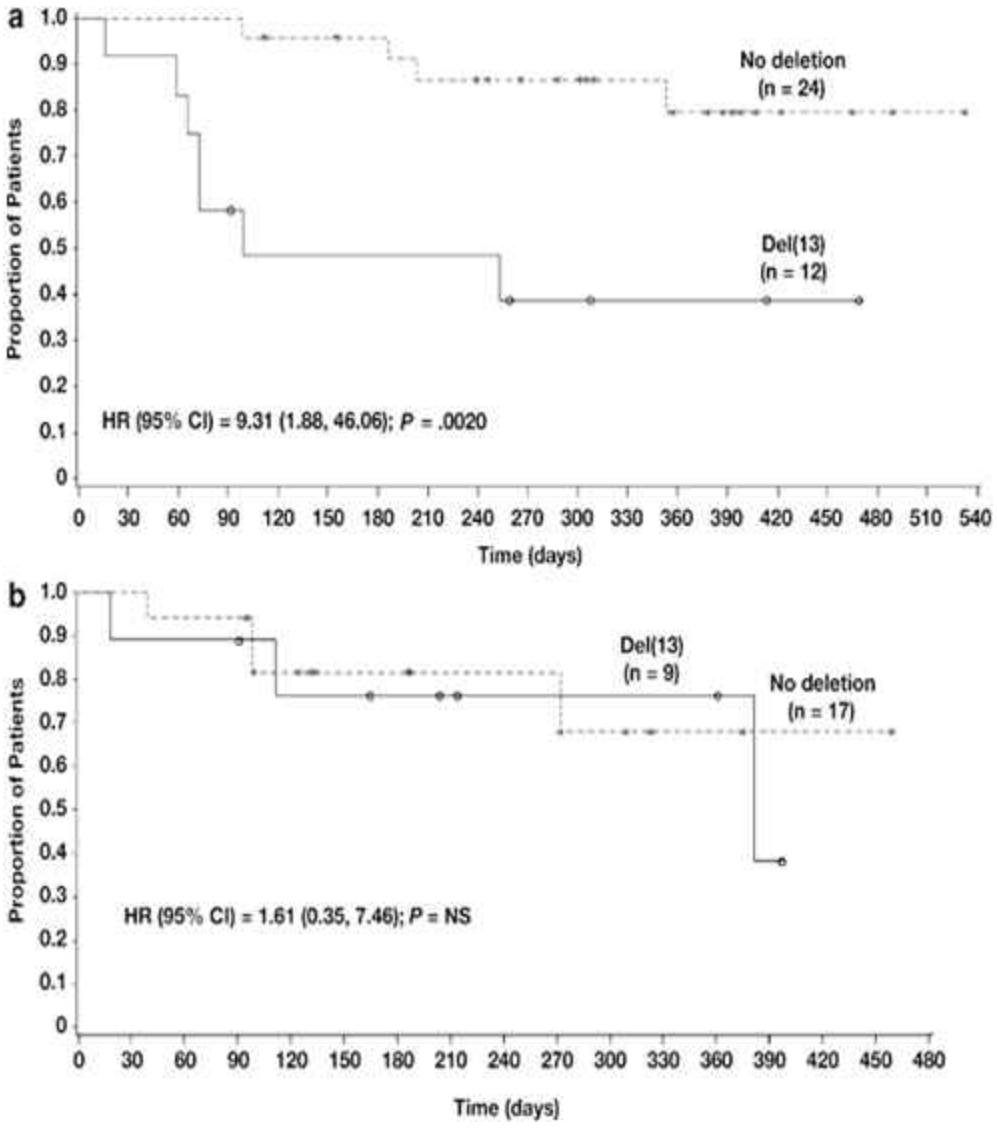
- Bortezomib + thalidomide + dex
- Bortezomib + lenalidomide + dex
- Cyclophosphamide + bortezomib + dex
- Cyclophosphamide + lenalidomide + dex
- Lenalidomide + adriamycin + dex
- CTX + bortezomib +doxil + dex
- CTX + bortezomib + lenalidomide + dex

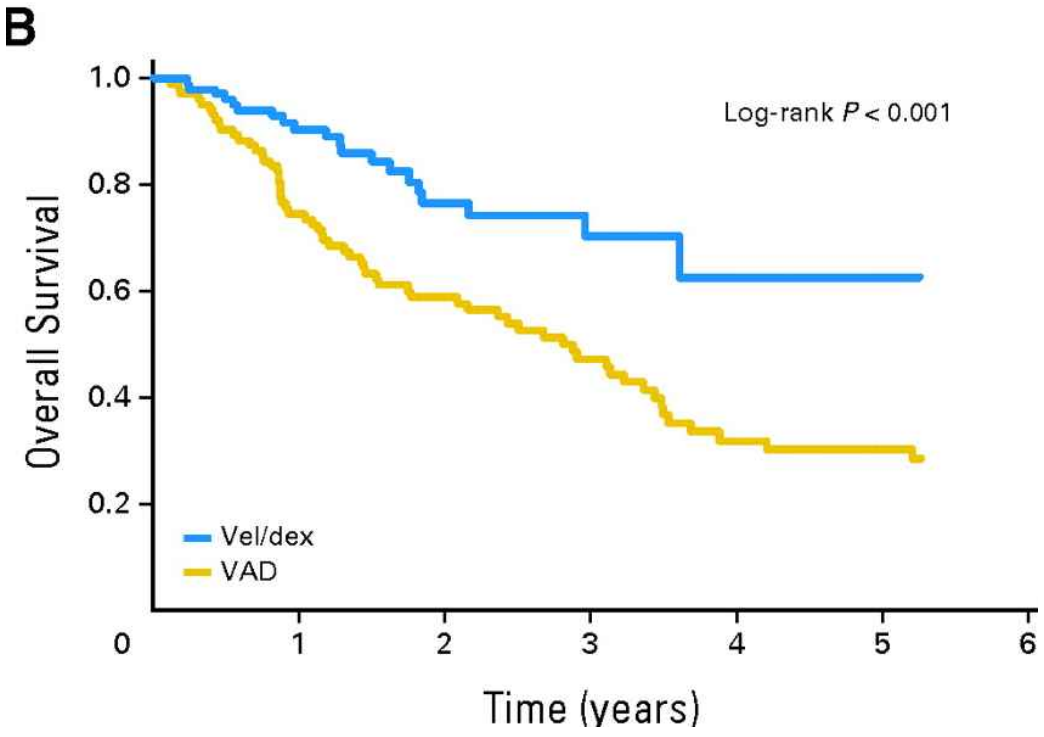
Efficacy improvements with novel induction regimens



Cavo M, et al. Blood. 2008;112:[abstract 158]. Harousseau J-L, et al. ASH/ASCO symposium at ASH, 2008. Lokhorst HM, et al. Haematologica. 2008;93:1247. Macro M, et al. Blood. 2006;108:[abstract 57]; updated data from ASH 2006. Morgan G, et al. Blood. 2007;110:[abstract 3593]; updated data from ASH 2007. Rajkumar SV, et al. ASH/ASCO symposium at ASH 2008. Richardson P, et al. Blood. 2008;112:[abstract 92]. Sonneveld P, et al. Blood. 2008;112:[abstract 653].

Bortezomib and high risk disease





Jagannath et al, Leukemia 2006; Avet-Loiseau H et al. JCO 2010;28:4630-4634

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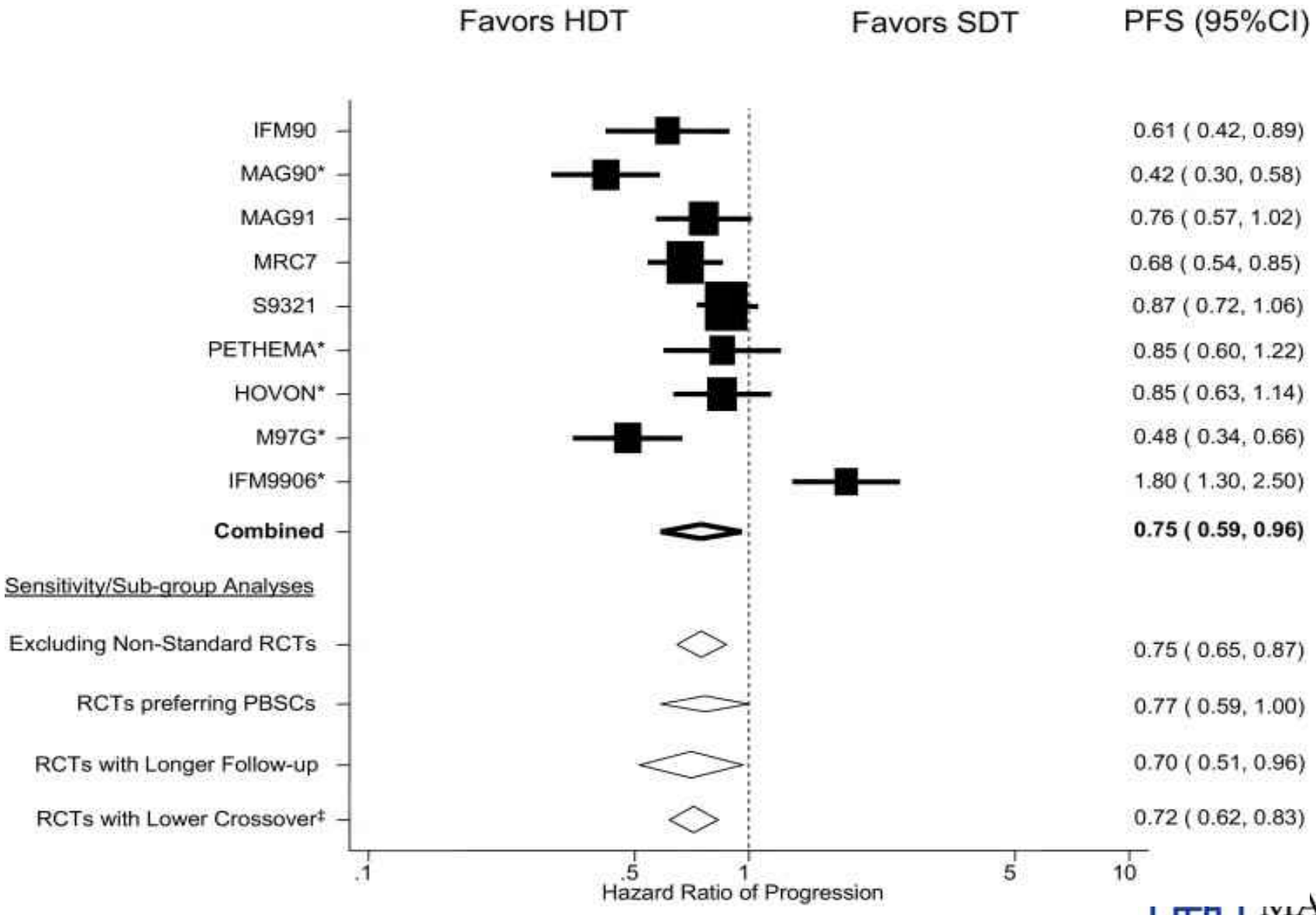
Consolidation:

To transplant or not?

Progression free survival: Meta-analysis



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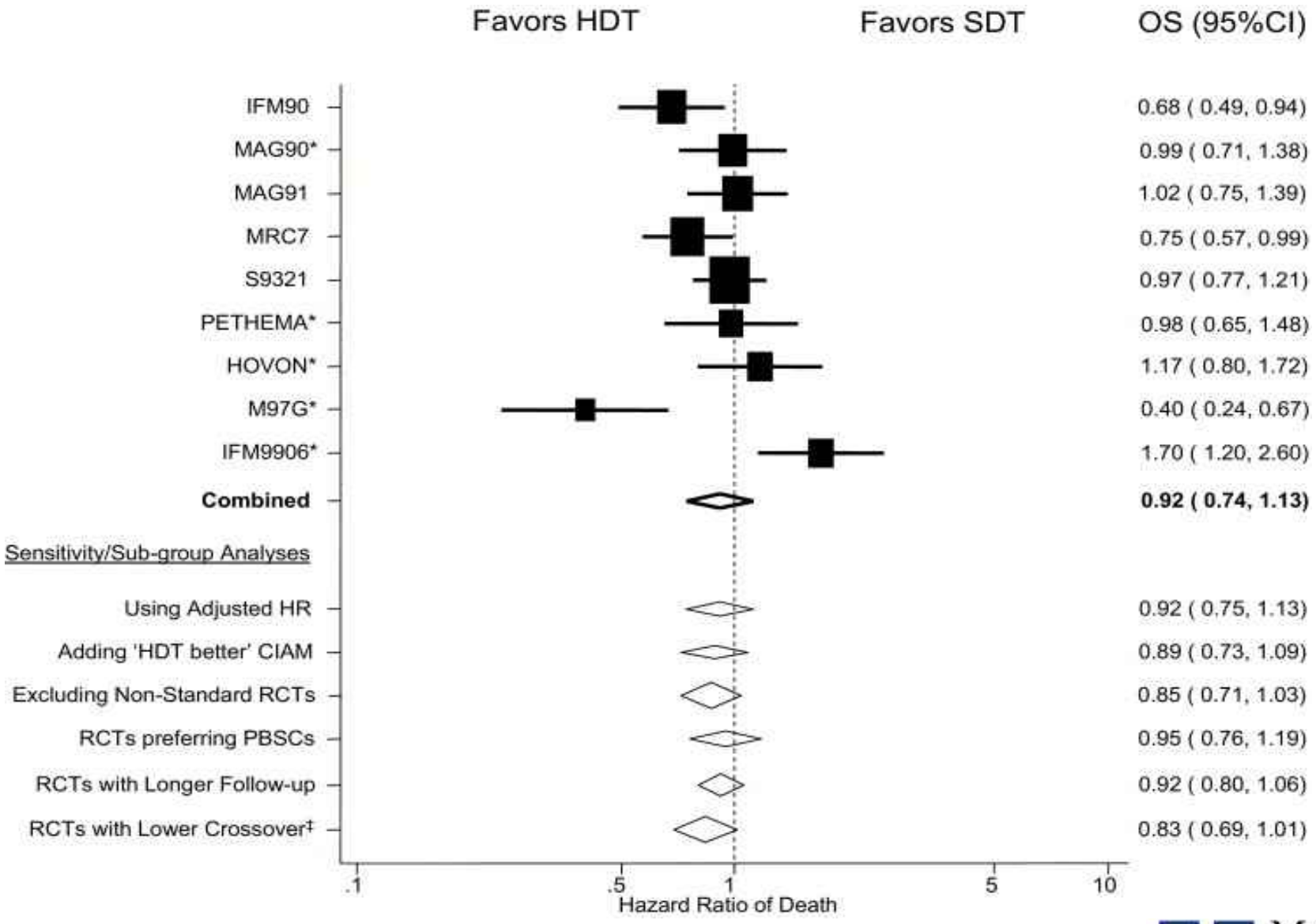
Koreth et al; Biology of Blood and Marrow Transplantation 13:183-196 (2007)

Overall survival: Meta-analysis



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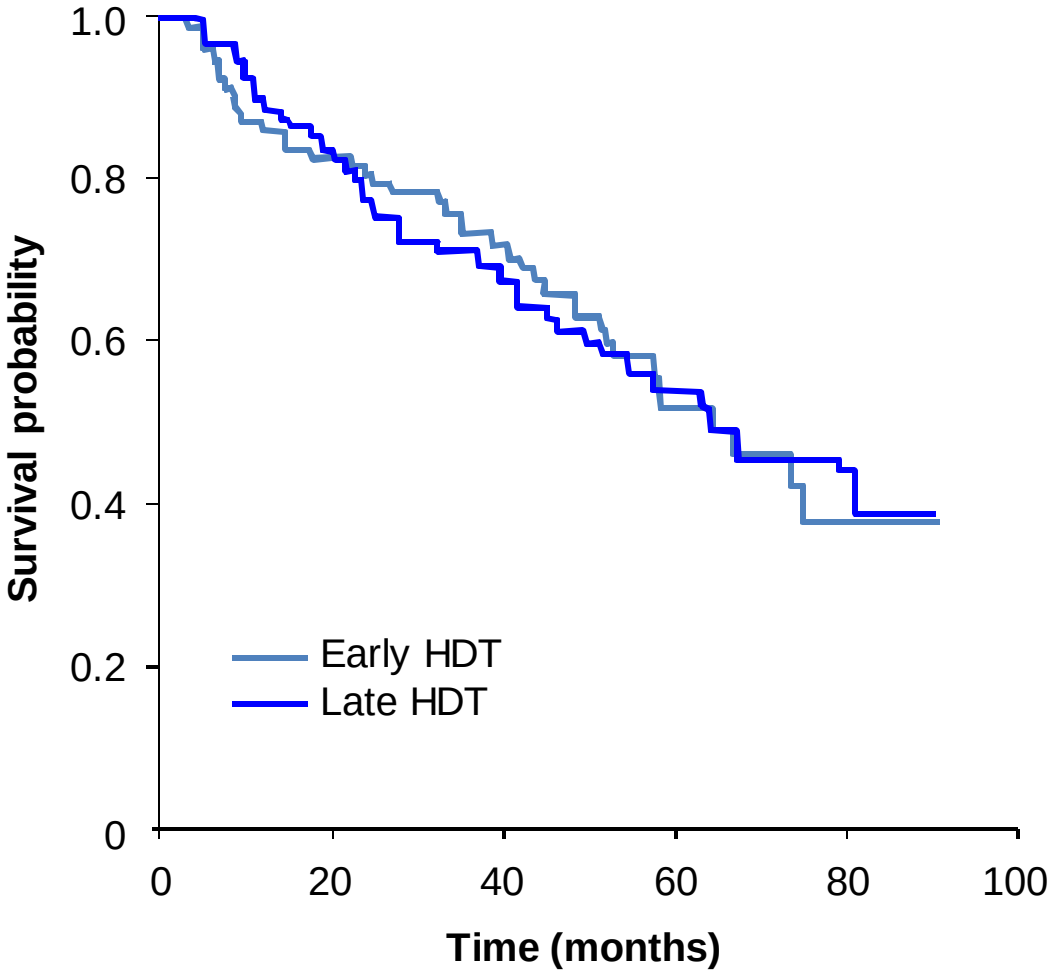
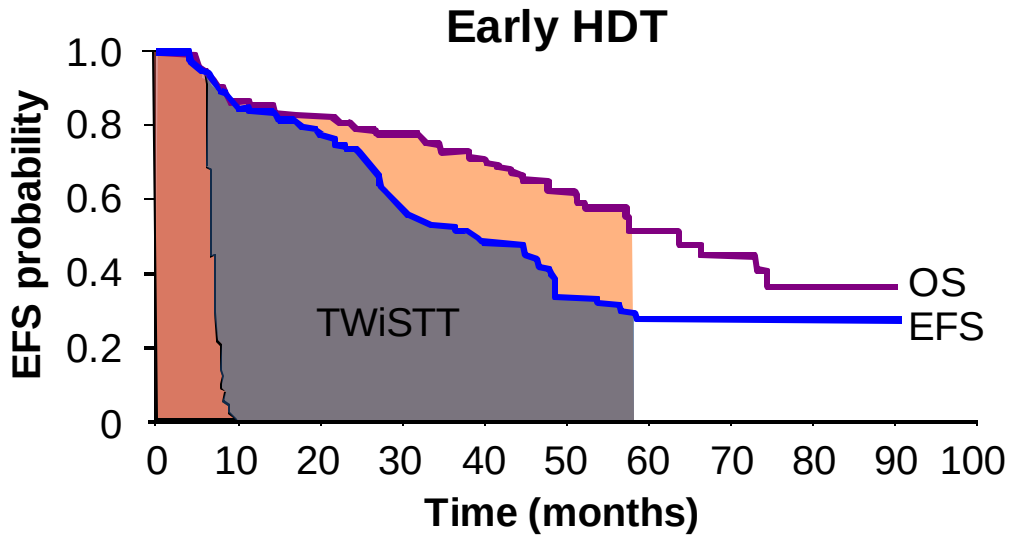
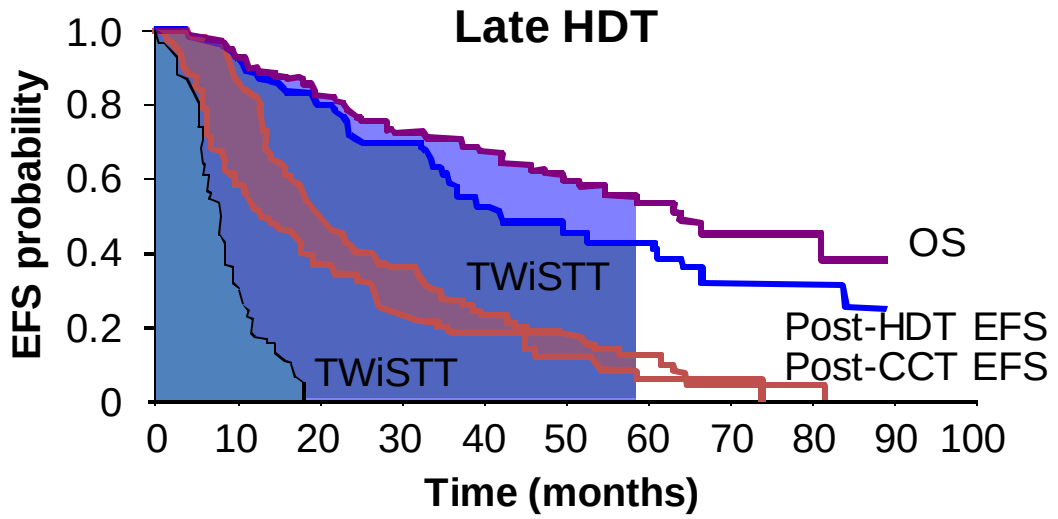
Koreth et al; Biology of Blood and Marrow Transplantation 13:183-196 (2007)

HDT and ASCT in MM patients < 55 years old: up-front or rescue treatment







HDT = high-dose therapy; TWiSTT = time without symptoms, treatment, or treatment toxicity.

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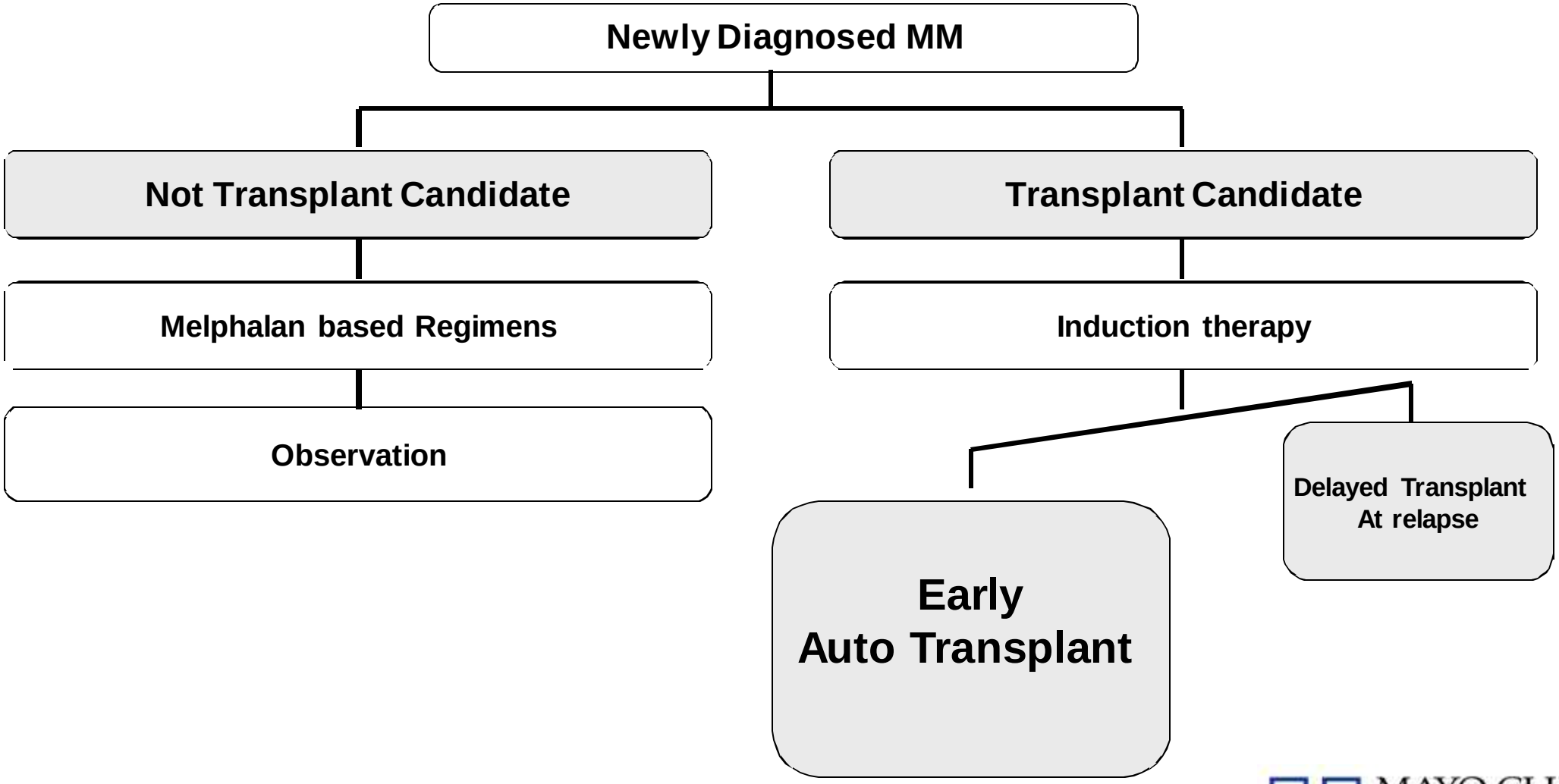
Fermand J-P, et al. Blood. 1998;92:3131-6.

Approach to Treatment



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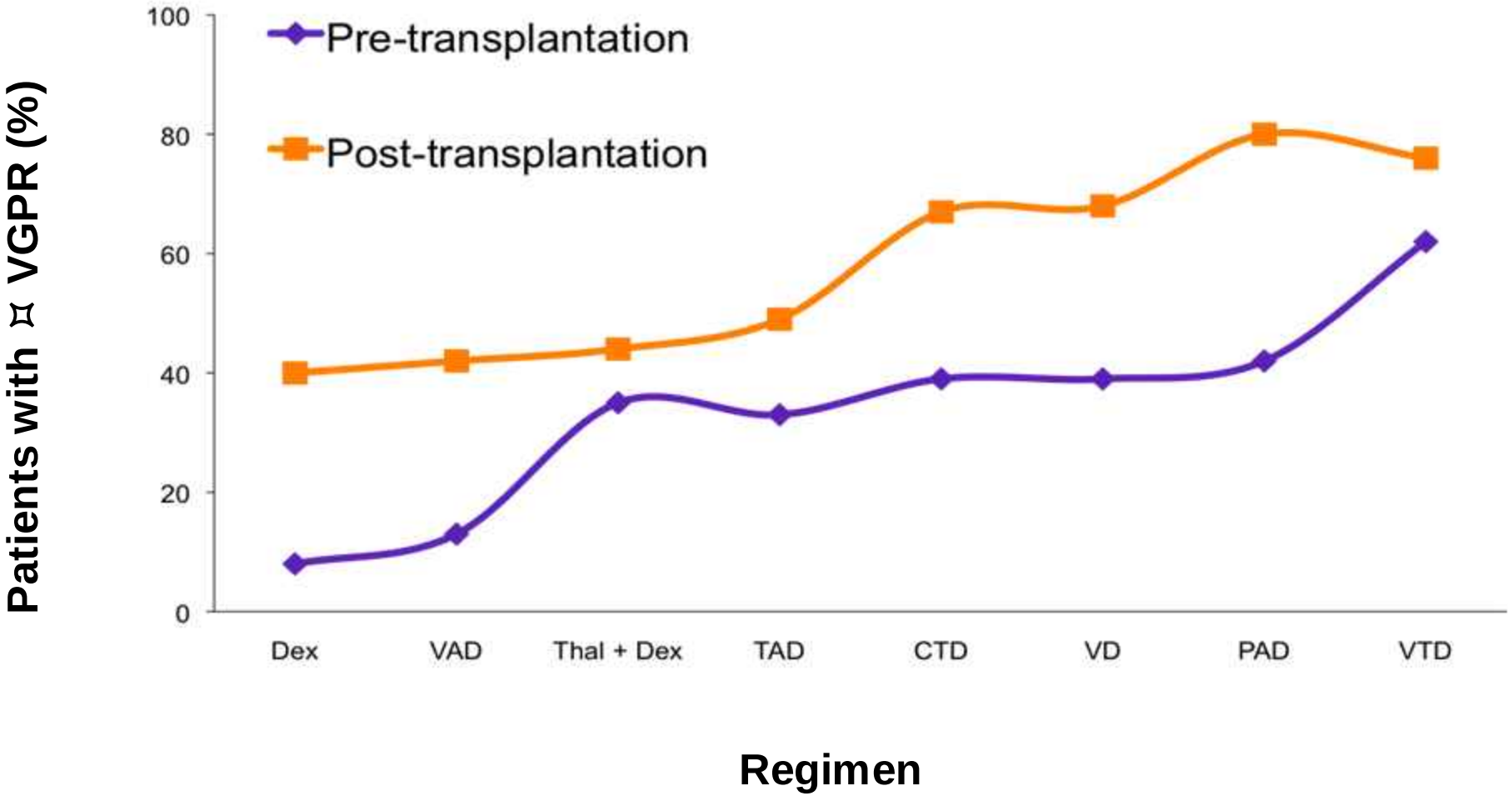
Does transplantation add anything?



Cavo M, et al. Blood. 2008;112:[abstract 158]; updated data presented at ASH 2008. Harousseau J-L, et al. ASH/ASCO symposium at ASH 2008. Lokhorst HM,et al. Haematologica 2008;93:124-7. Macro M, et al. Blood. 2006;108:[abstract 57]; updated data from ASH 2006. Morgan G, et al. Blood. 2007;110:[abstract 3593]; updated data from ASH 2007. Sonneveld P, et al. Blood. 2008;112:[abstract 653]; updated data from ASH 2008.

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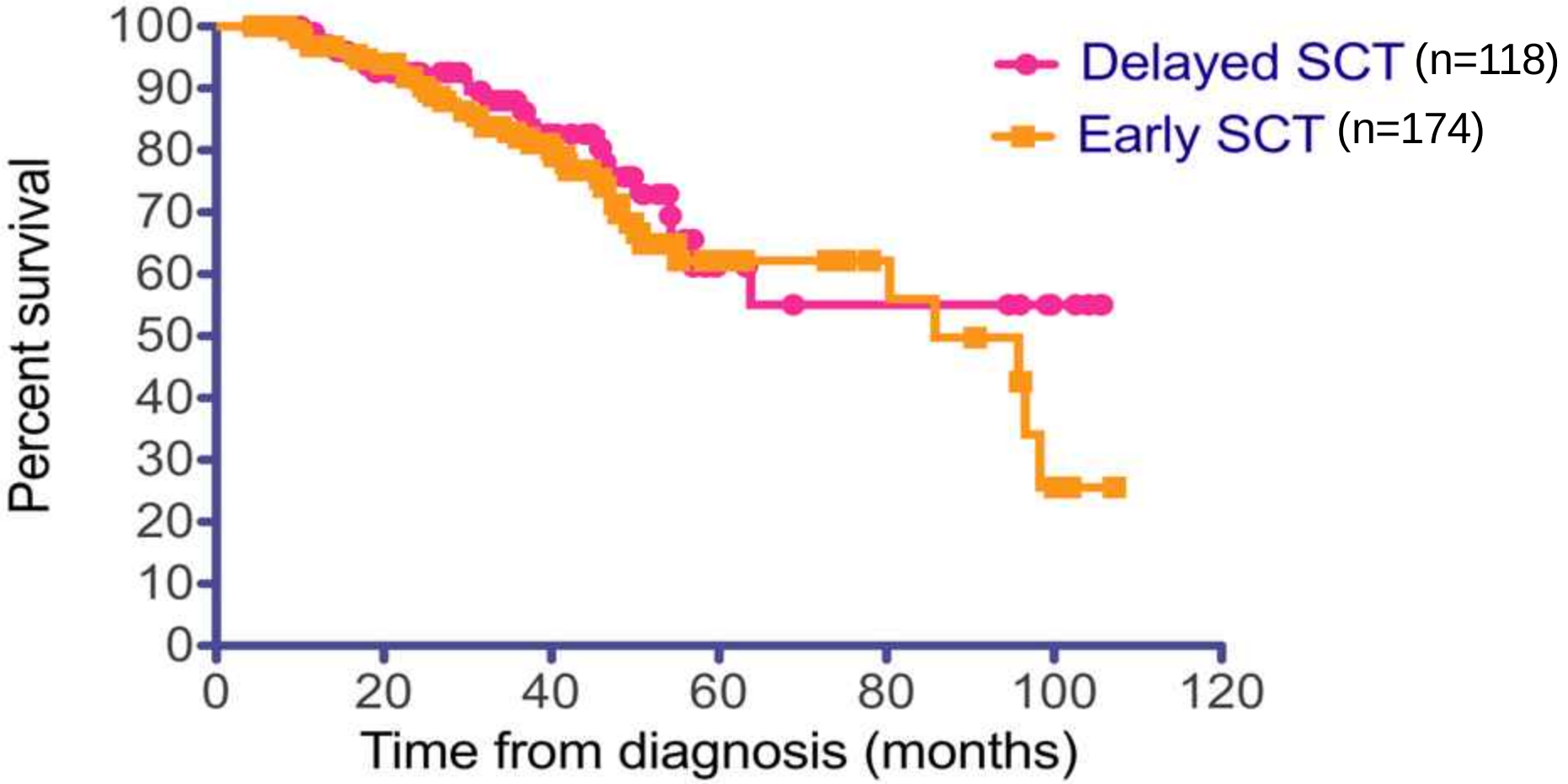
Overall survival from diagnosis



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

Kumar et al; Cancer 2011

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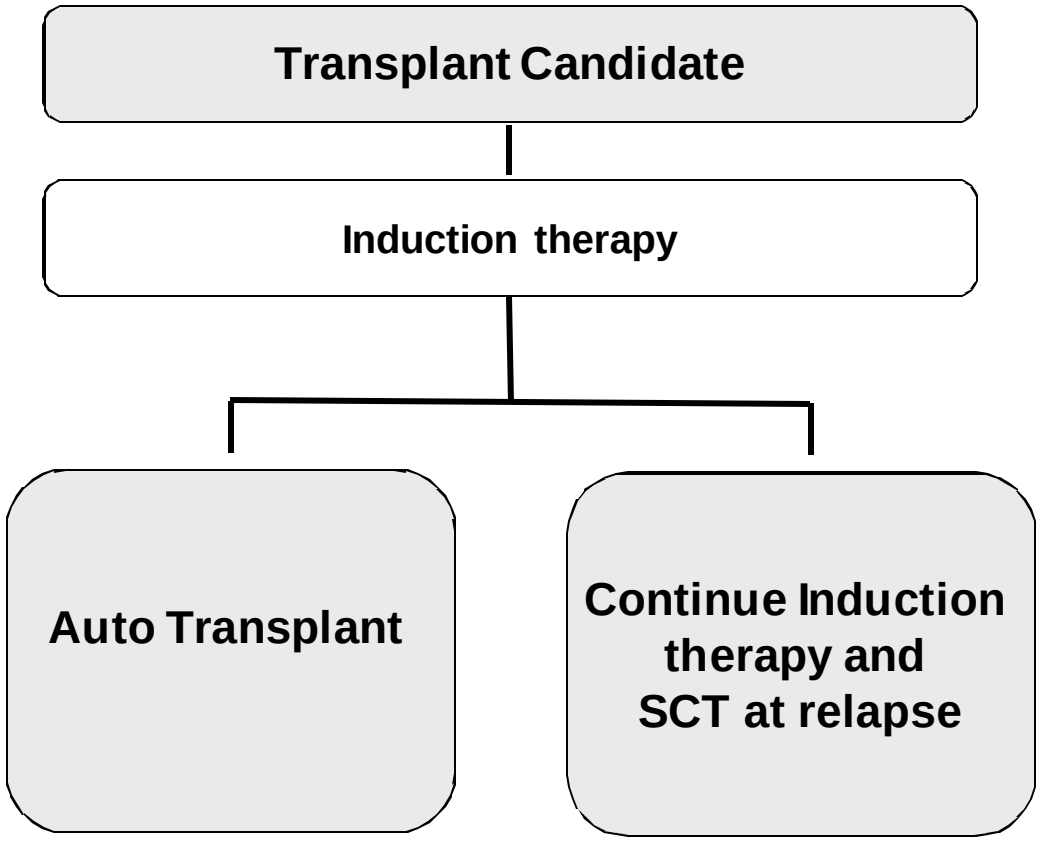
So early Novel Agent and delayed HDT?

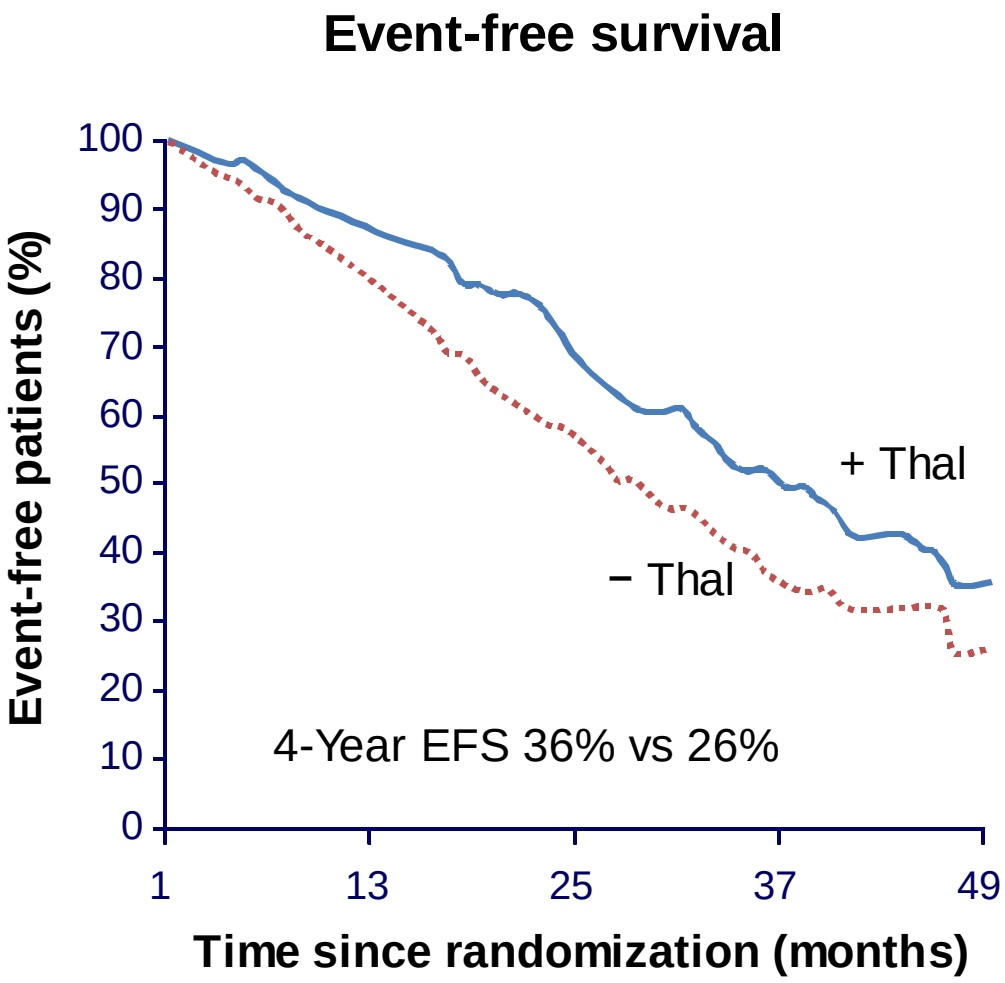
- Potential advantages of early HDT in alkylator era
  - No prolonged alkylator exposure: Not an issue with novel agents
  - Better quality of life/ TwiSST : Novel agents well tolerated
  - The use of tandem HDT: novel agent consolidation can replace second HDT

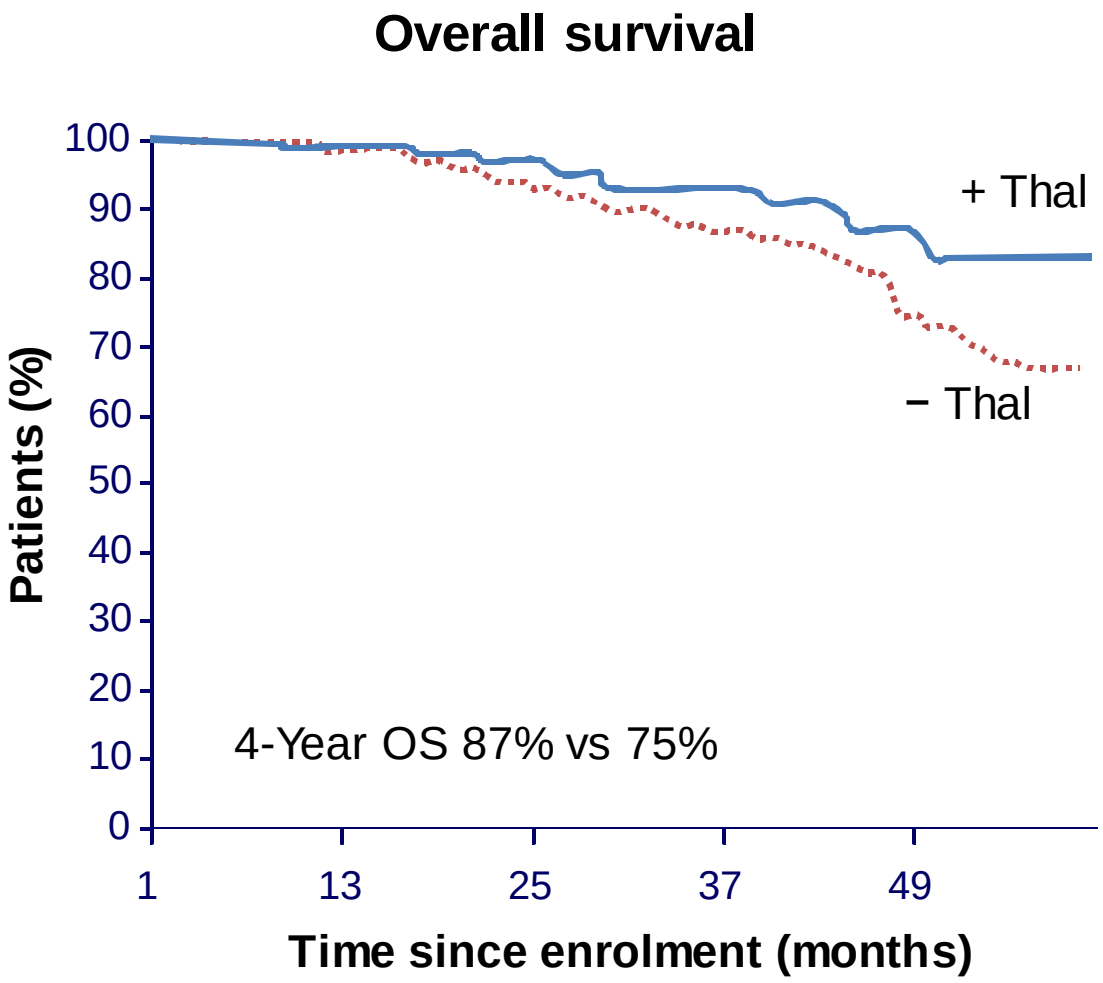


Post SCT Maintenance

- Early studies looked at Interferon or steroids
- Large randomized trials have looked at newer drugs as post SCT maintenance
- Recently concluded trial looked at Lenalidomide maintenance

Thalidomide maintenance: IFM 99-02





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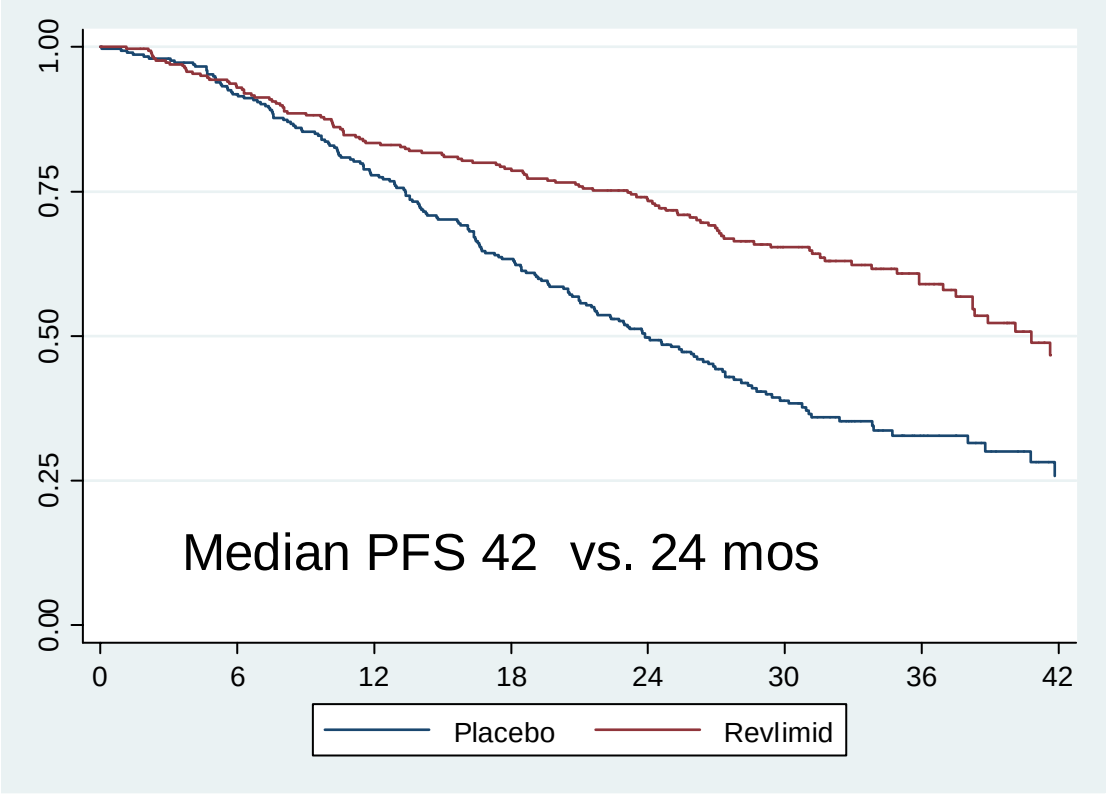
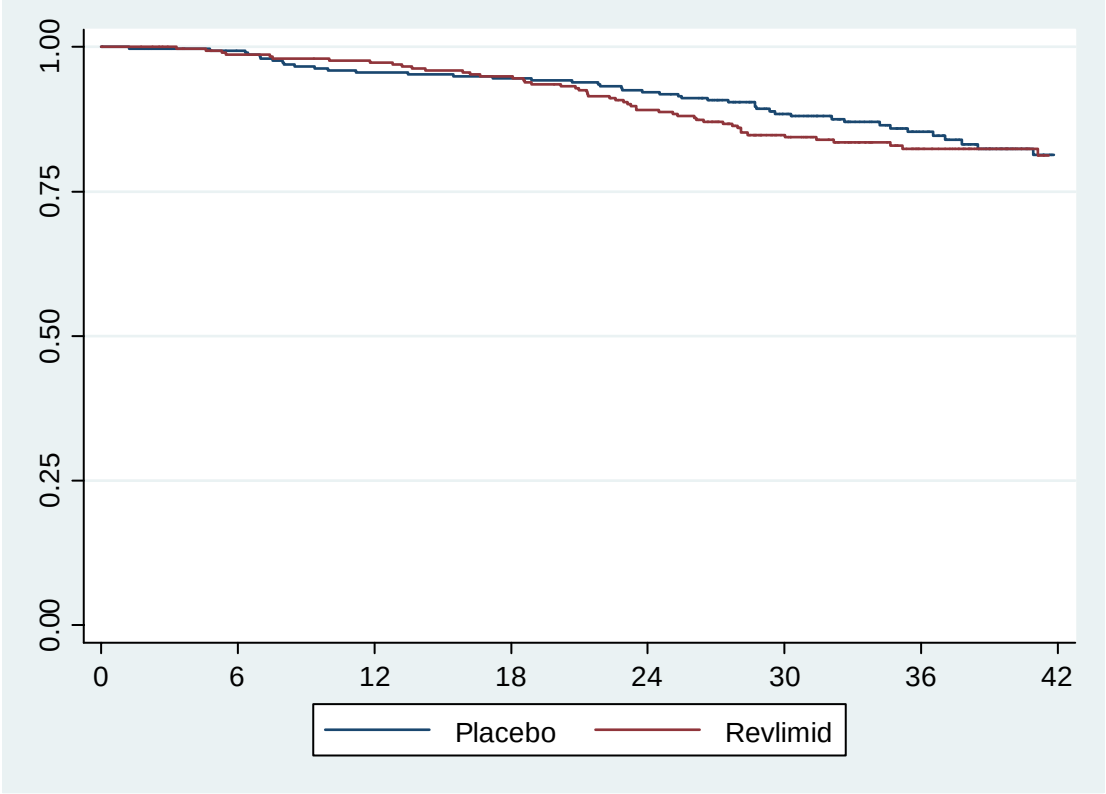
Attal M, et al. Blood. 2006;108:3289-94.

IFM-2005-02: Survival outcomes



PFS



OS

Attal et al; ASH 2010, Abstract #310

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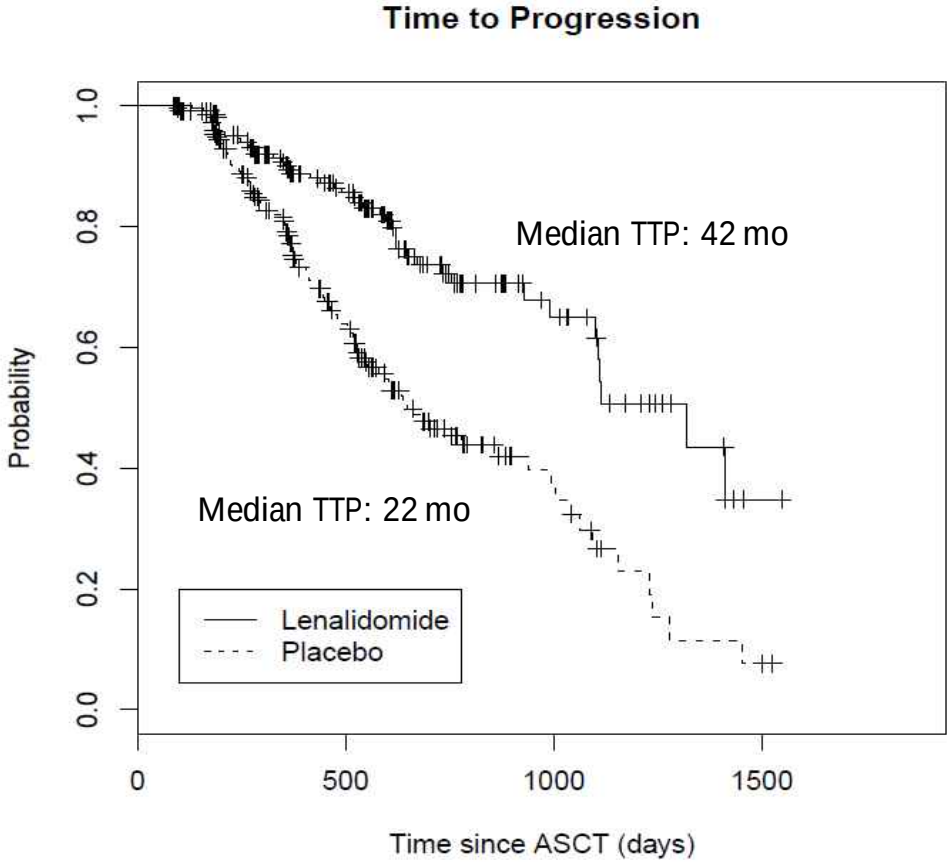
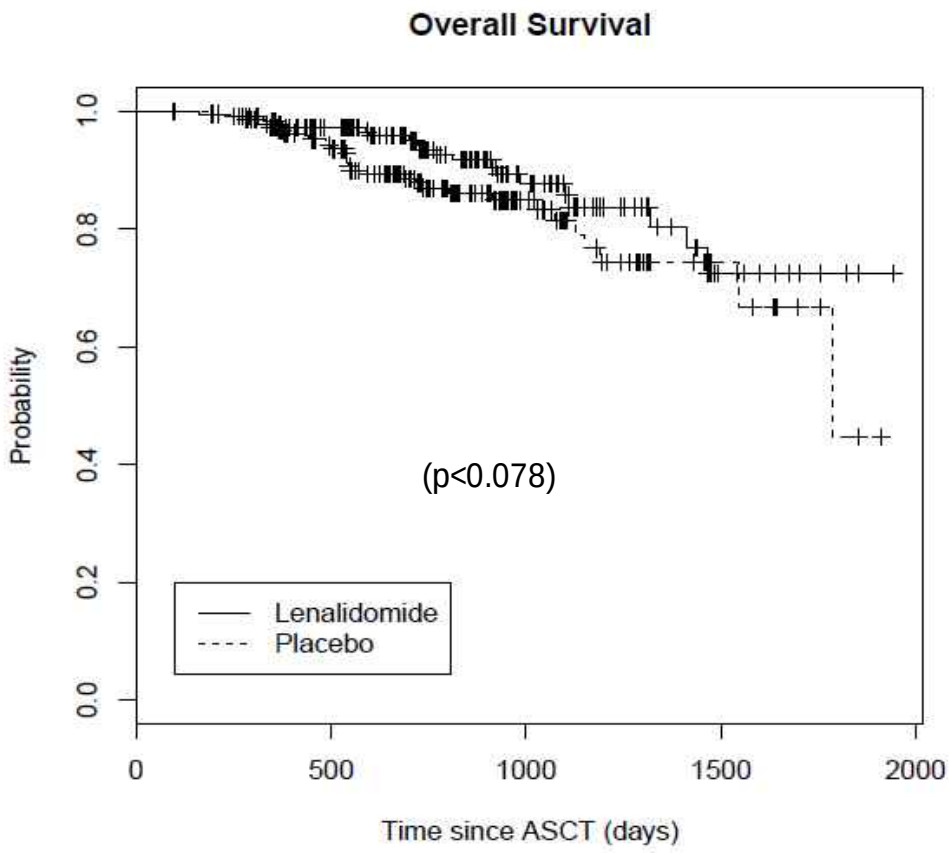
CALGB 100104: Survival Outcomes





McCarthy et al; ASH 2010, Abstract #37

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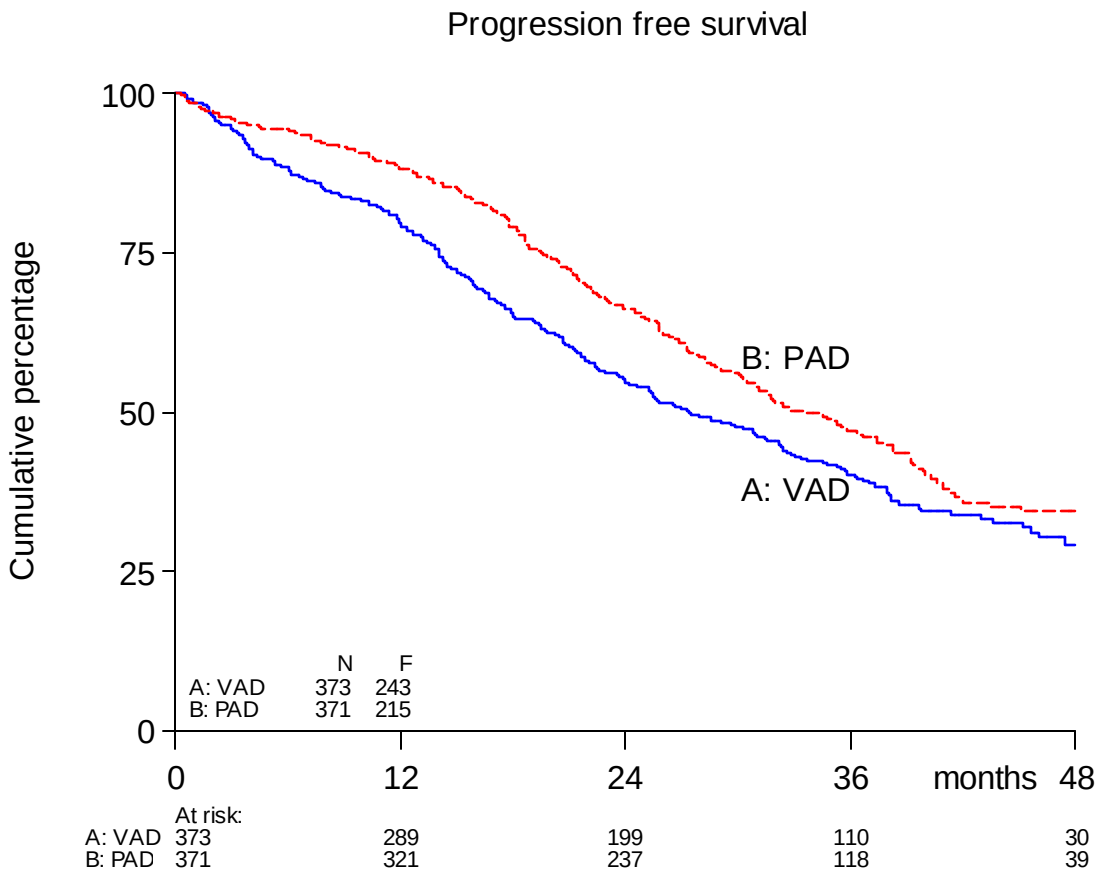
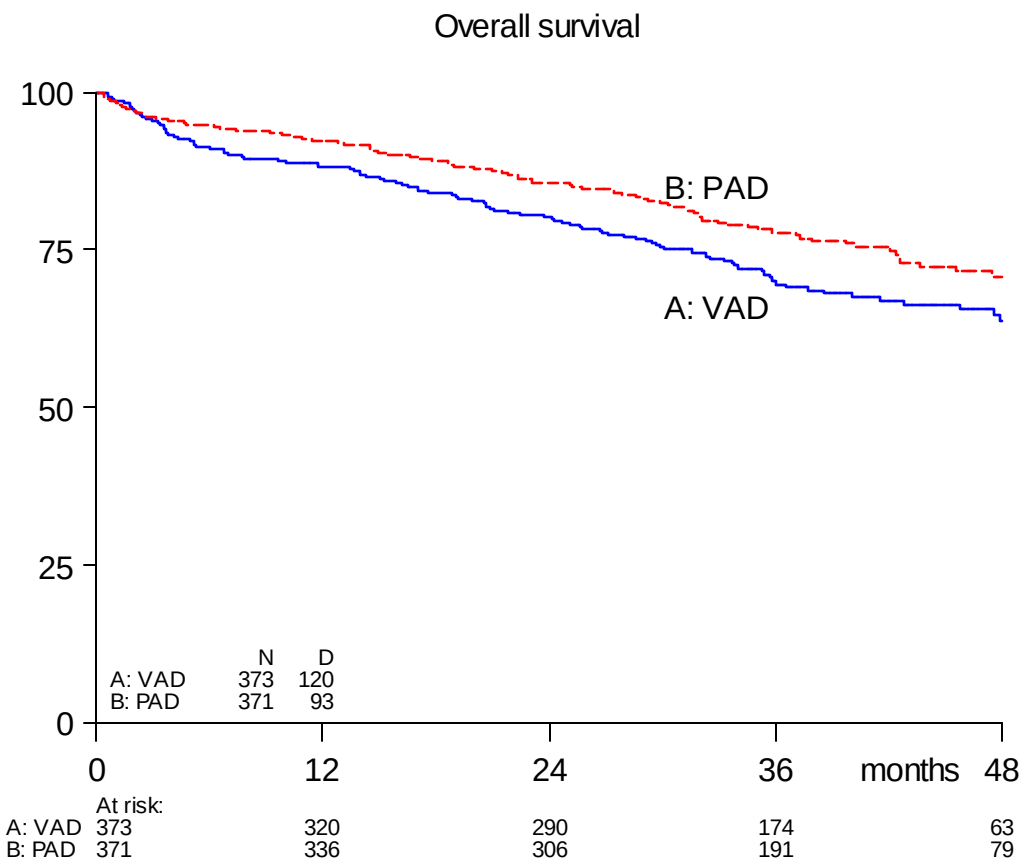
Bortezomib maintenance: Outcomes



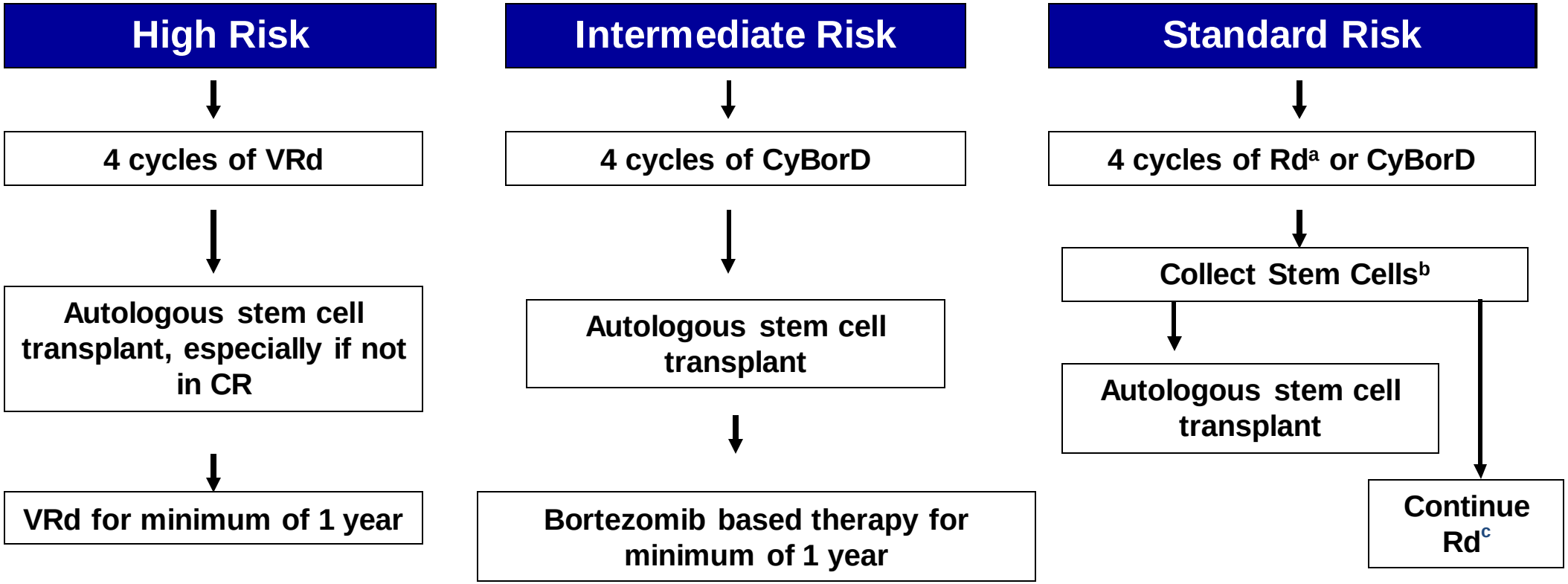


	VAD	PAD	
CR/nCR	**34**	**49**	**<0.001**
≥VGPR	**55**	**76**	**0.001**
≥PR	**83**	**91**	**0.003**

Sonneveld et al; ASH 2010, Abstract #40

mSMART – Off-Study

Transplant Eligible



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

[b] *If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor*

[c] *Continuing Rd is option for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110

v8 Revised and updated: Feb 2011

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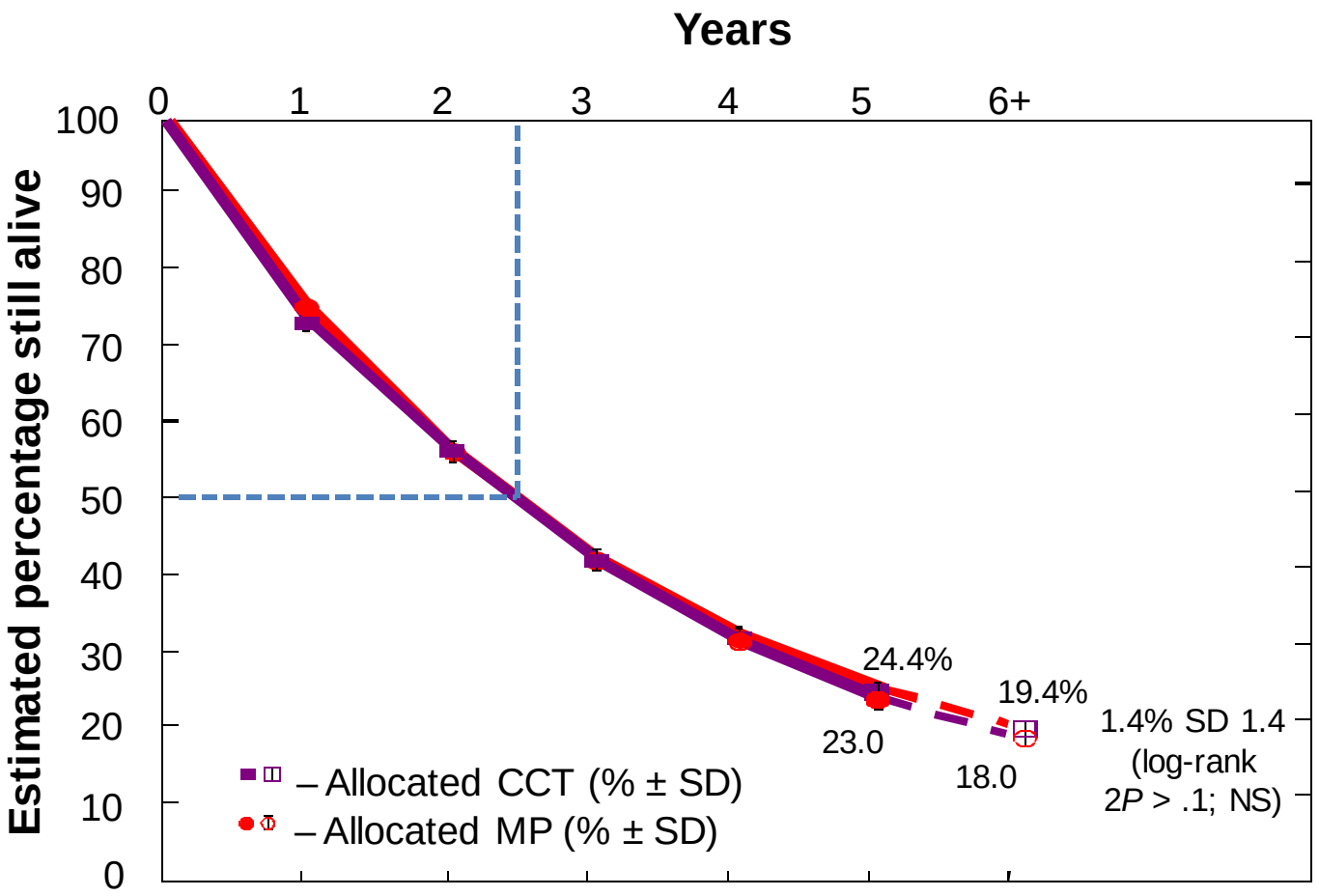
What about the transplant ‘ineligible’ population?

Melphalan + Prednisone



27 randomized trials

Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;12:3832

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MP vs MPT: progression-free survival and overall survival

	GIMEMA[1,2]	IFM 99-06[3]	IFM 01-01[4]	Nordic[5]	HOVON[6]
Median PFS, months					
MP	15	18	19	14	10*
MPT	22	28	24	16	13
p value	0.0004	< 0.0001	0.001	TTP‡	< 0.001
Median OS, months					
MP	48	33	29	39	30
MPT	45	52	44	29	37
p value	NS	0.0006	0.028	NS	NS

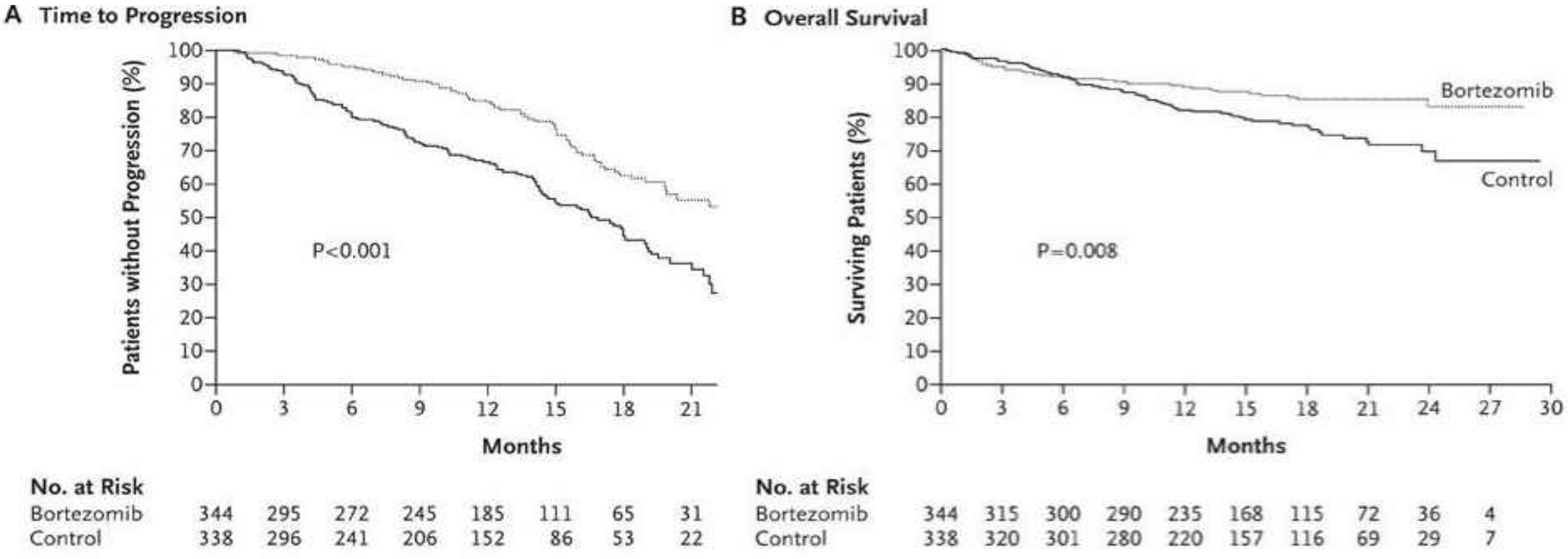
*Event-free survival.
‡Significant.

In 5 of 5 studies, MPT was superior to MP in terms of PFS or TTP (or both)

In 2 of 5 studies, MPT was superior to MP in terms of OS

1. Palumbo A, et al. Lancet. 2006;111:825-31. 2. Palumbo A, et al. Blood. 2008;112:3107-14. 3. Facon T, et al. Lancet. 2007;370:1209-18.
4. Hulin C, et al. J Clin Oncol. 2009; in press. 5. Waage A, et al. Blood. 2007;110:[abstract 78].
6. Wijermans P, et al. Blood. 2008;112:[abstract 241]; updated data presented at ASH, 2008.

VISTA: Randomized, Phase III Trial of VMP vs MP



24.0 months for bortezomib vs.
16.6 months in the control group

San Miguel et al. NEJM. 359 (9): 906

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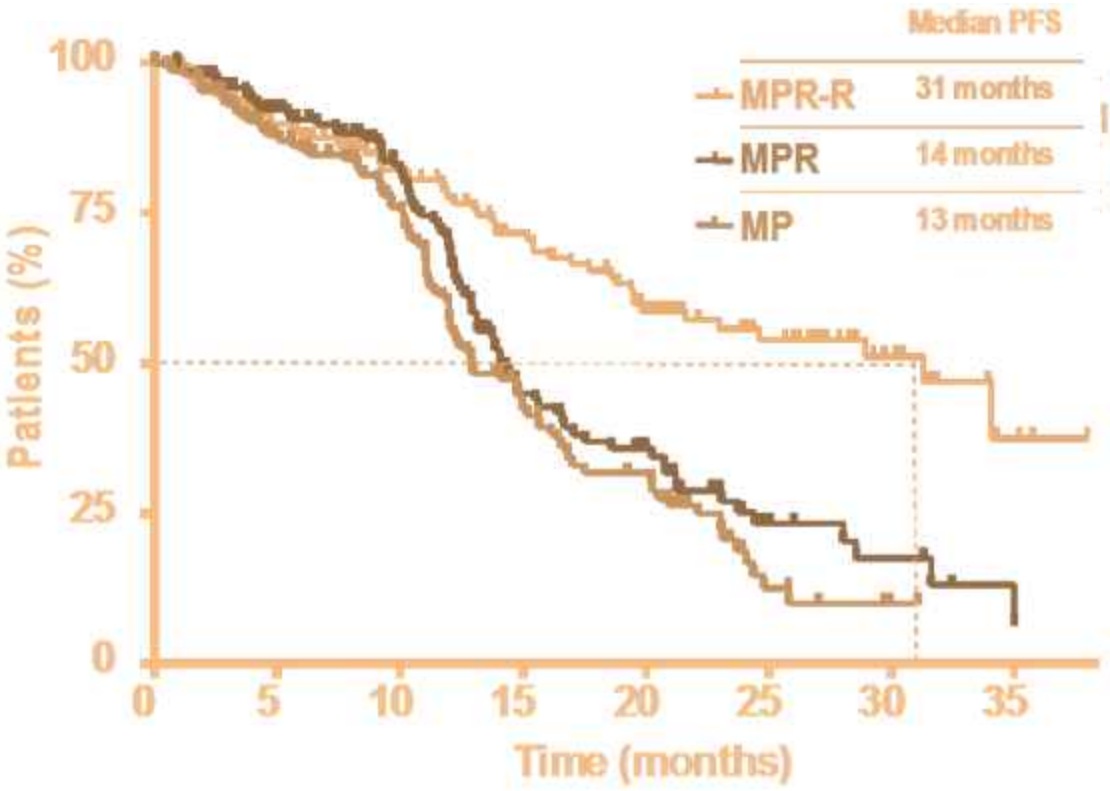
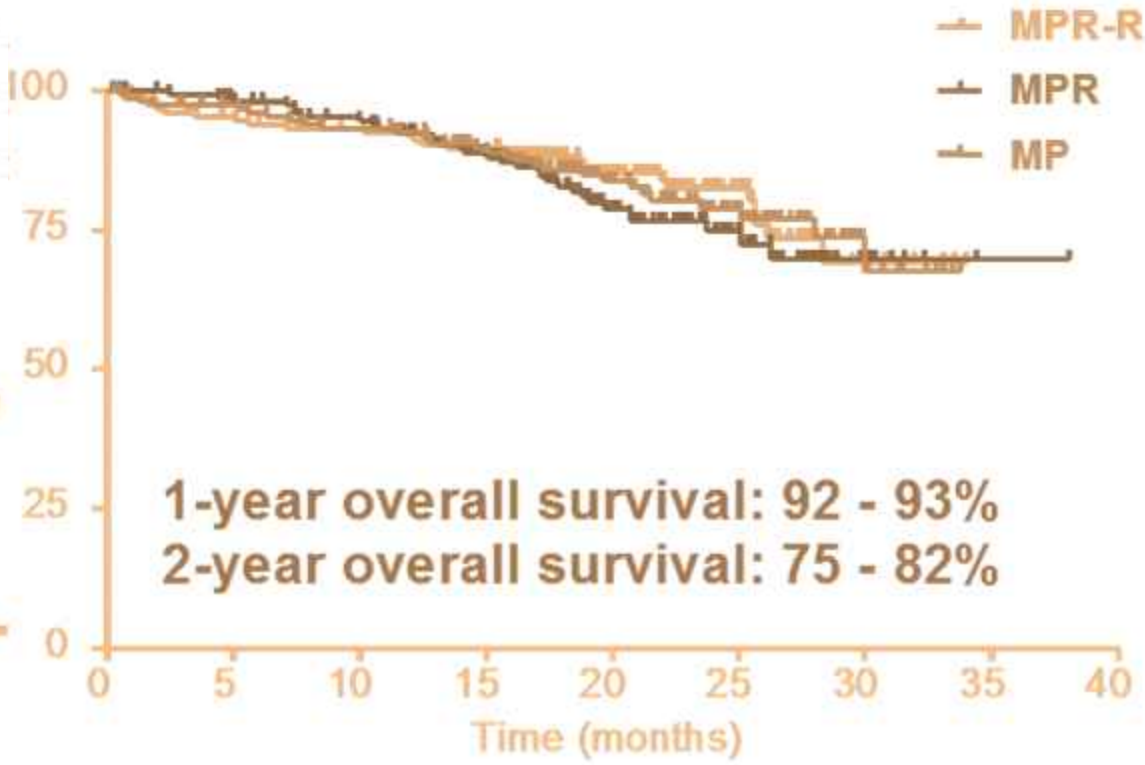
MP vs. MPR vs. MPR-R: Survival





Palumbo et al; ASH 2010, Abstract #620

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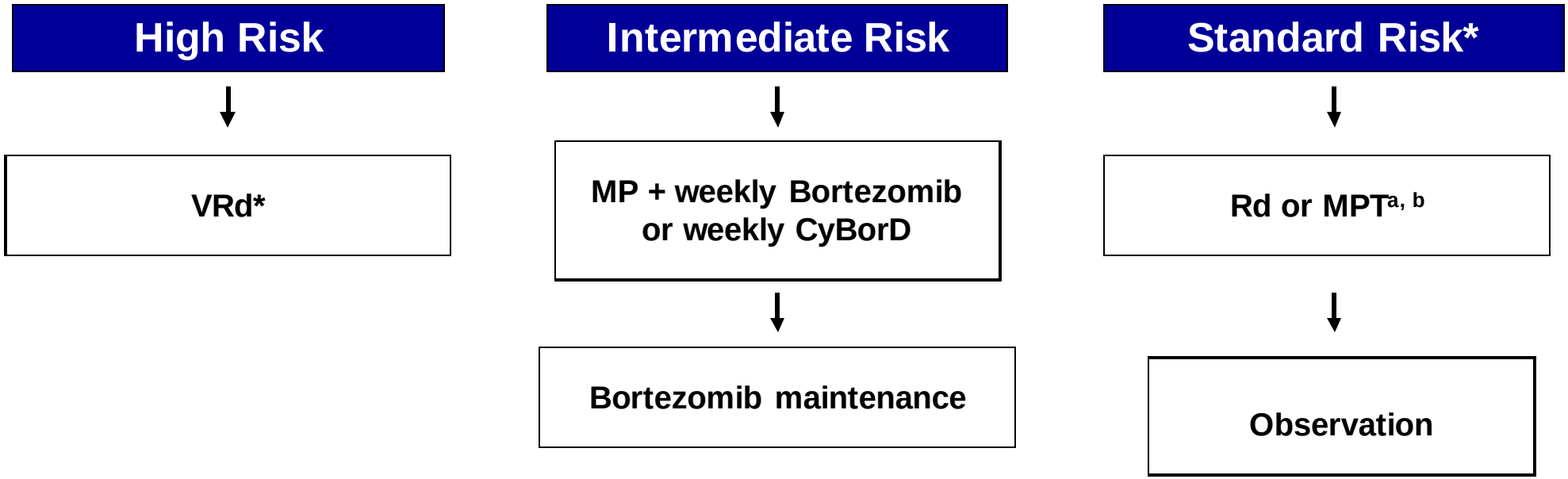
mSMART – Off-Study

Transplant Ineligible



[a] In patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; Dex is usually discontinued after first year

[b] Bortezomib containing regimens preferred in renal failure or if rapid response needed

**Clinical trials strongly recommended as the first option*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110

v8 Revised and updated: Feb 2011

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Supportive care

- Disease related complications common at diagnosis
  - Renal insufficiency
  - Bone pain
  - Fractures
  - Neurological compromise
  - Hypercalcemia
  - Infections
  - Neuropathy
- All can contribute to morbidity, early mortality and limitations on therapy

Renal Failure

- Fairly common
  - CrCl >=60 ml/min: 50%
  - CrCl 30-59 ml/min: 37%
  - CrCl < 30 ml/min: 13%
- Multifactorial
  - Cast nephropathy (Typically associated with increased light chains)
  - Hypercalcemia
  - Light chain deposition
  - Amyloidosis

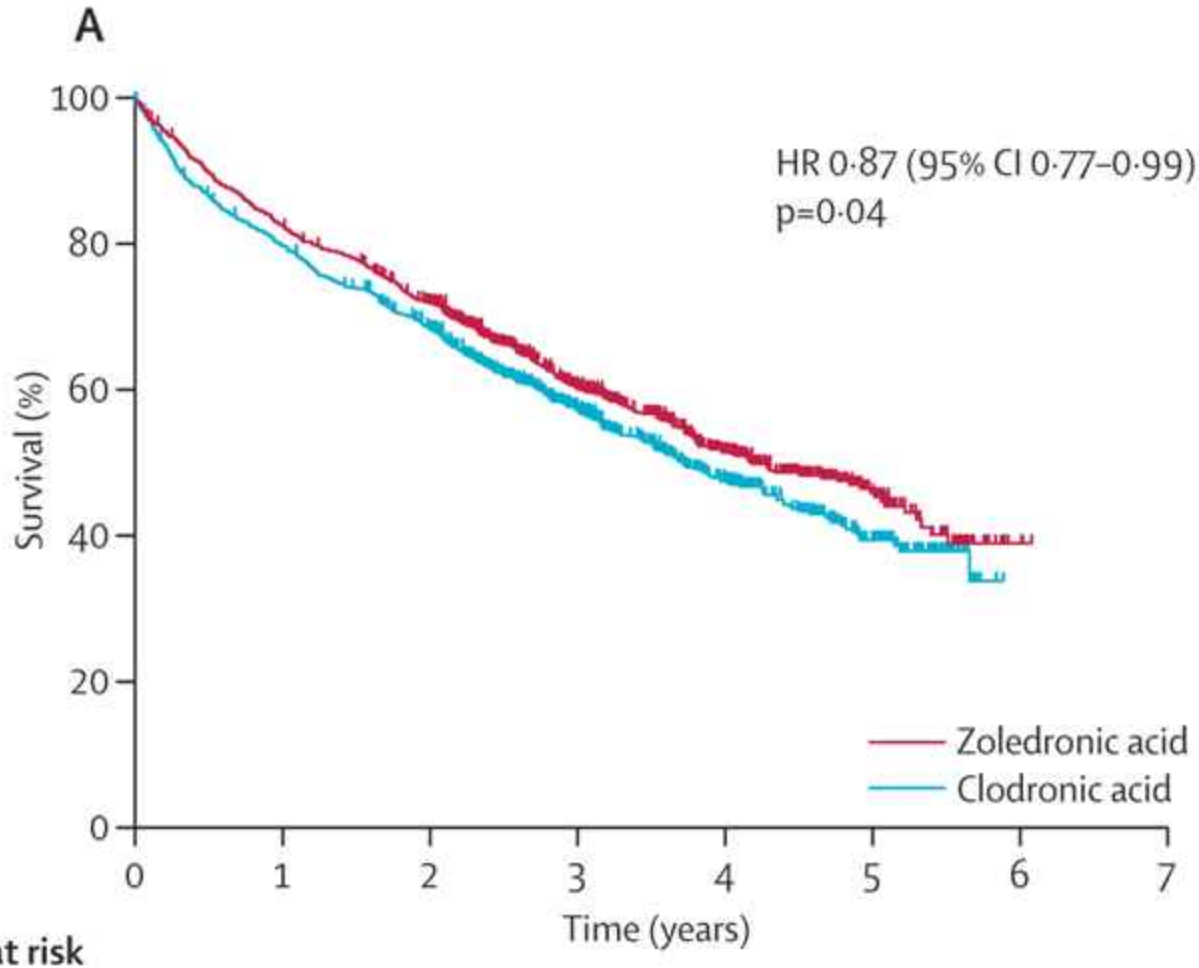
Renal failure: Management

- Identify cause
- Treatment of Hypercalcemia and dehydration
- Avoidance of nephrotoxic drugs
- Plasma exchange in selected patients
- Rapid initiation of therapy (bortezomib based therapy)

Bone disease

- Nearly 60% of patients with bone disease
- Commonly lytic lesions or osteopenia
- Compression fractures and or long bone fractures
- Potential neurological sequale
- Considerable morbidity
- Multiple mechanisms

MRC Myeloma IX



Number at risk

Zoledronic acid	981	806	675	418	222	79	3
Clodronic acid	979	776	642	399	208	69	0

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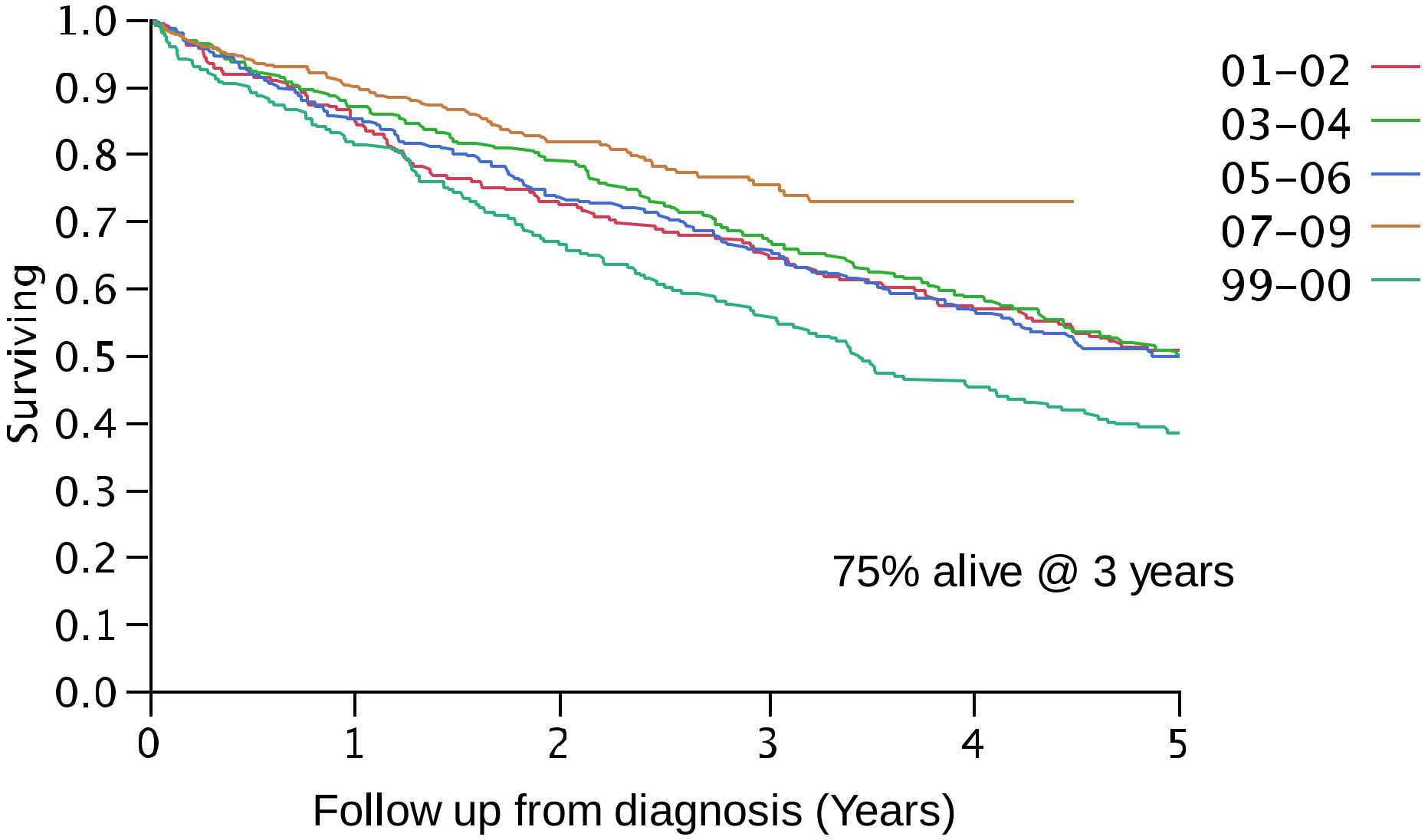
Bone disease management guidelines

- All patients should receive bisphosphonates
- Zoledronic acid or pamidronate
- Ideal duration of therapy unknown
- Recommendations 18-24 months
- Dental evaluation before starting, and care about procedures later
- Ensure calcium and vitamin D intake

Infections

- Antibiotic prophylaxis
- Immunoglobulin therapy
- Anti-zoster prophylaxis
- Immunizations: pneumococcal

Are we making progress?



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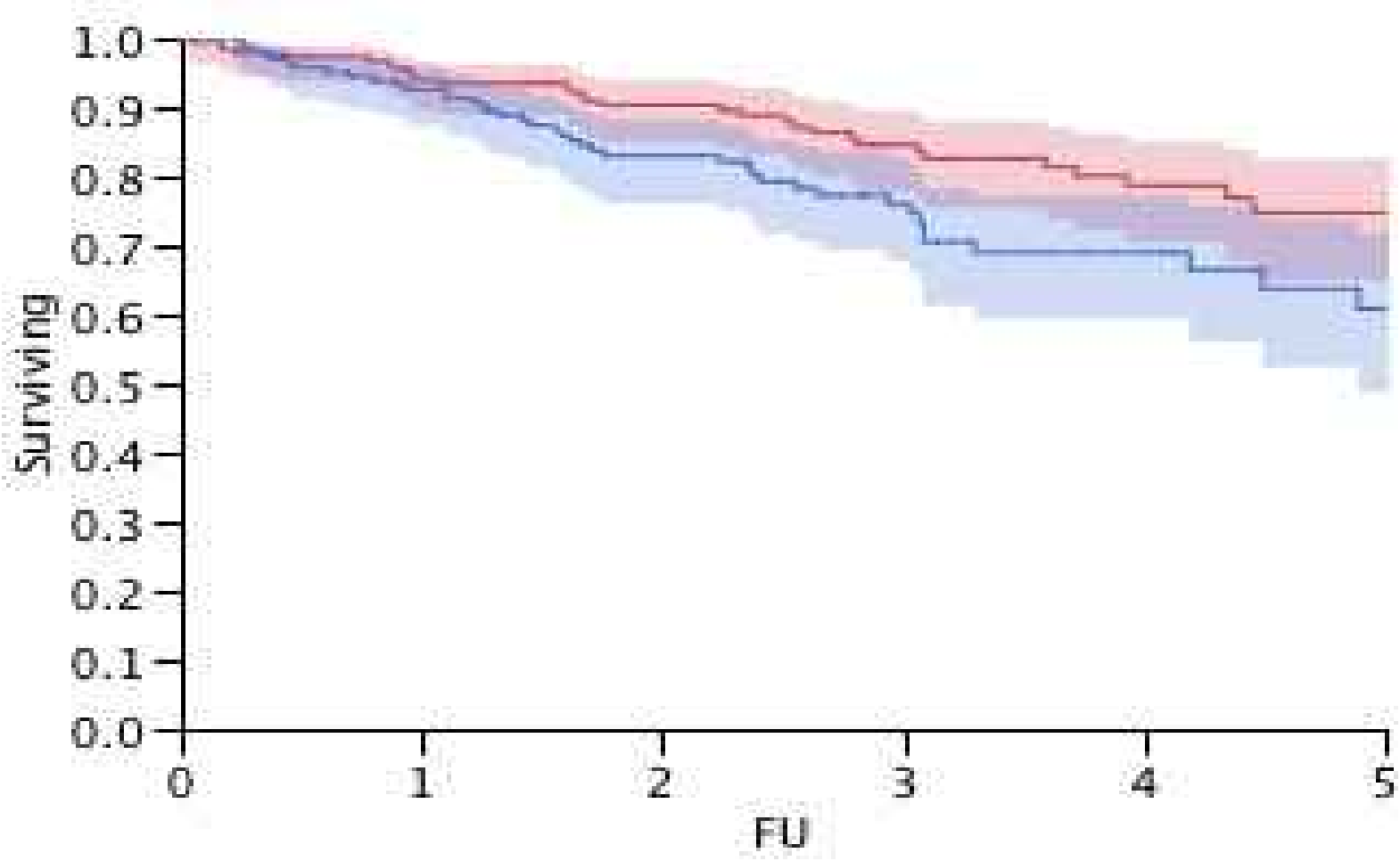
RD long term survival



5 year survival estimate: <=65 years: 75%, >65 years: 61%, P =0.01

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Thank You!