Update on the Initial Therapy of Multiple Myeloma

Donna E. Reece, M.D.
Princess Margaret Cancer Center
Toronto, ON
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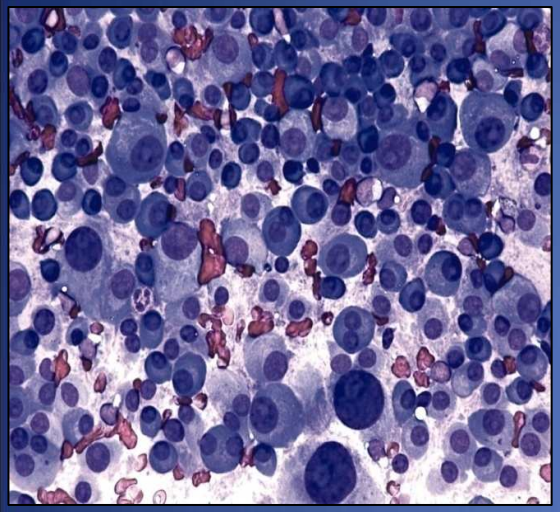
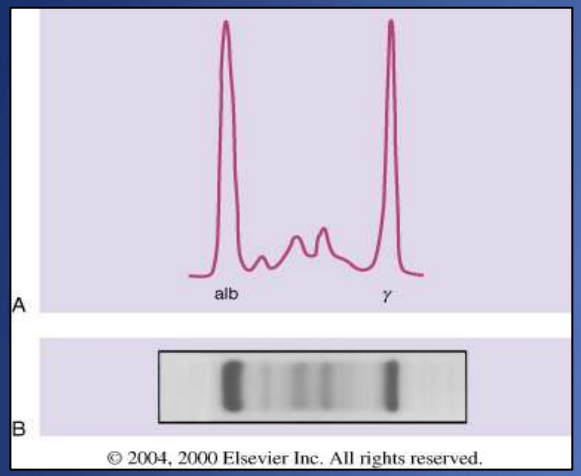
Multiple Myeloma

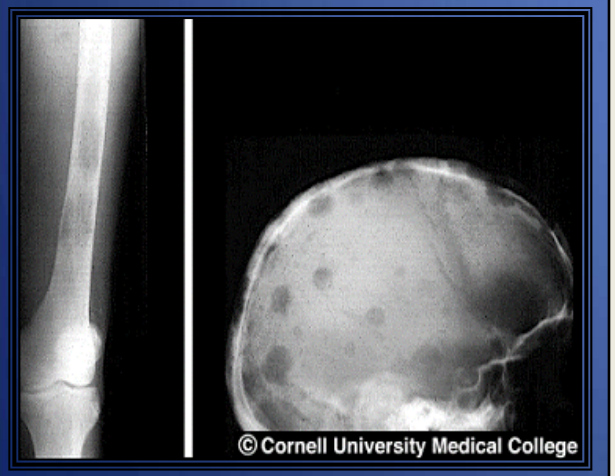


- **Clonal proliferation of malignant plasma cells**
- **Overall incidence 5/100,000 but much higher in the elderly**
- **Median age ~65 years**
- **Genetic component recently recognized[3]**
  - *15-35% of MGUS/MM derive from a chronic autoimmune response driven by hyperphosphorylated 'paratargs' in individuals with permissive HLA background*

[1]Grass S et al. Blood 2011; 118: 635637.

Multiple Myeloma

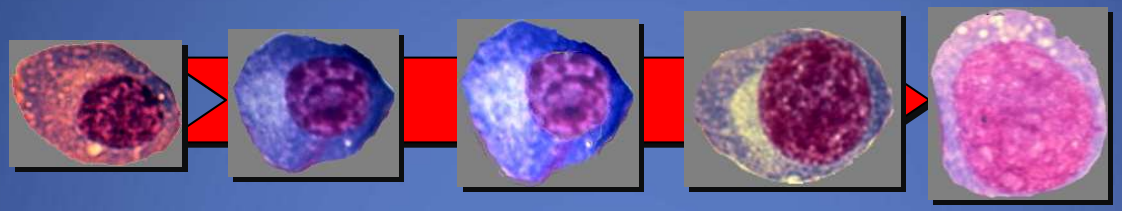




- **Diagnosis based on finding over 10% plasma cells in bone marrow**
- **In most cases, plasma cells make a monoclonal immunoglobulin protein**
- **"CRAB" = Symptomatic myeloma requiring treatment**
  - *Anemia—Hgb < 10 g/dL (or 2 g/dL below normal)*
  - *Bone lesions*
  - *Creatinine > 176 umol/L (2 mg/dL)*
  - *Hypercalcemia > 2.8 mmol/L (11.5 mg/dL)*

Multiple Myeloma
Key Features of Biology-1

- All patients progress through an MGUS phase[1]



- Myeloma is not one disease[2]
  - *At least 7 subtypes based on cytogenetic and molecular features*
  - *Highest risk cytogenetic subtypes by FISH*
    - *t(4;14)*
    - *t(14;16)*
    - *del 17p*
    - *abnormalities of chromosome 1*

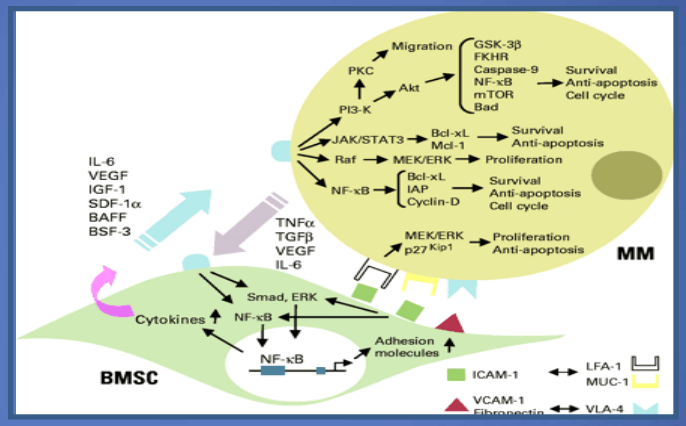
- End stage disease may be characterized by
  - *Extramedullary disease*
  - *Loss of monoclonal protein*

[1]Kristinsson SY, et al. Int J Cancer 2009; 125” 2147-2150; [2] Bergsagel L, Chesi M. Int J Hematol 2013; 97: 313-323.

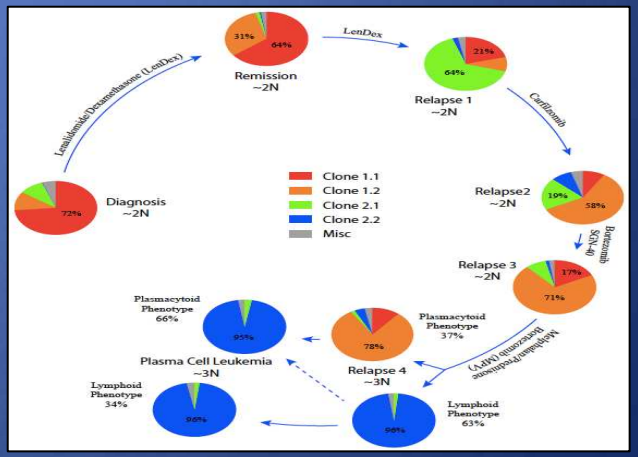
Multiple Myeloma

Key Features of Biology-2

- Pathophysiology depends on interaction with marrow microenvironment[1]



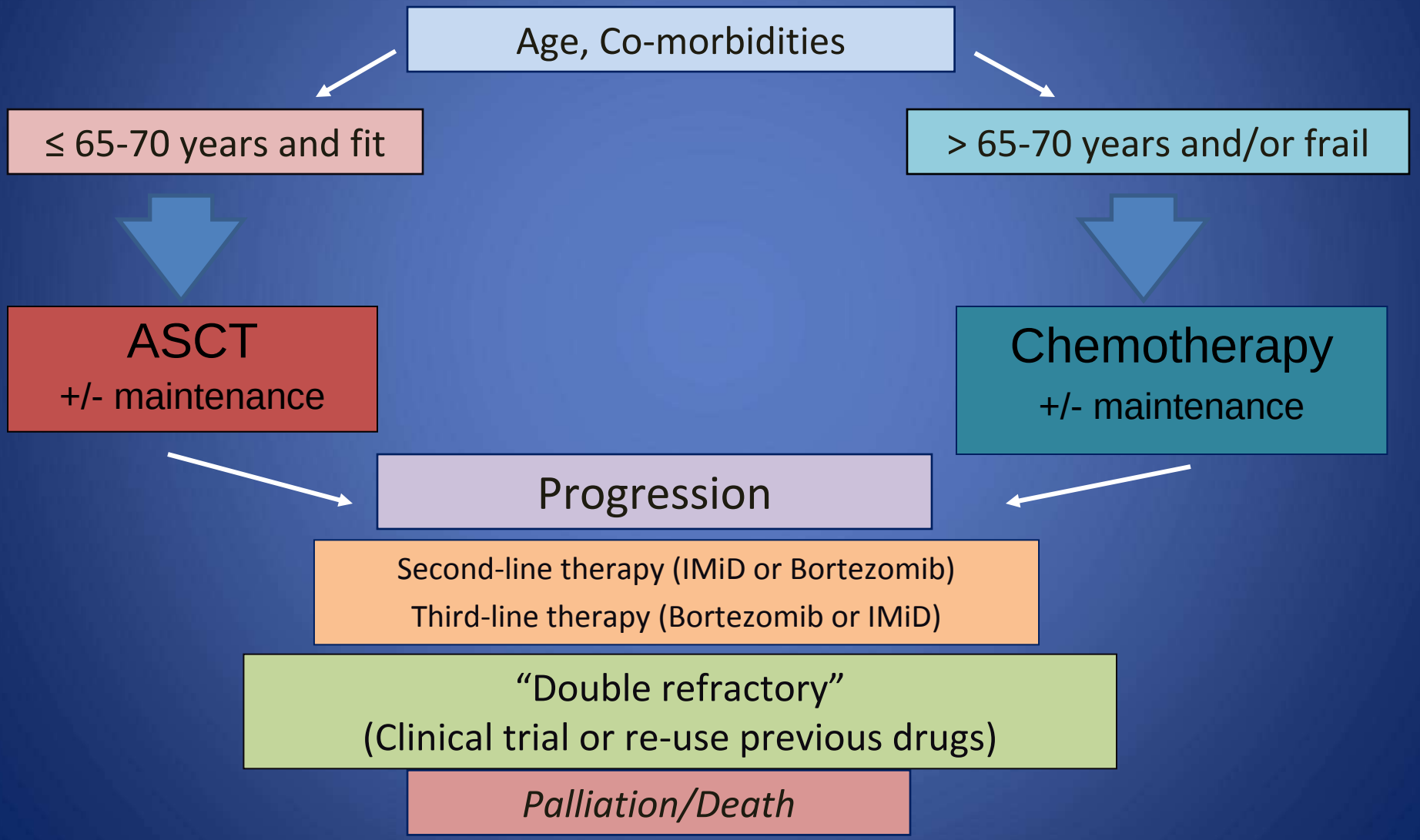
- Progression is not linear process[2]
  - -- *Concept of "clonal tiding"*



[1]Manier et al. J Biomed Biotechnol. Epub 2012 Oct ;
[2]Keats JJ, et al. Blood. 2012;120:1067-76.

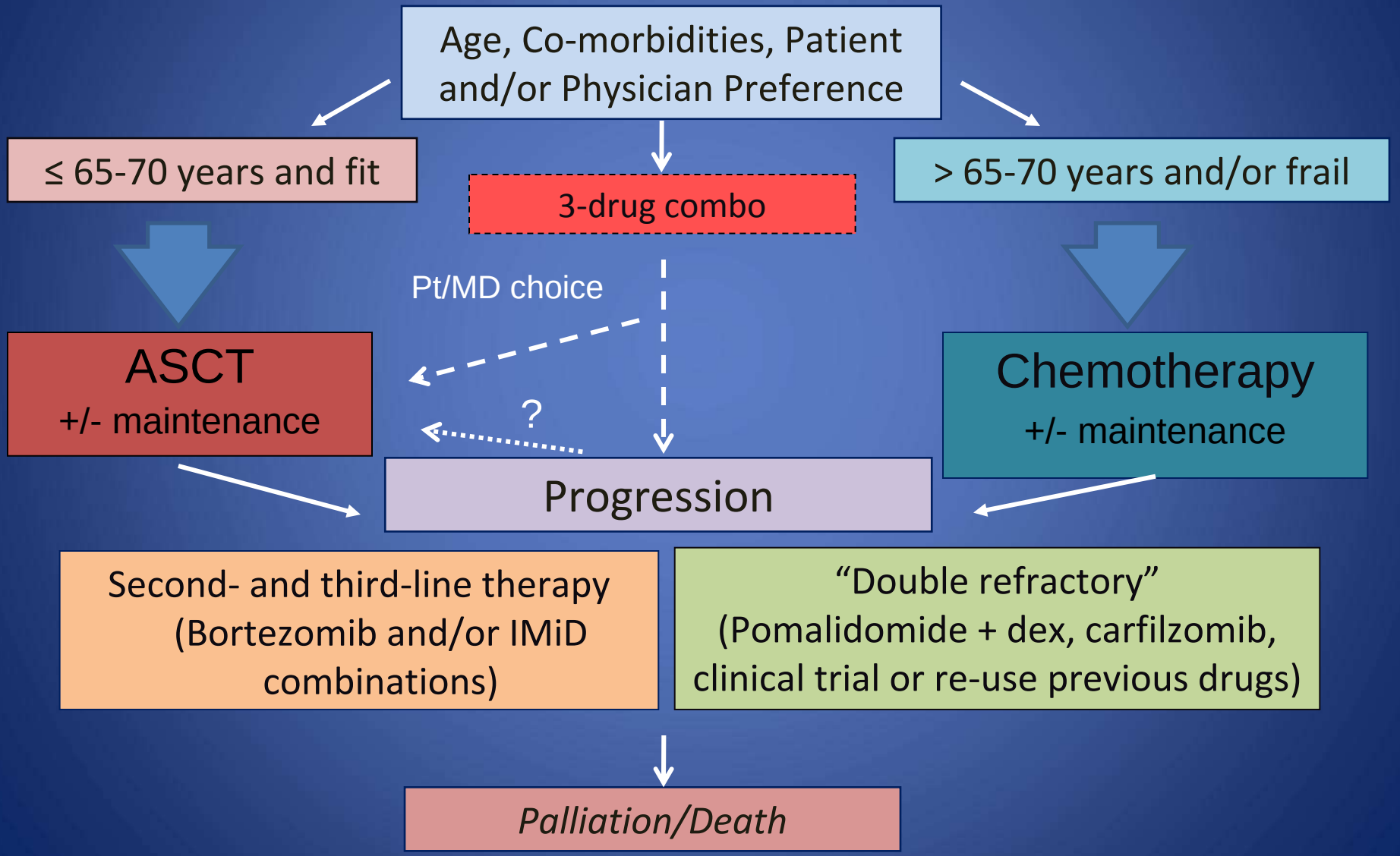
Canadian/European Treatment Algorithm

Multiple Myeloma



Evolving U.S. Treatment Algorithm

Multiple Myeloma



ASCT in Myeloma

….. *Where we were..*

Induction

VAD
Dexamethasone alone
Dexamethasone + thalidomide

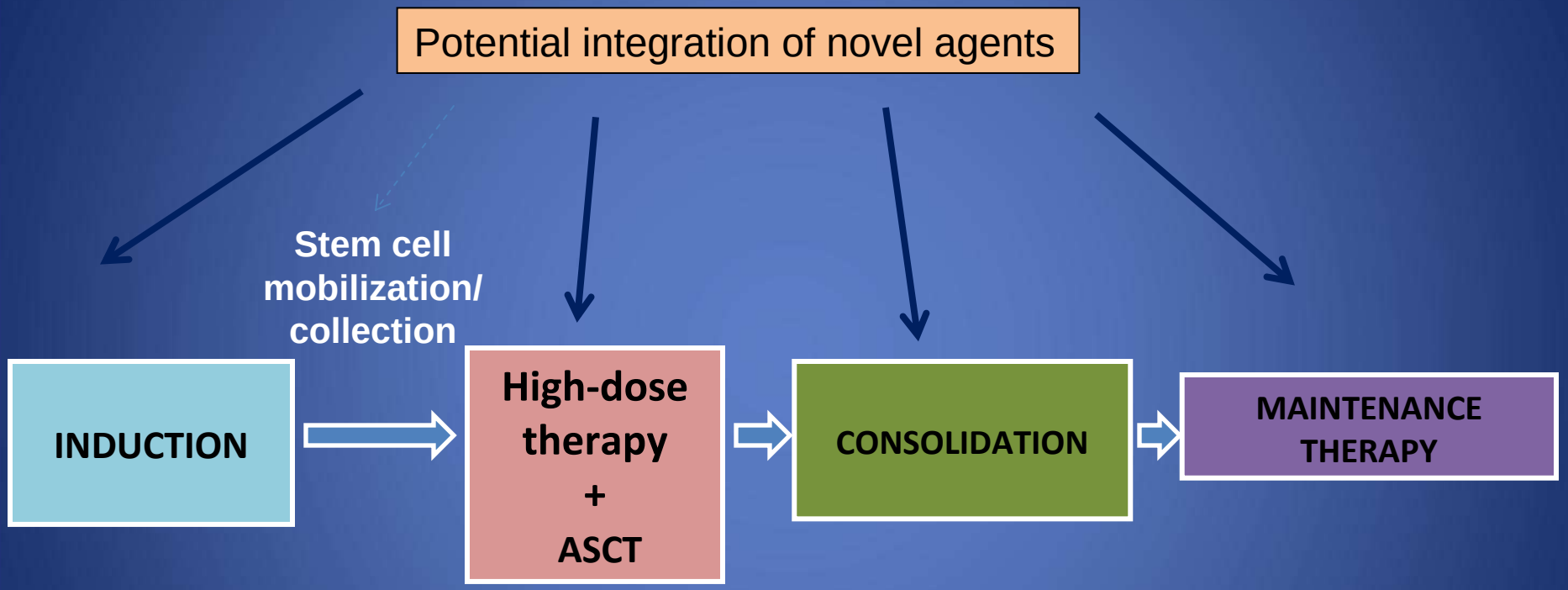
Stem cell mobilization/ collection

High-dose melphalan
+
ASCT

Outcomes

Overall response rate	80%
CR/nCR rate	20%
Median PFS	20-28 mos
Median overall survival	48-60 mos

Modern Components of ASCT



Considerations in interpreting phase III studies:

- Timing of randomization may affect results
- Most include novel agents before and after ASCT

Pre-ASCT Induction Therapy
Phase III Trials

- Bortezomib-based induction
  - *IFM 2005-02:* ***BD vs VAD***
  - *HOVON 65/GMMG-HD4:* ***PAD vs VAD***
  - *GIMEMA MMY-3006:* ***VTD vs thal + dex***
  - *PETHEMA:* ***VTD vs VBCMP/VBAD/Vel vs thal + dex***
  - *IFM 2007-02:* ***vTD vs BD***

- Thalidomide-based induction
  - *HOVON-50:* ***TAD vs VAD***
  - *MRC IX:* ***CTD vs CVAD***

A=adriamycin; B or vel=bortezomib; C=cyclophosphamide; D or dex=dexamethasone; P=proteasome inhibitor=bortezomib; T or thal=thalidomide

Post-Induction Results in Phase III Trials

Study/ Author	N	Induction regimen	Overall response rate (%)	≥VGPR (%)	CR/nCR (%)
IFM 2005-02 Harousseau	482	BD VAD	**78** 63	**38** 15	**15** 6
HOVON 65/GMMG-HD4 Sonneveld	613	PAD VAD	**83** 59	**42** 11	**15** 5
GIMEMA MMY-3006 Cavo	447	VTD Thal + dex	**93** 79	**62** 28	**31** 11
PETHEMA/GEM Rosinol	386	VTD Thal + dex VBMCP/VBAD/B	**82** 64 75	**60** 29 36	**35** 14 22
IFM 2007-02 Moreau	199	vTD BD	88 81	**49** 36	31 22

Do Novel Induction Regimens Confer Better PFS/OS?

Study/ Author	Induction regimen	Median PFS (mos)	3 year PFS (%)	Median OS (mos)	3-year OS (%)
IFM 2005-02 Harousseau	BD VAD	36 30	-- --	-- --	81% 77%
HOVON 65/GMMG-D4 Sonneveld	PAD VAD	**35** 28	**48%** 42%	-- --	**61%** 55% (5-year)
GIMEMA MMY-3006 Cavo	VTD Thal + dex	NYR NYR	**68%** 56%	-- --	86% 84%
PETHEMA/GEM Rosinol	VTD Thal + dex VBMCP/VBAD/B	**56.2** 28.2 35.5	-- -- --	-- -- --	74% 65% 70% (4-year)
IFM 2007-02 Moreau	vTD BD	26 30	-- --	-- --	-- --

Where we are now…….
Summary of Phase III Trial Results

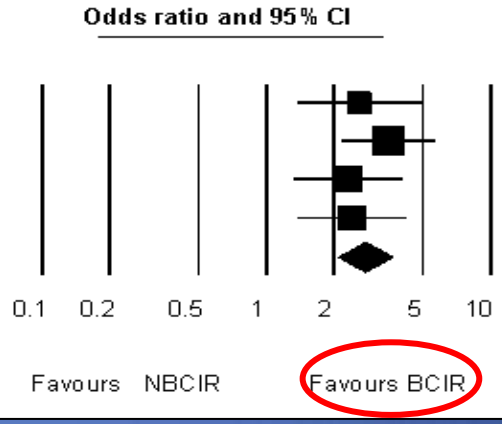
	Induction Rx	ASCT + Maintenance	≥ VGPR (CR+nCR) (%)	PFS (Median)	OS (Median)
Harousseau[1]	Bortezomib + Dex	1 or 2 (lenalidomide maintenance in some)	68% (39%)	36 mo	NYR 81% (3-year)
Cavo[2]	VTD	2 + VTD consolidation + dex maintenance	89% (71%)	NYR 68% (3-year)	NYR 86% (3-year)
Sonneveld[3]	PAD	1 or 2 + bortezomib maintenance	76% (49%)	35 mos	NYR 61% (5-year)
Rosinol[4]	VTD	1 + VT = bortezomib and thalidomide maintenance	NA (46%)	56.2 mos	NYR 74% (4-year)

[1]Harousseau JL, et al, J Clin Oncol 2012;28: 4621-4629; [2]Cavo M.et al. Lancet 2010;376: 2075-2085;[4]Sonneveld P, et al .J Clin Oncol 2012;30: 2946-2955; [4]Rosinol L, et al. Blood 2012;120: 1589-1596.

Phase 3 trials of Bortezomib-Containing Induction Regimens *Meta-Analysis (n=2086)*

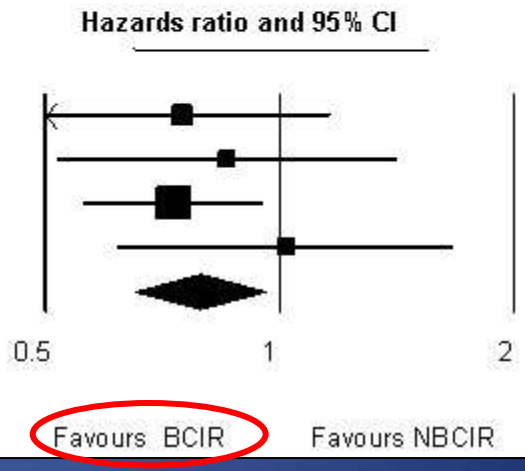
Impact of bortezomib induction on post induction CR

Study name	Odds ratio	Lower limit	Upper limit	Relative weight	p-Value
Harousseau, JL	2.596	1.352	4.987	18.30	0.004
Cavo, M	3.500	2.152	5.693	32.95	0.000
Sonneveld, P	2.315	1.317	4.070	24.49	0.004
Rosinol, L	2.422	1.374	4.270	24.27	0.002
Pooled OR	2.739	2.072	3.621		0.000



Impact of bortezomib induction on overall survival

Study name	Hazards ratio	Lower limit	Upper limit	Relative weight	p-Value
Harousseau, JL	0.749	0.483	1.162	19.26	0.197
Cavo, M	0.856	0.516	1.419	14.56	0.545
Sonneveld, P	0.730	0.558	0.956	51.24	0.022
Rosinol, L	1.018	0.618	1.676	14.94	0.945
Pooled HR	0.789	0.651	0.957		0.016



BCIR: bortezomib-containing regimens

Nooka et al. ASH 2011 (Abstract 3994), poster presentation

3- and 4-drug Bortezomib-based Induction Trials

Regimen	N	N With ASCT	Response (%) Post-induction			Gr 3/4 PN (%)
			≥PR	≥VGPR	≥CR/nCR	
VDD[1]	30	20	93	63	40	2.5/0
VRD[2]	31	31	94	39	23	NA
RVDD[3]	68	24	96	58	30	6/0
VTDC[4]	49	48	96	69	44	4/0
VTD[4]	49	40	100	69	51	8/2
CyBor-D[5] **(weekly)**	83	30	97	79	--	0/0

[1]Jakubowiak A, et al. Blood 2008; 112: abstract 3713; [2]Roussel M et al. Blood 2011; 118: abstract 1872; [3]Jakubowiak A, et al. Blood 2009; 114: abstract 132; [4]Ludwig H, et al. J Clin Oncol 2013; 31: 247-255.; [5] Areethamsirikul N, et al. Submitted IMW 2013

Weekly CyBorD (1.5 mg/m^2) Induction
PMH Experience (N=83)

- Pre-ASCT response (after 4 cycles)
  - *Overall response rate 93%*
  - *≥ VGPR 70%*
- Toxicity
  - *Grade 3-4 neutropenia 3.6%*
  - *Grade 3-4 thrombocytopenia < 1%*
  - *Grade 3-4 neuropathy 0*
  - *Dose reductions/delays of any drug 18%*
  - *Only 3 did not go to transplant 3.6%*
- Day 100 post-ASCT outcomes
  - *Overall response rate 97%*
  - *≥ VGPR 79%*

Areethamsirikul N, et al. IMW 2013: P-202.

Lenalidomide and Dex before ASCT

- No prospective phase III trials comparing Len + dex with other regimens specifically as pre-ASCT induction
- In ECOG E4A03, 90 pts undergoing ASCT had 2-year PFS of ~64% and 3-year OS of 92%
- GIMEMA Phase III trial compares Len + dex x 4 cycles followed by either ASCT x 2 **or** MPR (+/- len maintenance)

Parameter	ASCT x 2	MPR
Overall Response rate	96%	95%
VGPR	62%	60%
CR	25%	20%
3-year PFS	60%*	38%
3-year OS	80%	79%

*$p < 0.001$

Update ASCO 2013, Boccadoro M et al. Abstract 8509.

[1]Rajkumar SV et al. Lancet Oncol. 2010; 11(1): 29–37; [2]Cavelli F et al. Haematologica 2012; 97 (Suppl 1): 472-473.

Definitions of Post-ASCT Therapy

- Maintenance therapy—any treatment administered after the completion of induction therapy in patients whose disease is either responsive or non-progressive, with the goal of prolonging survival[1]
  - *Steroids*
  - *Interferon-alpha*
  - *IMiDs (thalidomide, lenalidomide)*
  - *Bortezomib*
- Consolidation therapy—relatively intensive short-term post-ASCT therapy
  - *Total therapy programs (DPACE[2], VTDPACE[3] , VRD[3])*
  - *VTD=bortezomib + thalidomide + dex*
  - *RVD=lenalidomide + bortezomib + dex*
  - *Lenalidomide alone*
  - *Bortezomib alone*

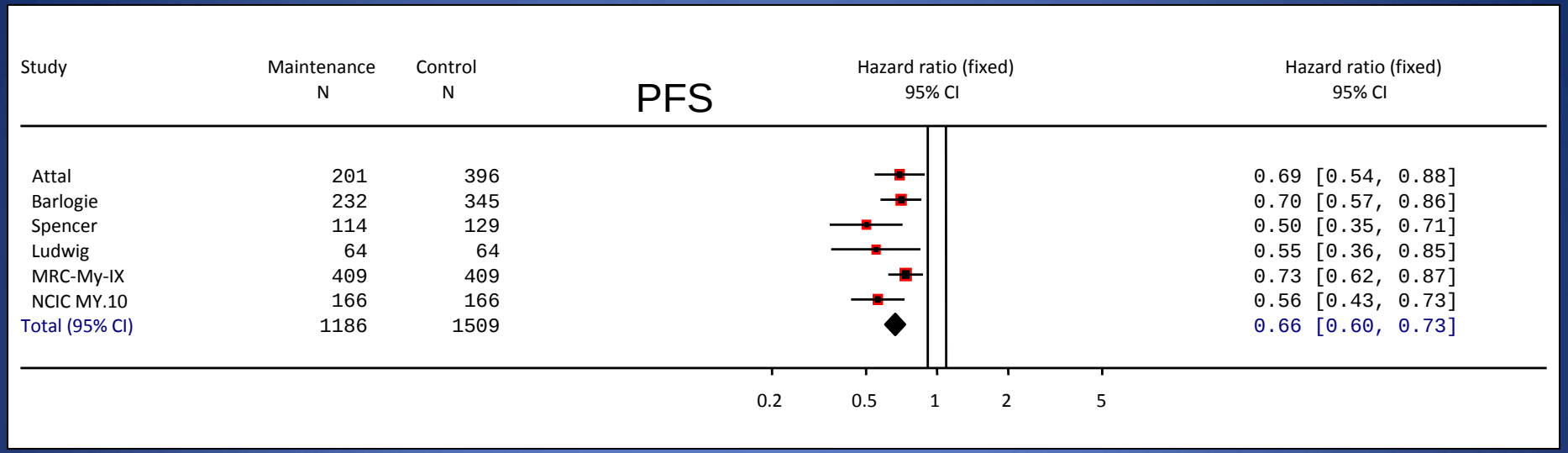
[1]Anderson KC, et al. Leukemia 2008; 22: 231-239.; [2]Zangari M et al. Br J Haematol 2008; 141: 433-444; [3]Nair B, et al. Blood 2010; 115: 4168-4173.

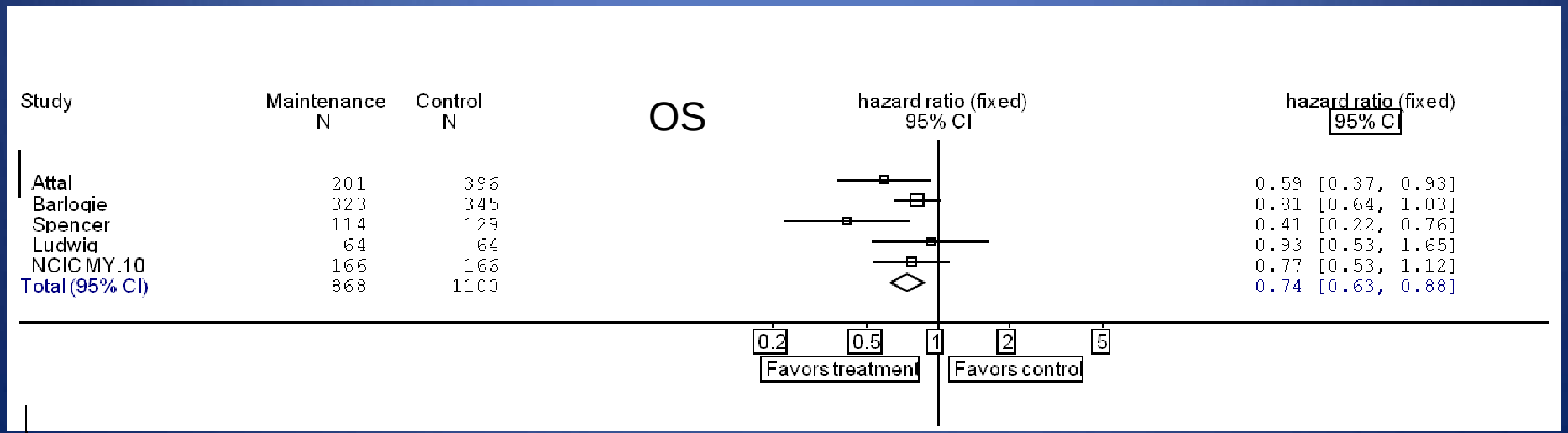
Post-ASCT Maintenance Therapy
Phase III Trials

- Thalidomide—7 trials
- Bortezomib
  - *HOVON MM 65/GMMG-HD4*
  - *Nordic Myeloma Study Group trial*
  - *PETHEMA/GEM trial—VT vs thal vs interferon-α*
- Lenalidomide—2 trials
  - *IFM 2005-02 with lenalidomide consolidation + maintenance*
  - *CALBG 100104 trial*

Thalidomide Maintenance post-ASCT

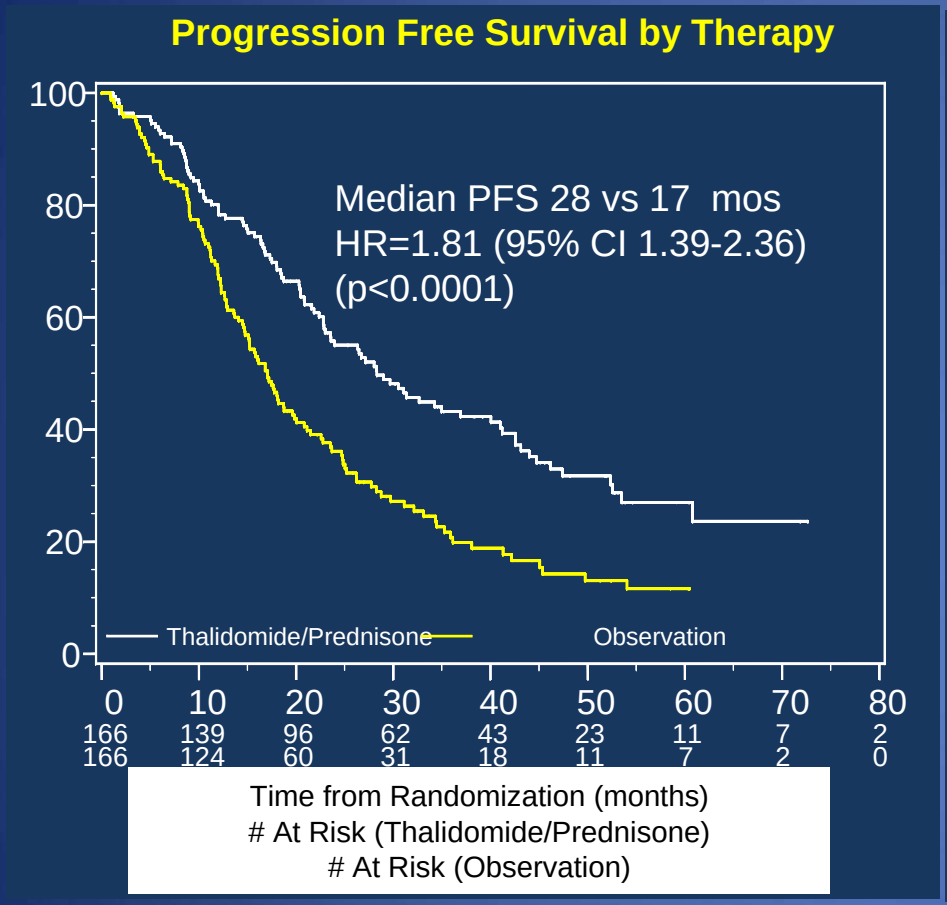
Meta-analysis

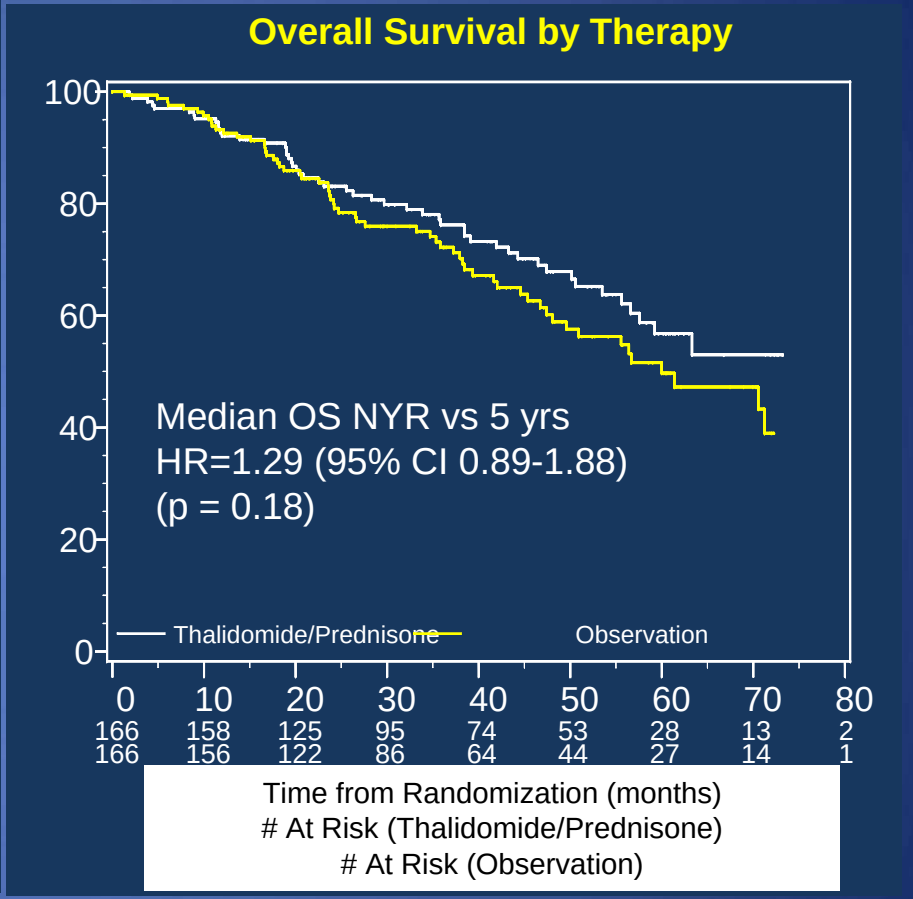




Nooka AK, et al. ASH 2011, abstract #1855.

Results of Canadian MY-10 Trial





However, QOL compromised:

Physical: 34% vs. 21% worsened (p=0.03)
Role: 29% vs. 17% (p=0.04) Cognitive:
54% vs. 41% (p=0.01)
Global: 40% vs. 26% (p=0.01)

Issues with tolerability:

Median time to thal dose reduction	*3.4 months*
Median duration thal	*16.1 months*

Summary of Phase III Trials of Lenalidomide Maintenance vs Placebo after ASCT

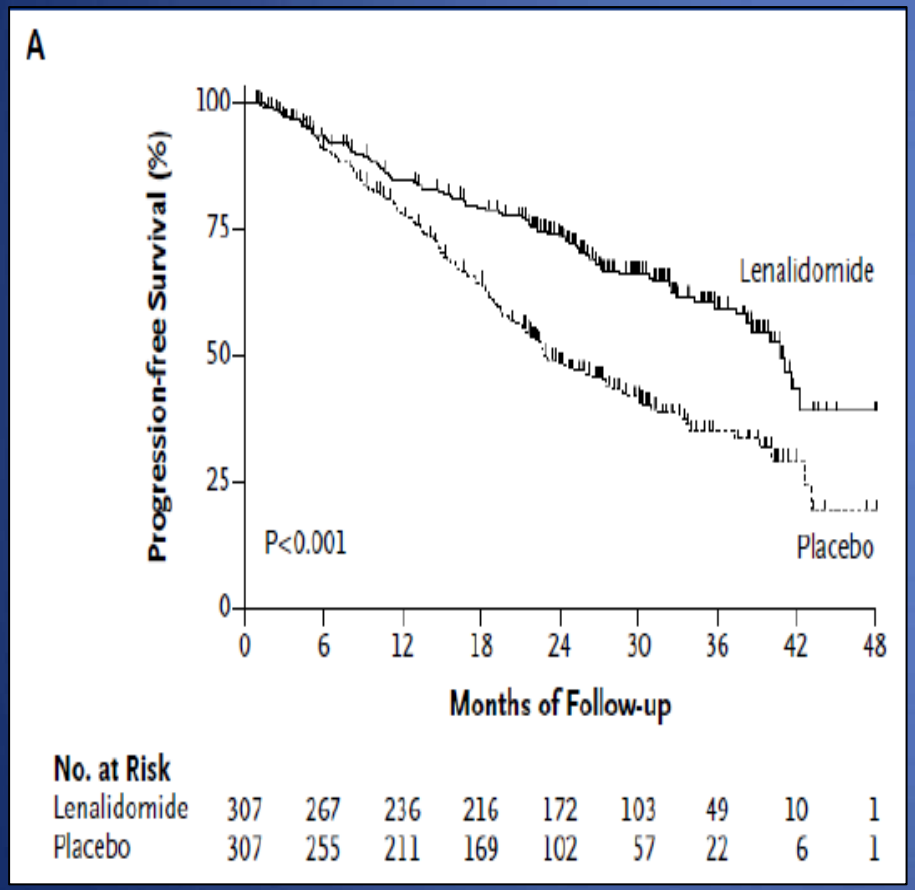
Author/Year	N	Pre-ASCT Induction	# ASCT	Consolidation	PFS/TTP Median (months)	Overall Survival (%)
Attal (IFM 2005-02)	614	VAD or BD	1 or 2	Len 25 mg x 2 mos in all	Lenalidomide **41** Observation 23	73% 75% (4-year)
McCarthy (CALBG 100104)	568	Lenalidomide 32% Bortezomib 42% Thalidomide 16%	1	--	Lenalidomide **46** Observation 27	**88%** 80% (3 year)

Attal M, et al. N Engl J Med 2012: 366: 1782-1791. McCarthy PL, et al. N Engl J Med 2012: 366: 1770-1781.

Lenalidomide Maintenance

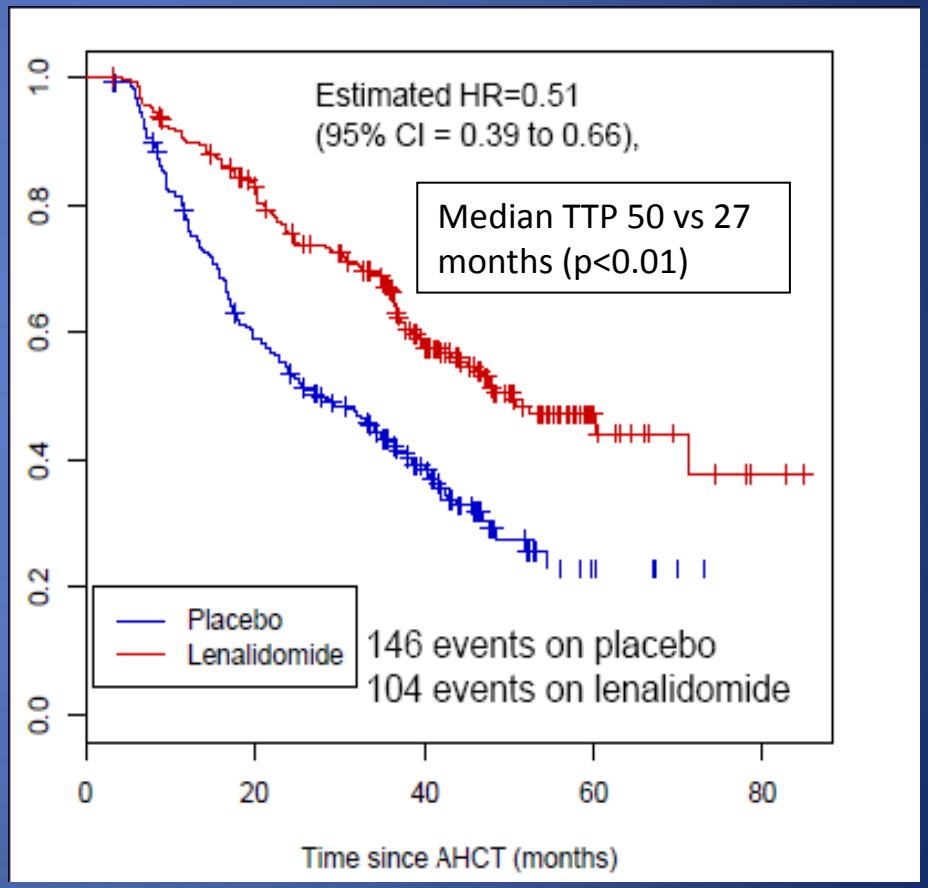
Effect on PFS/TTP

IMF 2005-02



Median follow-up 45 mos.

CALGB 100104



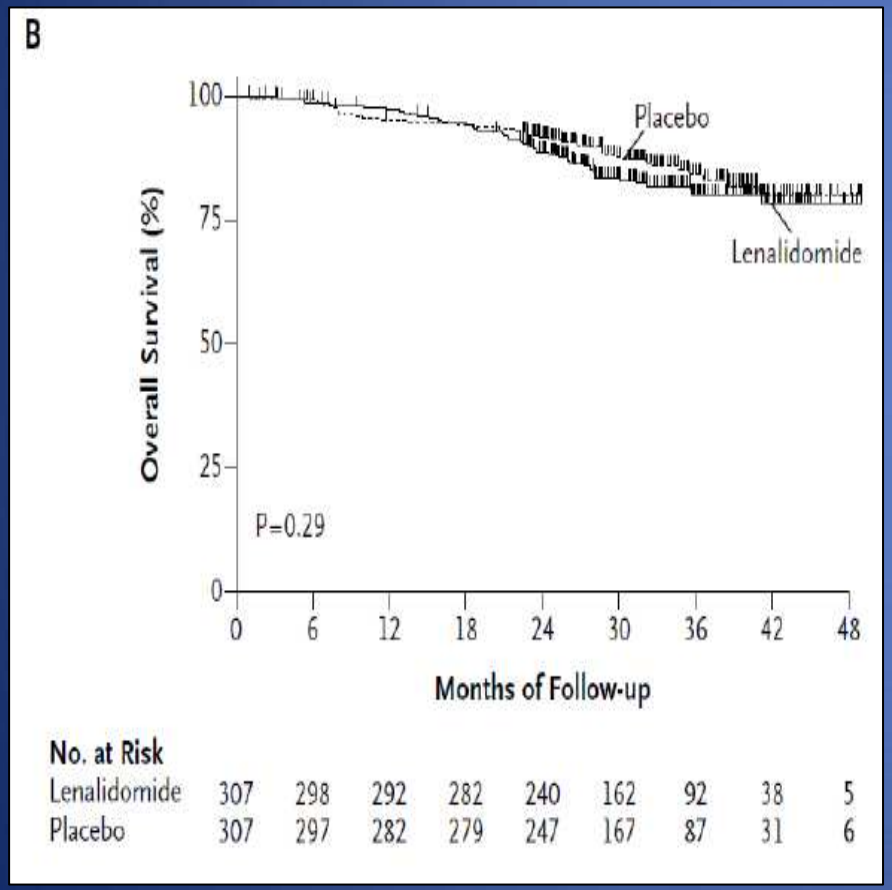
Median follow-up of ~ 48 mos.

Attal M, et al. N Engl J Med 2012; 366: 1782-1791. McCathy PL, et al. Clin Leuk Lymph Myeloma 2013: Suppl 1: abstract.

Lenalidomide Maintenance

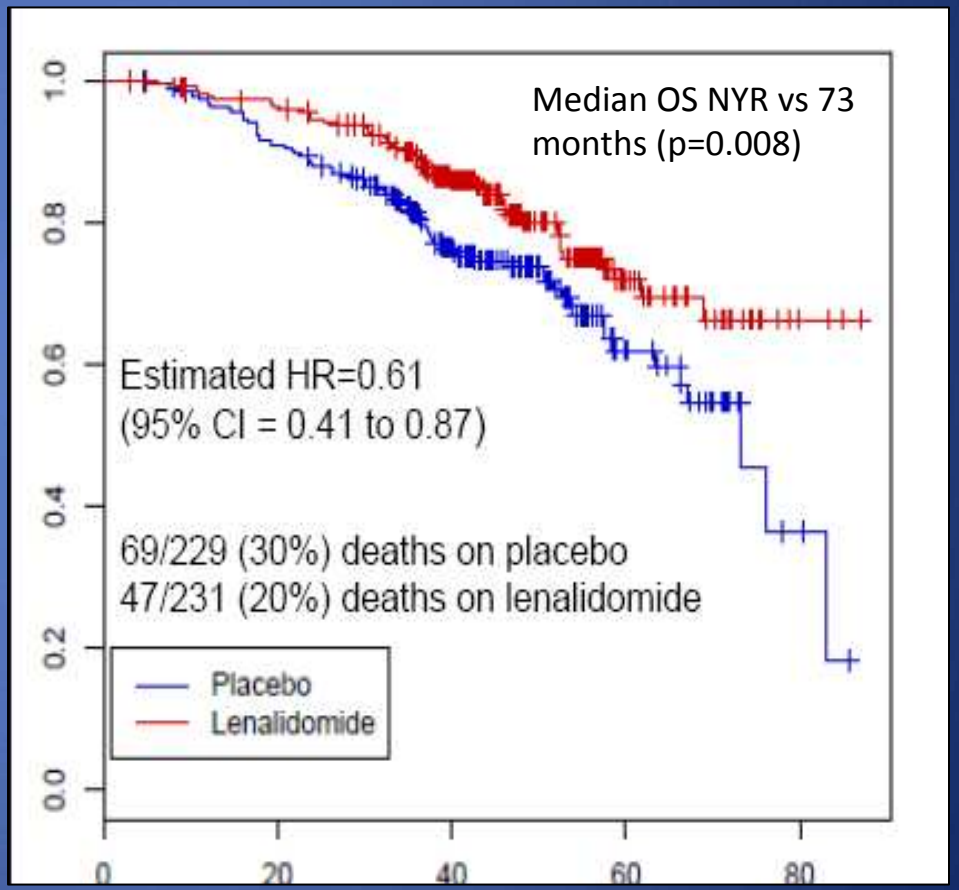
Effect on Overall Survival

IMF 2005-02



Median F/U mos. P=NS

CALGB 100104



Median follow-up of ~48 mos. P=0.008

Attal M, et al. N Engl J Med 2012; 366: 1782-1791.

McCathy PL, et al. Clin Leuk Lymph Myeloma 2013: Suppl 1: abstract.

Significant Toxicity with Lenalidomide Maintenance Phase III Trials

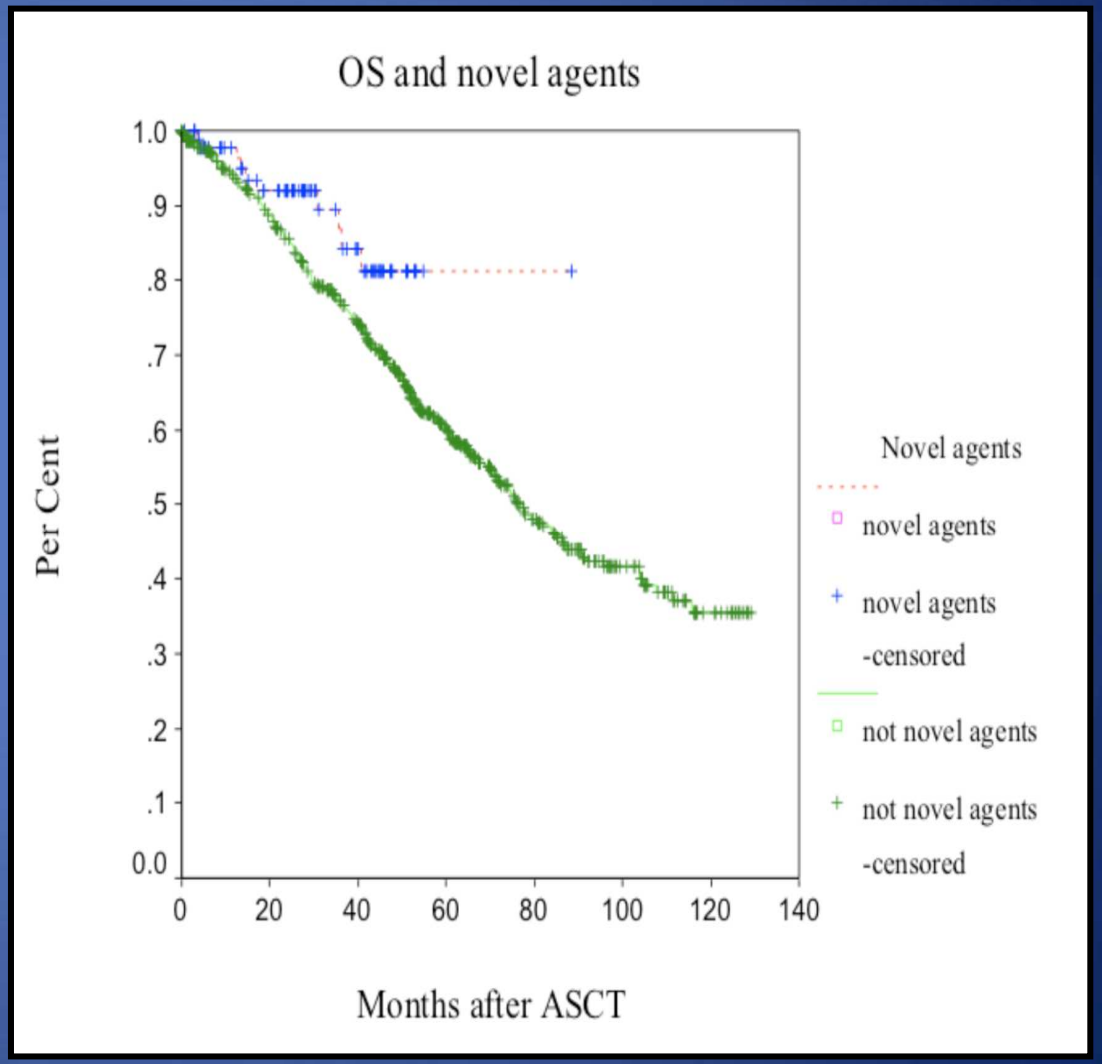
Toxicity	IMF 2005-02		CALGB	
	Len	Placebo	Len	Placebo
Neutropenia	43%	14%	43%	9%
Thrombocytopenia	12%	6%	13%	4%
Febrile neutropenia	2%	0.1%	6%	2%
Documented Infection	10%	4%	16%	5%
Discontinuation of lenalidomide	6%	4%	13%	2%
2º malignancy	N=23 (6.8%)	N=6 (1.6%)	N=18 (6.5%)	N=4 (2.6%)

Attal M, et al. ASCO 2010; abstract #8018; McCarthy PL, et al. ASCO 2010; abstract #8017; Attal M, personal communications; IMWG Feb 2011.

Effect of Novel Agents in Induction Therapy on ASCT Outcomes at PMH (N=754)

PMH Approach

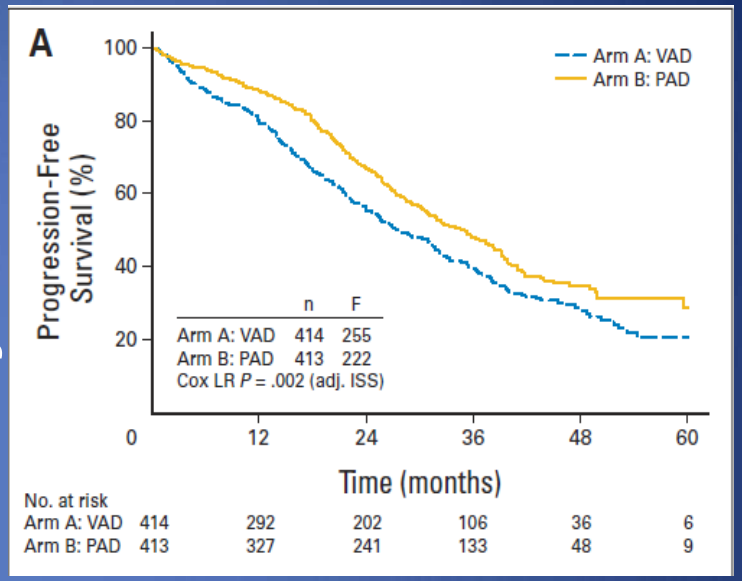
- Bortezomib-based regimens introduced in 2008
- Thalidomide maintenance used when possible until 2011
- Lenalidomide maintenance (until progression) introduced in 2011



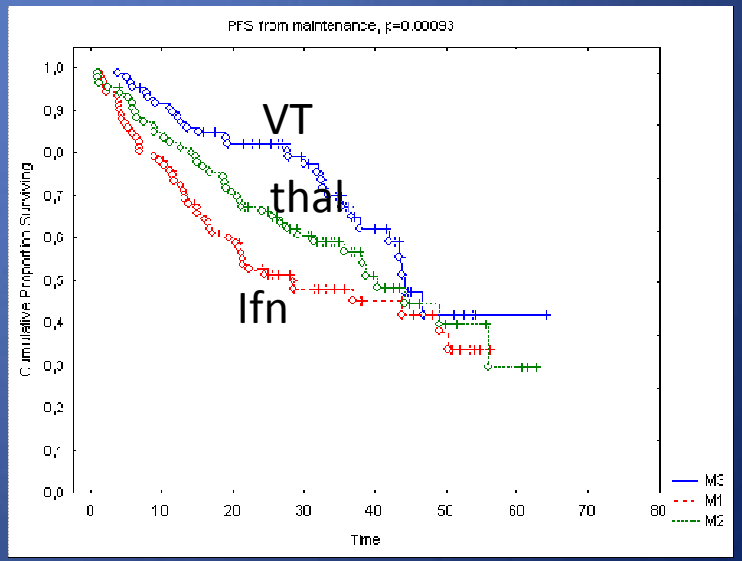
Jimenez-Zepeda, V et al. Unpublished data

Bortezomib-Based Maintenance

- HOVON MM 65/GMMG-HD4
  - *PAD + **bortezomib maintenance** vs VAD + thal maintenance*
  - *1 or 2 ASCTs*
  - *Significant improvement in PFS and OS for **PAD + B maintenance***
  - ***Improvement for del 17p subset***



- PETHEMA/GEM study
  - *VTD vs TD vs VBCMP/VBAD+ B*
  - *1 ASCT*
  - *VT vs thal vs interferon maintenance*
  - *Significant improvement in PFS for **VT maintenance***



Sonneveld P, et al. J Clin Oncol 2012; 30: 2946-2955;
Rosinol L, et al. Blood 2012; 120:

Post-ASCT Measures
Consolidation Trials

- Cavo et al.(GEMIMA study)
  - VTD x 3 → *ASCT x 2 → VTD x 3*
- Roussel et al. (IFM 2008)
  - VRD x 3 → *ASCT → VRD x 2 → lenalidomide maintenance x 1 year*
- Sonneveld et al. (HOVON)
  - CTD* x 4 → *ASCT → CTD* x 4*

*Carfilzomib + thalidomide + dex

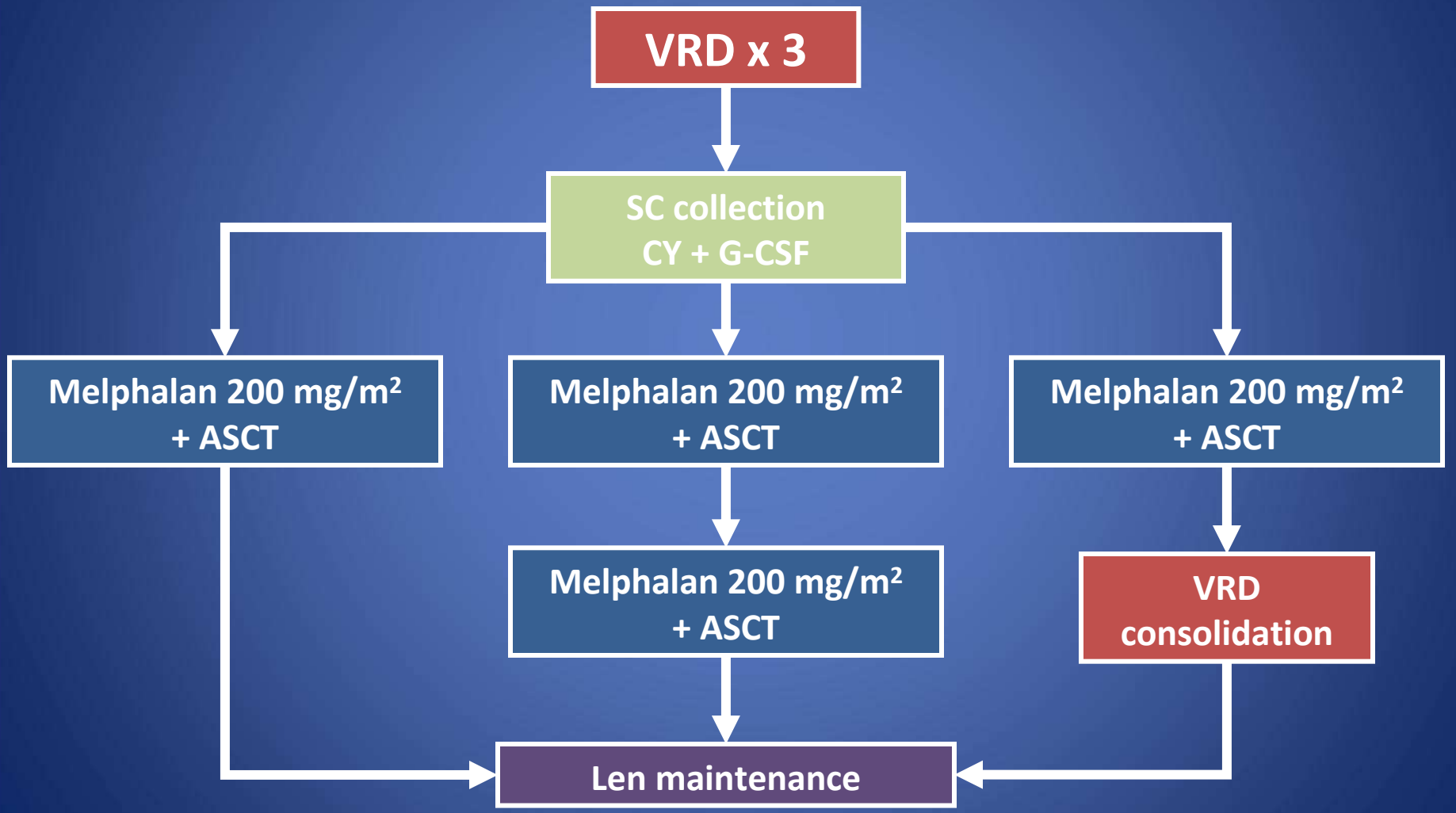
[1]Cavo M, et al. Blood 2012; 120: 9-19; [2] Roussel M, et al. Blood 2011; 118: abstract 1872; [3]Sonneveld P, et al. Blood 2012; 120: abstract 333.

Results of Post-ASCT Consolidation

Study	Trial Type	Rx	Maint	Post-ASCT Response (%)			Post-consolidation Response (%)			PFS
				≥PR	≥VGPR	CR	≥PR	≥VGPR	CR	
Cavo[1]	III	VTD	Dex			55			61	60% (3 yr)
Roussel[2]	II	VRD	Len x 1 yr	91	26	42	94	36	48	
Leleu[3]	Retro	VTD	None	96	43	33	96	31	52	
Sonneveld[4]	II	CTd	None	91	60	18	94	84	44	97% (1 yr)

[1]Cavo M, et al. Blood 2012; 120: 9-19; [2] Roussel M, et al. Blood 2011; 118: abstract 1872; [3] Leleu X, et al. Leukemia Epub ahead of print 4 April 2013; [4]Sonneveld P, et al. Blood 2012; 120: abstract 333.

Post-ASCT Therapy: CTN Trial



ASCT in Myeloma
Summary-1

- Improved response rates after newer frontline regimens
- Median PFS has improved from 2 to 3 years
  - *Should target minimum PFS of 3 years with your approach*
- Post-transplant therapy can improve response rates and PFS further
  - *Both maintenance and consolidation have efficacy*
  - *Impact on survival less clear but 2 studies and a meta-analysis show benefit*

ASCT in Myeloma
Summary-2

- More individualized approaches desirable
  - *Reliable identification of subsets most likely to benefit from post-ASCT therapy*
  - *Use of MRD to direct need for and duration of therapy*

- It is important to have a strategy for transplant-eligible patients
  - *Should be able to provide PFS for initial therapy with your approach*
  - *Keep in mind that minimal data is available for PFS after deferred ASCT in any risk group*
    - Phase III trials are in progress

Treatment Strategies in Older Multiple Myeloma Patients: Phase III Trials

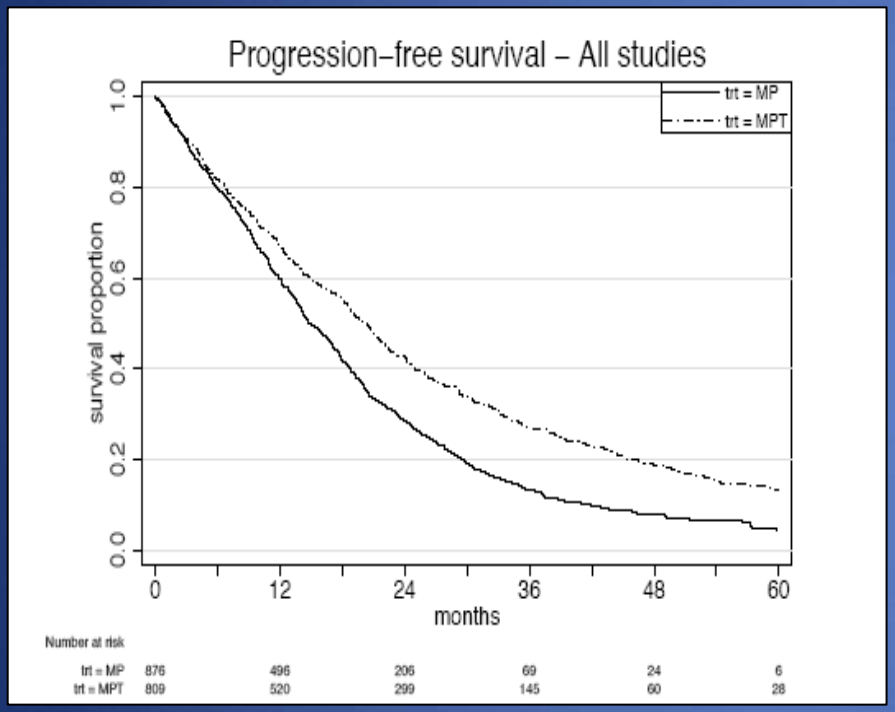
- Addition of novel agent to melphalan and prednisone
  - *MP + thalidomide (MPT)*
  - *MP + bortezomib (VMP) +/- VP or VT maintenance*
  - *MP + lenalidomide with lenalidomide maintenance (MPR + R)*
  - *VMPT + VT maintenance*

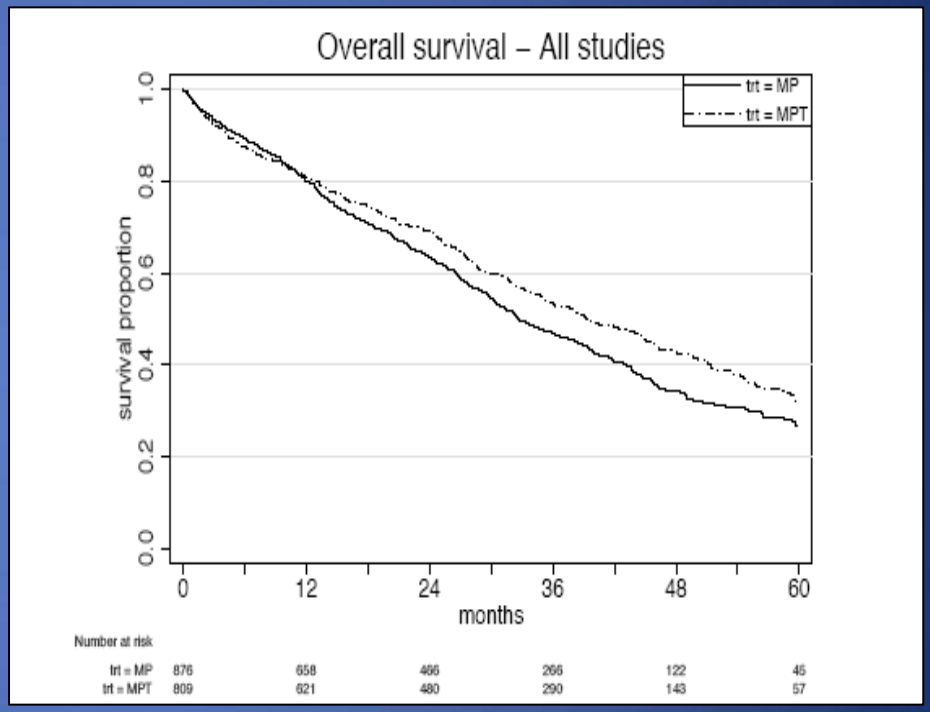
- Continuous treatment with IMiD and steroids
  - *Thalidomide + dex--generally too toxic*
  - *Lenalidomide + weekly dex promising*
    - *Widely used in US based on ECOG trial*
    - ***MM020 trial results awaited (MPT vs Len + dex)***

- Other 3- and 4-drug regimens
  - *aCTD*

Meta-analysis: MPT vs MP (n=1685)

Progression-Free and Overall Survival



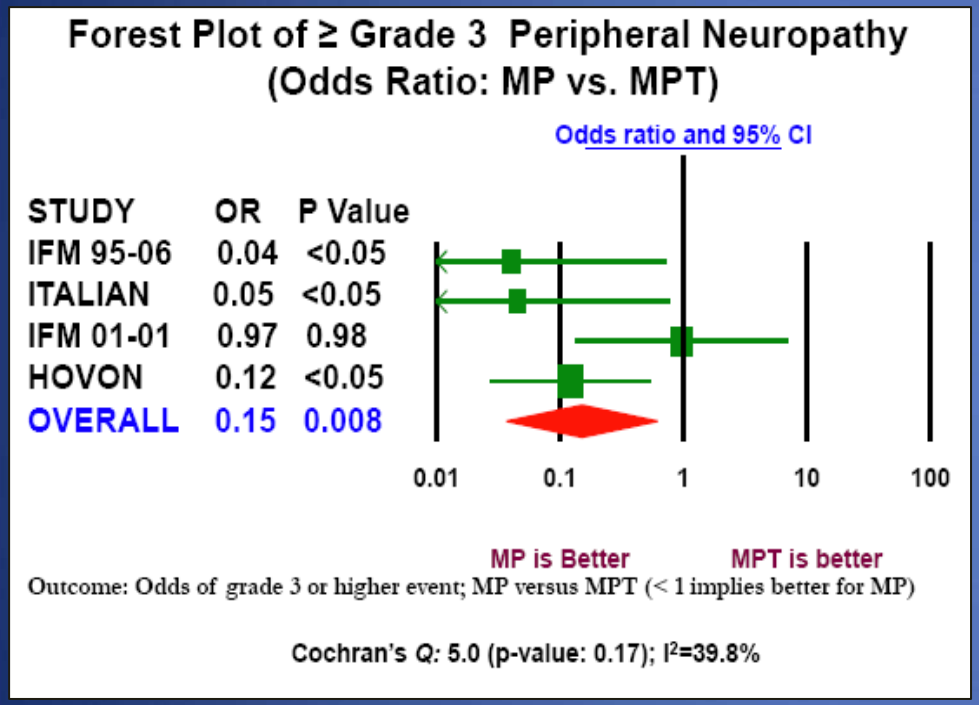


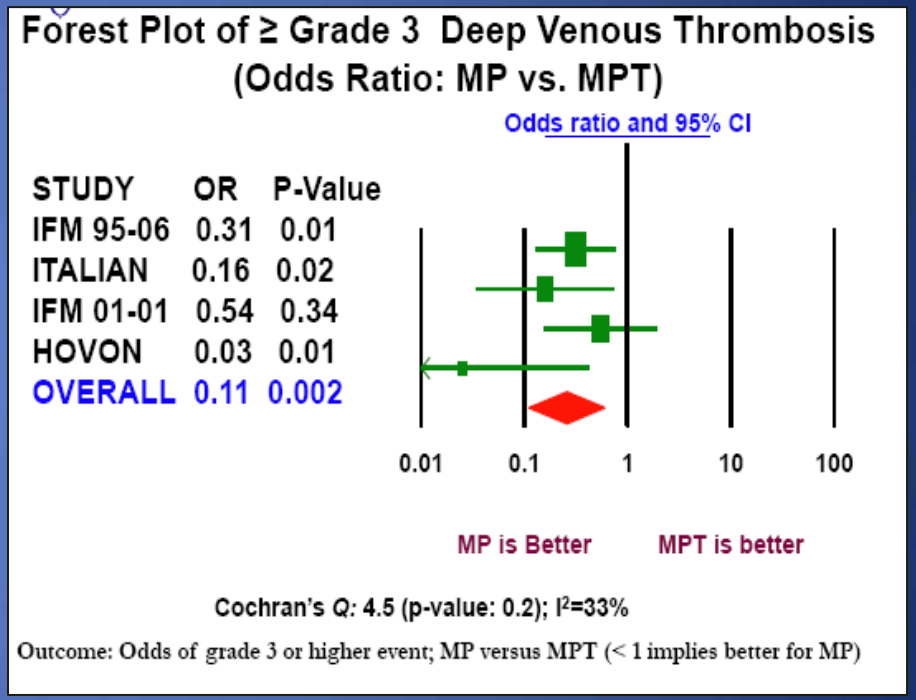
- *Addition of thalidomide to MP demonstrates significant improvement in PFS and overall survival*

Fayers PM, et al. Blood 2011; 118: 1239-1247

Meta-analysis: MPT vs MP

Adverse Events ≥ Grade 3





- *Addition of thalidomide to MP is associated with significantly greater incidence of grades 3-4 neurotoxicity and DVT*

Kapoor *et al*. ASH 2009 (abstract 615); Presentation Slides: http://myeloma.org/pdfs/ASH2009_Kapoor_615.pdf

Newer Induction Regimens for Elderly Patients

Bortzomib-Containing Regimens

Regimen	Maintenance	Trial type	ORR (%) (CR/nCR)	Median PFS (mos)	Median OS (mos)
MP[1]	-	III	35%(4%)	16.6	43.1
VMP[1]	-	III	71% (30%)	24	56.4
VMP[2]	+ (VT or VP)	III	91-95% (39-46%)	32-39	50-69% (5-year)
VMP[3]	+ (V)	III	69% (33%)	17.3	88.9% (1-year)
VTD[3]	+ (V)	III	80% (40%)	13.8	86.1% (1-year)
Bor + dex[3]	+ (V)	III	73% (30%)	14.7	87.4% (1-year)
VMPT[4]	+ (VT)	III	89% (38%)	35.3	61% (5-year)

[1] San Miguel JF, et al. N Engl J Med 2008; 359: 906-917; San Miguel SF, et al. J Clin Oncol 2013; 31: 448-455; [2]Mateos MV et al. Blood 2012: 120: 2581-2588; [6]Niesvizky R, et al. Blood 2011; 118: abstract 478; [4]Palumbo A, et al. Blood 2012; 120: abstract 200.

Newer Induction Regimens for Elderly Patients

IMiD-Based

Regimen	Maintenance	Trial type	ORR (%) (CR/nCR)	Median PFS (mos)	Median OS (mos)
MP[1]	-	Meta	37%	14.9	32.7
MPT[1]	+/-	Meta	59%	20.3	39.3
MPR-R	+ (R)	III	77% (10%)	31	70% (3-year)
Len+ dex[3]	NE	III	74%	22	73% (3-year)
aCTD[7]	+/-	III	64% (13%)	13	31

[1]Fayers PM, et al. Blood 2011; 118: 1239-1247; [2]Palumbo A, et al. N Engl J Med 2012; 366: 1759-1769; [3]Jacobus S et al. Haematologica 2010; 95 (Suppl 2): 149, abstract 0307.; [4]Mrogan GJ, et al. Blood 2011; 118: 1231-1238;

Toxicity Concerns in Elderly Patients

Drug	Peripheral Neuropathy	Fatigue	Myelosuppression	VTE	Secondary cancers
Melphalan	-	(+)	+++	-	++
Cyclophosphamide (weekly or daily)	-	+	+	-	+
Thalidomide	+++	+++	-	++	-
Bortezomib	+++	+	+	-	-
Lenalidomide	-	++	++	++	++ (mostly with alkylating agents)

Patient tolerance improved with:

-- Weekly dosing of bortezomib in combinations

-- Low- dose weekly dexamethasone

Selection of Therapy in Elderly Patients
Considerations

- Disease-related factors
  - Aggressive disease
  - Renal failure

  → Bortezomib-based

- Patient-related factors
  - Fragility
  - Age over 75 years
  - Mobility
  - Co-morbidities (diabetes, PN, hx VTE)

  → Two agents (Len + dex)

- Treatment-related
  - Myelosuppression
  - PN

  → Avoid melphalan and lenalidomide

  → Avoid bortezomib and thalidomide

Future Directions

- MP + MLN 9708[1]
- MP + carfilzomib

ASCO 2013, Touzeau C ,et al. Abstract 8513.

- Lenalidomide + dex +/- elotuzumab[2]
- Lenalidomide + dex +/- MLN 9708[3]
- CRd = carfilzomib + lenalidomide + dex

ASCO 2013, Jakubowiak AJ,et al. Abstract 8513.

- CCd = carfilzomib + cyclophosphamide + dex[4]

[1]Kumar S, et al. Blood 2012; 120: abstract 633; [2]Lonial S, al. J Clin Oncol 2012; 30: 1953-1959; [3]Richardson PG, et al. Blood 2012; 120: abstract 727; Palumbo A, et al. Blood 2012; 120: abstract 730.

Elderly Myeloma Patients
Summary-1

- Addition of novel agent to MP improves TTP/PFS
  - *Toxicity is increased*
  - *MPT and VMP are both effective*
    - Weekly bortezomib much better tolerated
    - Shingles prevention required with bortezomib
  - *Mixed results for overall survival*

- Maintenance therapy prolongs PFS
  - *Survival benefit noted in one study*

Elderly Myeloma Patients
Summary-2

- Thalidomide + dexamethasone not recommended
  - Too toxic
- Lenalidomide + weekly dex very well tolerated
  - *PFS appears similar to MP + novel agent but no phase III data yet*
- Regimens using newer proteasome inhibitors (carfilzomib and MLN 9708) under development

Summary/Conclusions

- Laboratory insights are helping to dissect biology of disease and stratify patients
- New drugs/combinations are improving outcomes
- Improvements in toxicity management in progress
- Newer classes of drugs are under development
- New methods to evaluate myeloma burden will be useful
- Efforts to personalize myeloma treatment are evolving