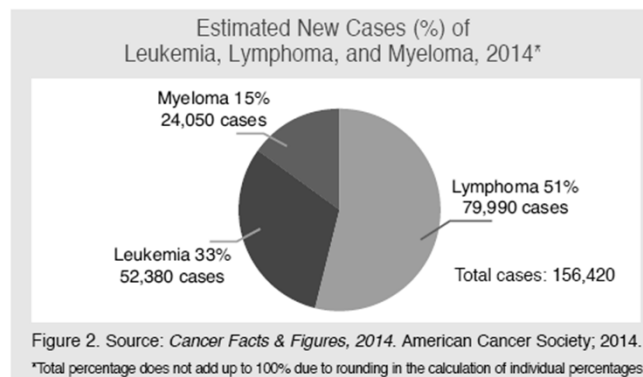


Multiple Myeloma in the Aging Adult

Ashley Rosko, MD
Assistant Professor-Clinical
Division of Hematology
The Ohio State University Wexner Medical Center

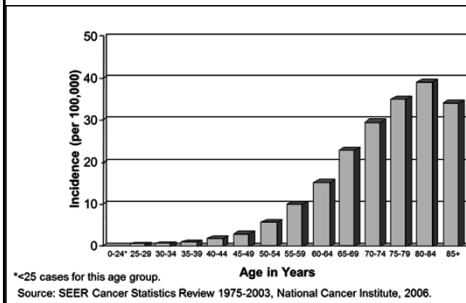
Hematologic Malignancy



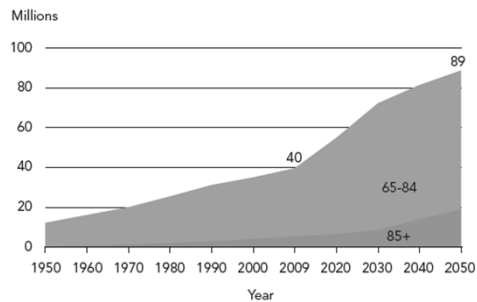
Myeloma Dynamic Field
Epidemic
57% Increase by 2030

Myeloma is a disease of aging adults

- Median age diagnosis: 69



U.S. Population Ages 65 and Older, 1950 to 2050



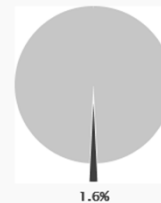
Surveillance, Epidemiology, and End Results (SEER) Program Populations
U.S. Census Bureau

MM is a rare blood cancer

Blood
Cancer
4th

Common Types of Cancer	Estimated New Cases 2015	Estimated Deaths 2015
1. Breast Cancer (Female)	231,840	40,290
2. Lung and Bronchus Cancer	221,200	158,040
3. Prostate Cancer	220,800	27,540
4. Colon and Rectum Cancer	132,700	49,700
5. Bladder Cancer	74,000	16,000
6. Melanoma of the Skin	73,870	9,940
7. Non-Hodgkin Lymphoma	71,850	19,790
8. Thyroid Cancer	62,450	1,950
9. Kidney and Renal Pelvis Cancer	61,560	14,080
10. Endometrial Cancer	54,870	10,170
-	-	-
14. Myeloma	26,850	11,240

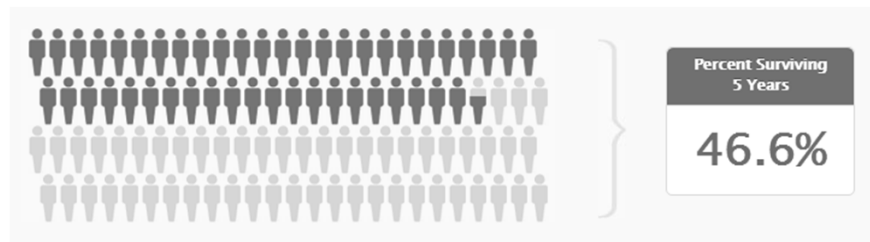
Myeloma represents 1.6% of all new cancer cases in the U.S.



- Older adults
- Male : Female 1.5:1
- 2-3X African American Population
- 3.7 fold higher risk (+) family member

Surveillance, Epidemiology, and End Results
(SEER) Program Populations

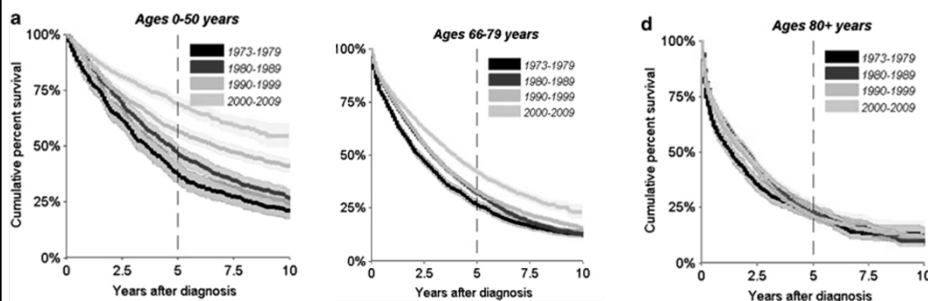
Myeloma Highly Treatable: Not Curable



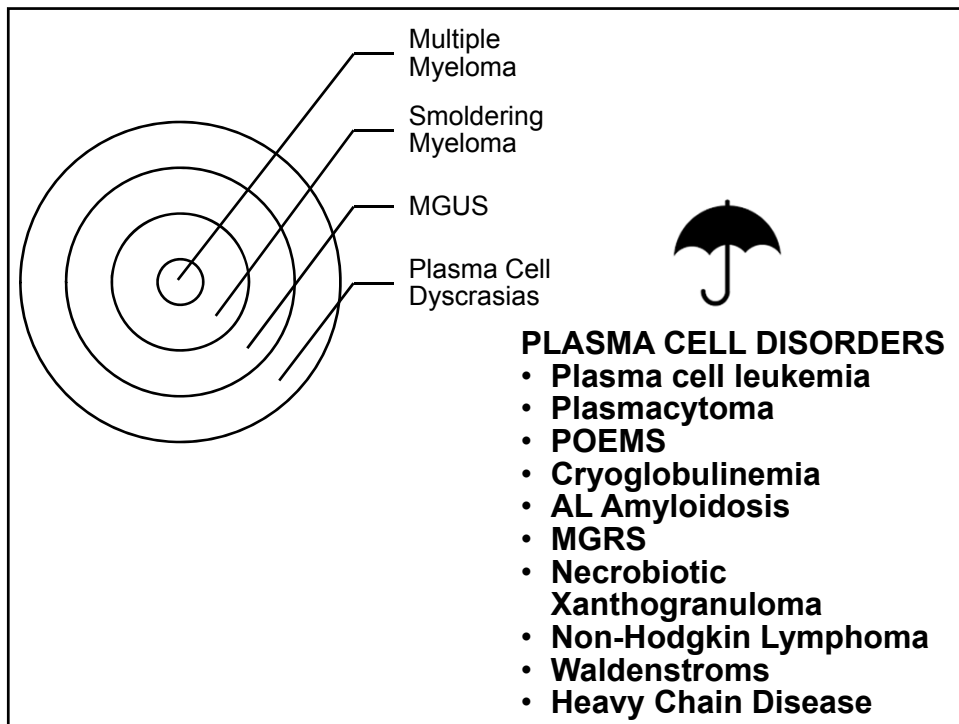
Surveillance, Epidemiology, and End
Results (SEER) Program Populations

Challenges: Age Disparities in MM Survival

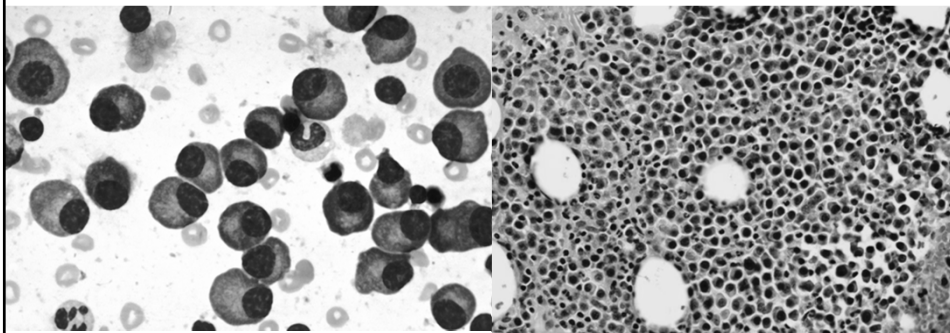
- 5 year survival: 48.5%
- Significant improvement in long term survival
- Modest improvements in survival for aging adults



Improved long-term survival in multiple myeloma up to the age of 80 years
S Y Kristinsson, W F Anderson and O Landgren Leukemia May 2014



Multiple Myeloma: Clonal expansion of malignant plasma cells



Normal: 2-3% Bone marrow population
Polyclonal

C: Calcium elevated
 -fatigue, drowsiness, confusion
 - severe abdominal pain

R:Renal failure
 - poor urine output
 - swelling of legs / feet
 - poor control of electrolytes and minerals

A: Anemia
 fatigue, SOB, exhaustion

B: Bone disease
 lytic lesions
 severe osteoporosis
 -fractures

- *****E: Extra**
- Clonal plasma cells in BM $\geq 60\%$
 - Serum FLC ratio ≥ 100
 - > 1 MRI focal lesion ≥ 5 mm on MRI



Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Revised IMWG Diagnostic Criteria for Multiple Myeloma*

Multiple Myeloma

- Clonal BM plasma cells $\geq 10\%$ or ≥ 1 biopsy-proven plasmacytoma AND 1 or more MM-defining events:
- ≥ 1 CRAB[†] feature
- Biomarkers of malignancy:
 - Clonal plasma cells in BM $\geq 60\%$
 - Serum FLC ratio ≥ 100
 - > 1 MRI focal lesion ≥ 5 mm on MRI, positive PET or CT,

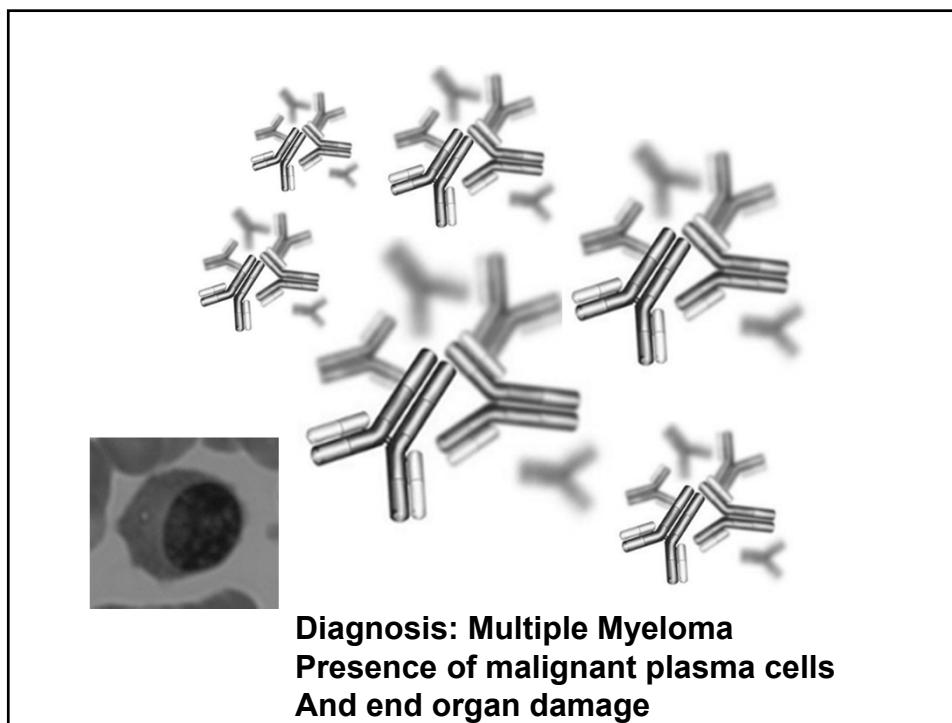
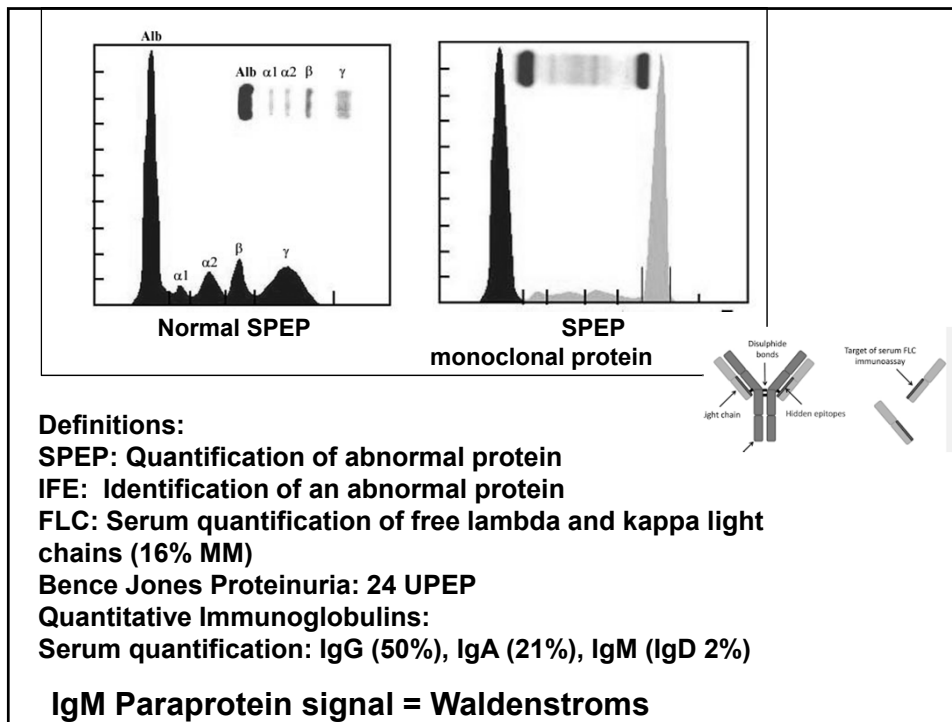
C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)

R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)

A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)

B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.



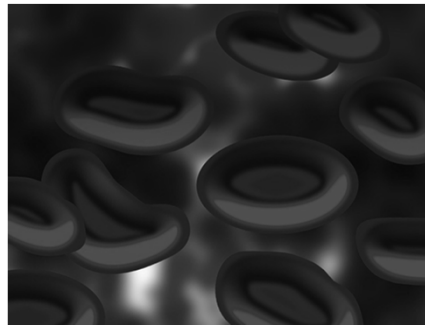
Anemia Under recognized: Not a normal part of aging

Table 1.

Prevalence of Anemia in Nursing Home Residents

	NGRC ²³	Beverly Healthcare ²⁴
Sample size	900	6,200
Age, median (yr)	79	83
≥65 years	87%	100%
Female	63%	70%
Anemia		
Hb, mean (g/dL)	11.9 female	11.8 (total)
	12.9 male	
Prevalence*	48%	60%
Hb < 10 g/dL	11%	13%

* Who checked on the 10 g/dL for men and 11.5 g/dL for women.



- Anemia work-up
- 2/3 MM have Anemia at Dx
- Protein-albumin – 97% M protein

Artz 2008 Semin Hematol

Half of patients will have bone disease at presentation



- Hypercalcemia**
- 1/3 Patients At diagnosis

Primary and Secondary Osteoporosis Challenge in MM Population

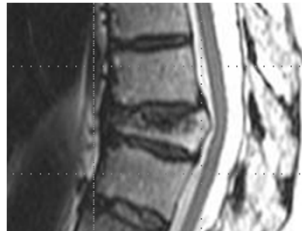


Primary osteoporosis:

Deterioration of bone unassociated with other chronic illness and is related to aging and decreased gonadal function.

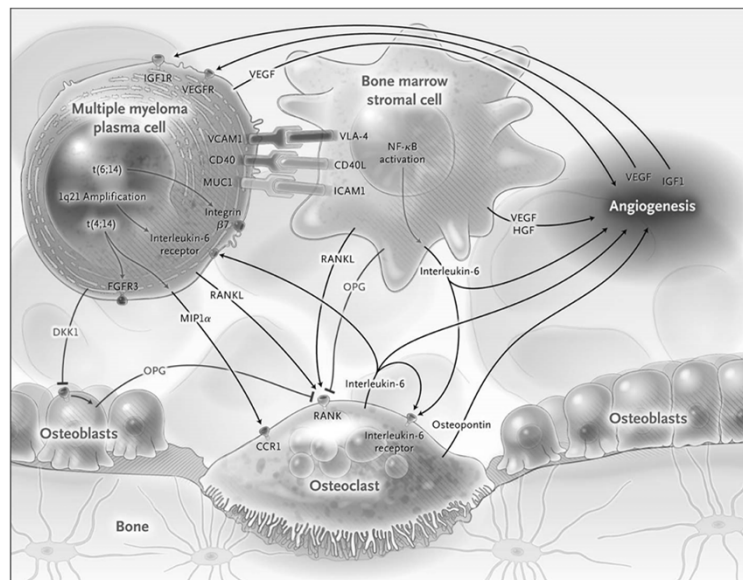
Secondary osteoporosis:

2/2 chronic conditions that accelerated bone loss



Clinically, distinguishing fragility fractures related to primary osteoporosis from MM induced compression fractures is problematic.

- Steroid use
- Tempo? Sudden onset more than 1 fracture
- Other bone pain



Palumbo A, Anderson K. N Engl J Med 2011;364:1046-1060

How do you image?

- Bone Scan = osteolytic and osteoblastic activity
- Bone Surveys (Plain x-rays) = pick up lytic lesions
MM unopposed osteolytic activity
- 50% of bone needs to be gone to pick them up
 - Osteoporosis
- MRI and sometimes PET scans
 - Extramedullary disease 7%
 - Non-secretory disease
- Supportive care: Bisphosphonates and/or Radiation

Half of MM patients present with Renal Disease

Renal Injury = TREATMENT ASAP

Renal Recovery?

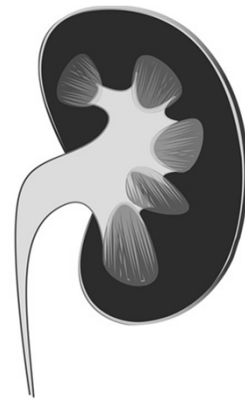
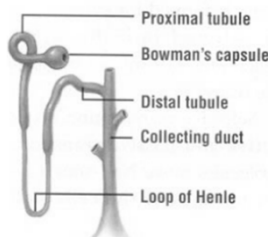
Type of Protein

Underlying Renal Disease

Medications (NSAIDS, contrast)

Renal Entities

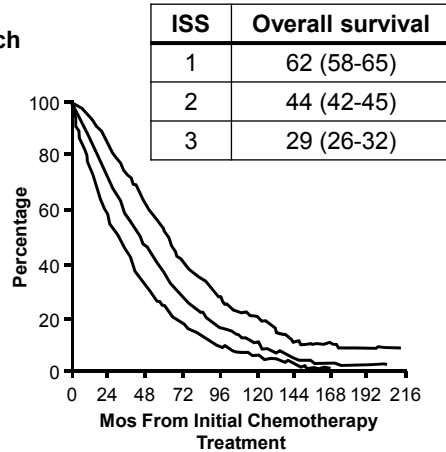
- MGRS
- Hyperviscosity
- Controversial
- Plasma exchange



International Staging System for Myeloma

How proliferative is MM and how much
End organ damage?

Stage	Criteria
Stage I	β_2 -M < 3.5 mg/L and serum albumin \geq 3.5 g/dL
Stage II	Not stage I or III
Stage III	β_2 -M \geq 5.5 mg/L



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

Cytogenetics Highly Informative

High Risk	Intermediate Risk	Standard Risk
17p deletion	t(4;14)	Hyperdiploidy (trisomies)
t(14;16)	Deletion 13 by karyotyping	t(11;14)
t(14;20)	hypodiploidy	t(6;14)
High risk gene expression profiling	1q abnormality	Normal cytogenetic
Complex Karyotype		Del 13 by FISH (molecular)
Del 17p or P53		

Rajkumar SV. Treatment of multiple myeloma. Nat Rev Clin Oncol 2011; 26:479.

Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. Am J Hematol 2012; 87:78.

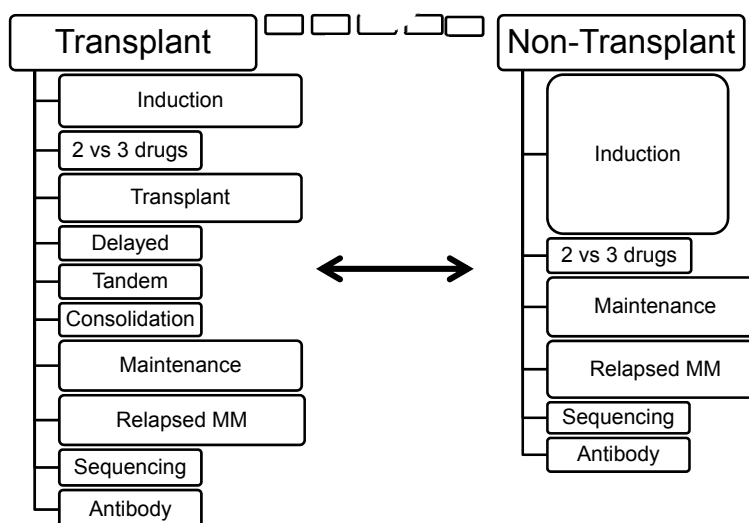
Revised International Staging System (R-ISS)

- 4,445 newly diagnosed patients enrolled onto 11 multicenter trials 2005-2012.
- Presence of Del(17p), t(4;14), or t(14;16) were considered high risk.

R-ISS	ISS	iFISH	LDH	OS
1	$\beta 2M < 3.5$, Alb ≥ 3.5	Standard	Normal	NR
2				83 mos.
3	$\beta 2M \geq 5.5$	High risk or high		43 mos.

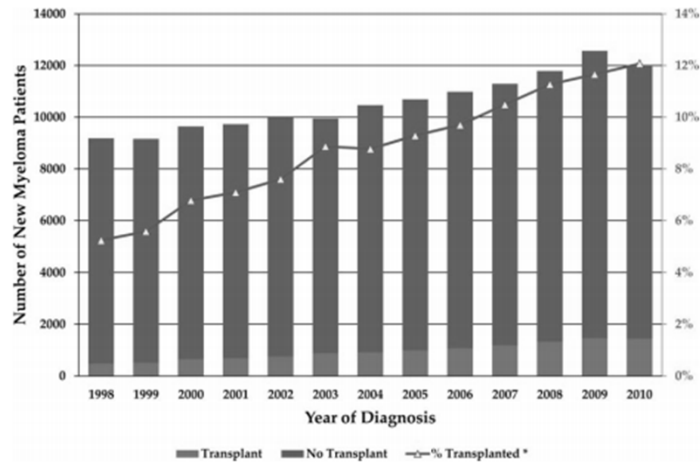
Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. *JCO* 33, 3-Aug-2015.

Treatment: Standard of Care Autologous Hematopoietic Stem Cell Transplant



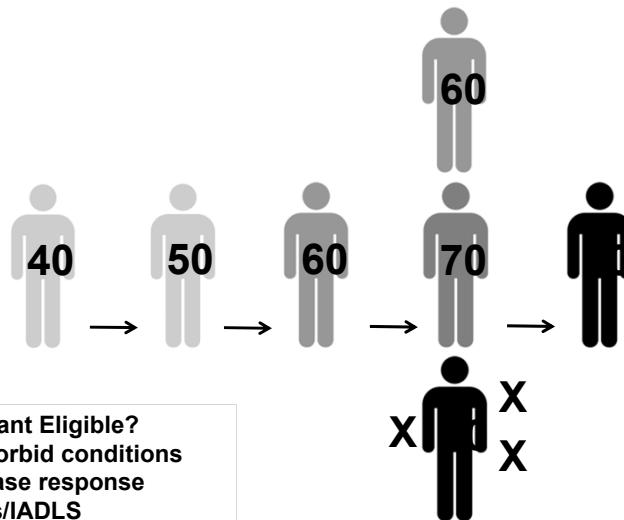
22

Majority of Myeloma Patients do not receive Transplant



Am. J. Hematol. 89:825-830, 2014

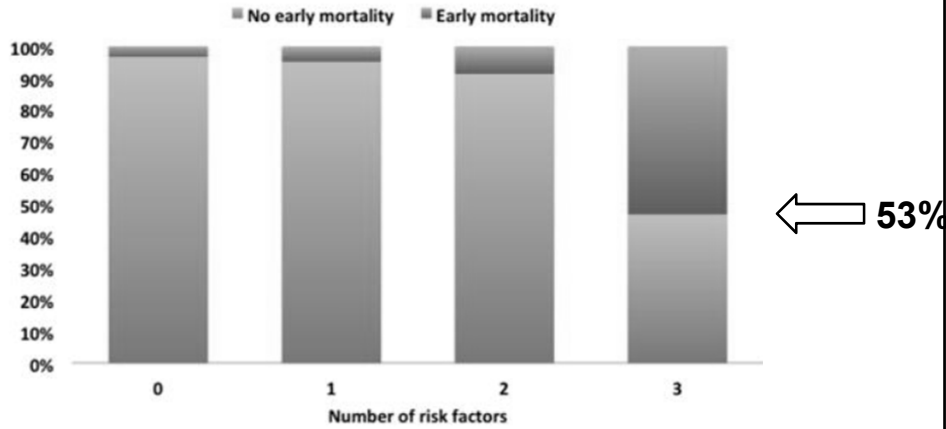
Approach to treatment based on Physiologic Reserve Biologic age \neq chronologic age



- Transplant Eligible?**
- Comorbid conditions
 - Disease response
 - ADLs/IADLS
 - Psychosocial support
 - Patient goals of care

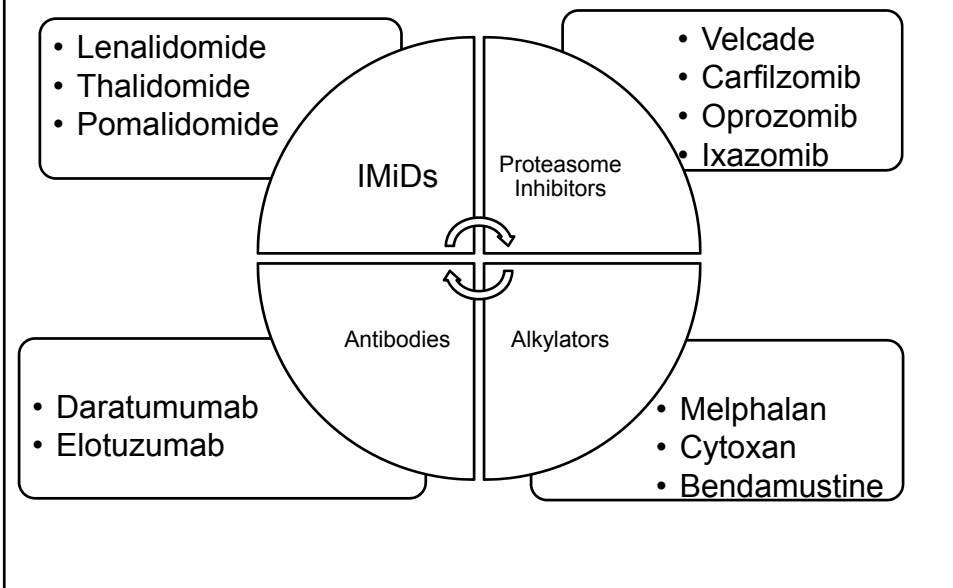
Prompt Recognition and Referral: Early Death in Older Adults with Myeloma

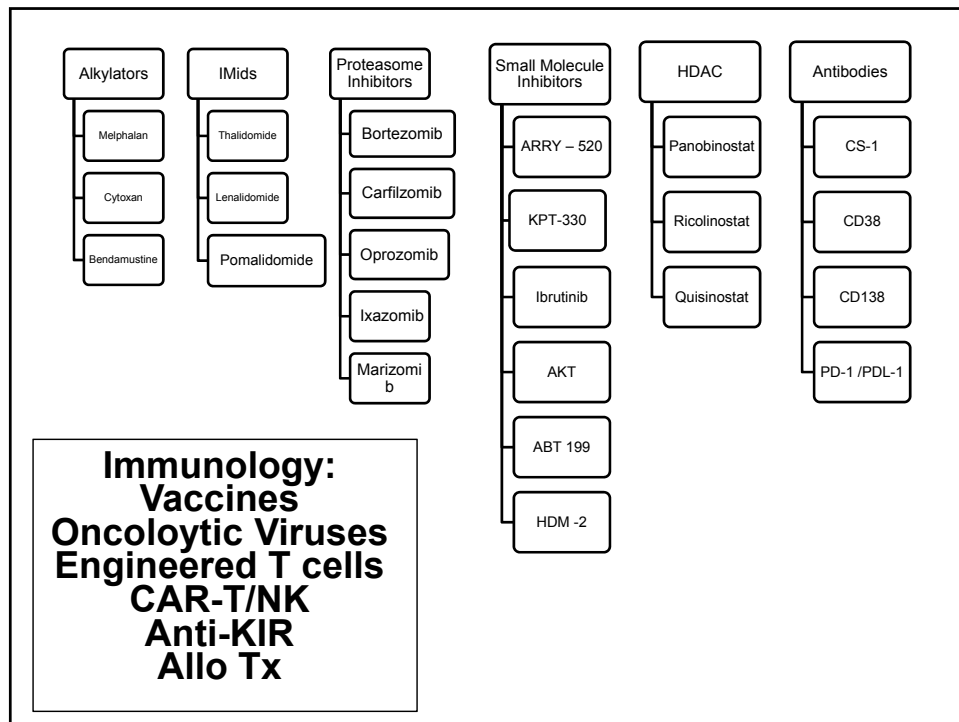
- MM deaths overall are highest: aged 75 years and greater
- Early mortality (death within one year of diagnosis) is most common in those 70 years and older



Kumar SK, et al *Leukemia*. May 2014;28(5):1122-1128.

Targeted Novel Therapy: Pills, shots, and immunotherapy





Diagnosis Of Multiple Myeloma and Treatment of Transplant Eligible Patients

Yvonne Efebera, MD, MPH
 Associate Professor-Clinical
 Division of Hematology
 The Ohio State University Wexner Medical Center

Objectives

- Know the difference between MGUS, smoldering Myeloma, Symptomatic multiple Myeloma
- Understand the general clinical features of plasma cell myeloma including the diagnosis, and steps required for evaluation.
- Understand Treatment strategy:
 - Newly diagnosed Multiple Myeloma Patients Eligible for Transplant
 - Newly diagnosed Multiple Myeloma Patients not Eligible for Transplant – Ashley Rosko

Revised IMWG Diagnostic Criteria for Multiple Myeloma*		
MGUS	Smoldering	Multiple Myeloma
<ul style="list-style-type: none"> ▪ M protein < 3 g/dL and ▪ Clonal plasma cells in BM < 10% ▪ No myeloma defining events 	<ul style="list-style-type: none"> ▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM 10% to 60% ▪ No myeloma-defining events 	<ul style="list-style-type: none"> ▪ Clonal BM plasma cells ≥ 10% or ≥ 1 biopsy-proven plasmacytoma AND 1 or more MM-defining events: ▪ ≥ 1 CRAB[†] feature ▪ Biomarkers of malignancy: MDE <ul style="list-style-type: none"> • Clonal plasma cells in BM ≥ 60% • Serum FLC ratio ≥ 100 • > 1 MRI focal lesion ≥ 5 mm on MRI, positive PET or CT,
<p>†C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN) R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL) A: Anemia (Hb < 10 g/dL or 2 g/dL < normal) B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)</p> <p>*New criteria associated with ≥ 80% risk of progression to MM within 2 yrs.</p> <p>Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.</p>		

Risk of MGUS → Myeloma

Risk group	Relative Risk	Risk @ 20 yrs
Lowest risk: 1. M protein < 1.5 g/dL 2. IgG subtype 3. Normal FLC ratio (K/L)	1	5%
Any 1 factor abnormal	5.4	21%
Any 2 factors abnormal	10.1	37%
All 3 factors abnormal	20.8	58%

Rajkumar, V et al. *Blood* . 2005

Smoldering Multiple Myeloma (SMM)

% of cases that transition from Smoldering Myeloma to Multiple Myeloma in 5 years

Mayo Clinic Criteria	3 criteria:	1/3	2/3	3/3
	1. M-protein ≥ 3 g/dL 2. $\geq 10\%$ clonal bone marrow plasma cells 3. Free light-chain < 0.125 or > 8	25%	51%	76%

NO consensus on

1: if to treat SMM

2: When to start treatment

Clinical trials ongoing

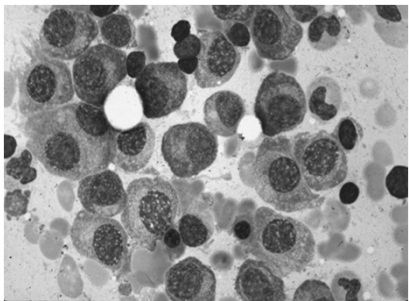
Currently: watch until Progression to MM

Symptomatic Multiple Myeloma

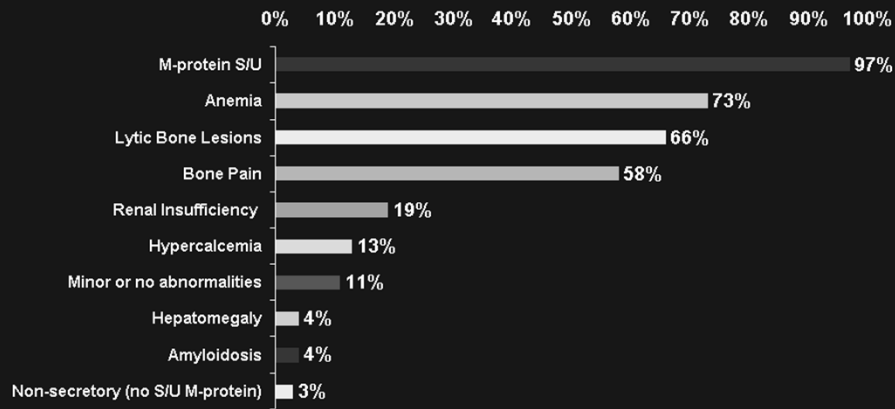
- ◎ About 20,000-22,000 new cases a year in the US
- 10% of hematologic malignancies – 2nd most common blood Cancer
 - 1% of all cancers
- About 75,000 patients living with MM in the US today
- Blacks > white (2:1) Males>Females (1.4:1)
- About 700 new cases in Ohio annually
- Causes: mainly unknown, but some environmental exposures are associated:
 - Ionizing radiation, organophosphates, benzene, agent orange,
 - First responders at WTC on 9/11/01

Most Important: it is not Curable BUT VERY TREATABLE

Every Myeloma Doc's Nightmare



Presenting Features of MM



Others: Wt loss (24%), paresthesias, LAD, splenomegaly

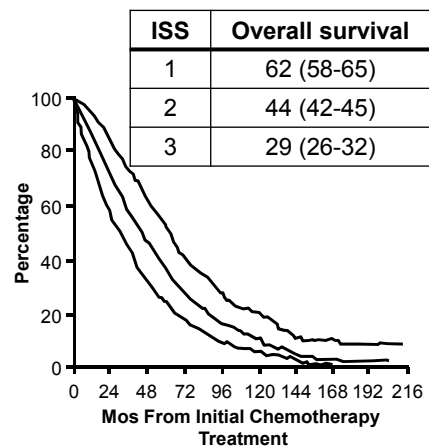
Adapted with permission from Kyle RA et al. *Mayo Clin Proc.* 2003;78:21

© 2007 IJ cmo

International Staging System for Symptomatic Myeloma

OLD and Older treatments used

Stage	Criteria
Stage I	β_2 -M < 3.5 mg/L and serum albumin \geq 3.5 g/dL
Stage II	Not stage I or III
Stage III	β_2 -M \geq 5.5 mg/L



Greipp PR, et al. *J Clin Oncol.* 2005;23:3412-3420.

Risk stratification: multiple myeloma is not one disease!

High Risk	Intermediate Risk	Standard Risk
17p deletion	t(4;14)	Hyperdiploidy (trisomies)
t(14;16)	Deletion 13 by karyotyping	t(11;14)
t(14;20)	hypodiploidy	t(6;14)
High risk gene expression profiling	1q abnormality	Normal cytogenetic
Complex Karyotype		Del 13 by FISH (molecular)
Del 17p or P53		

Myeloma patients are risk-stratified at initial diagnosis based on fluorescence in situ hybridization (FISH) studies on the bone marrow for t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, and trisomies of odd numbered chromosomes. If FISH is unavailable, conventional cytogenetics can be used as an alternative, but is much less sensitive.

Rajkumar SV. Treatment of multiple myeloma. Nat Rev Clin Oncol 2011; 26:479.

Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. Am J Hematol 2012; 87:78.

Revised ISS and Novel agents

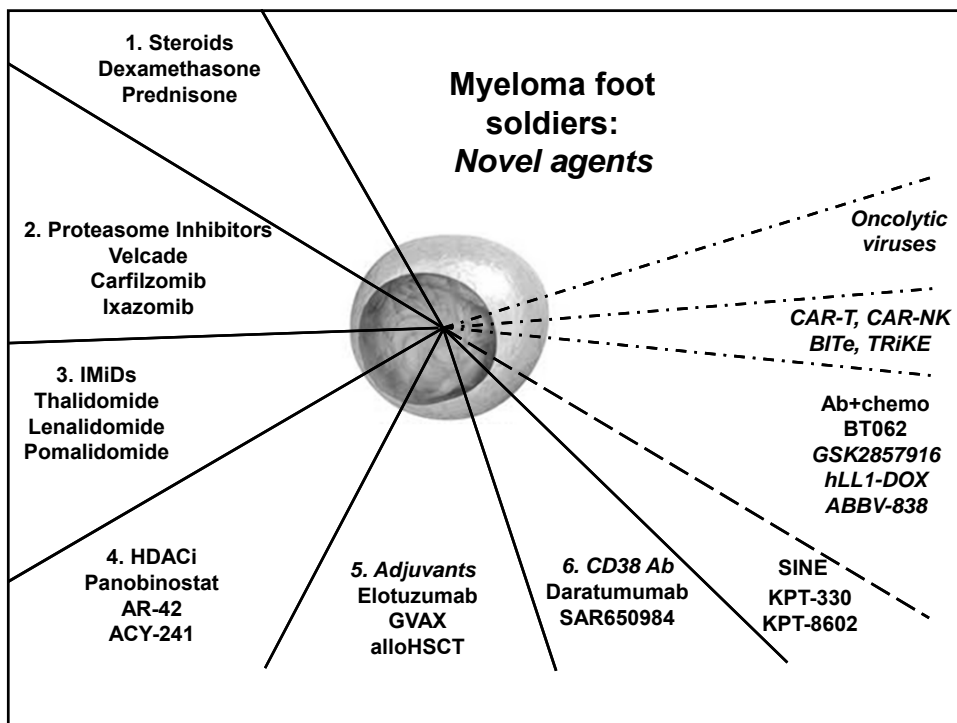
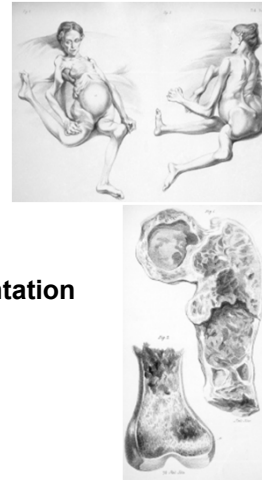
- 4,445 newly diagnosed patients enrolled onto 11 multicenter trials 2005-2012.
- Goal was to incorporate CD138-selected interphase FISH and tested for del(13), del(17p), and 14q32 translocations.
- Presence of Del(17p), t(4;14), or t(14;16) were considered high risk.

R-ISS	ISS	iFISH	LDH	OS
1	$\beta 2M < 3.5$, Alb ≥ 3.5	Standard	Normal	NR
2				83 mos.
3	$\beta 2M \geq 5.5$	High risk or high		43 mos.

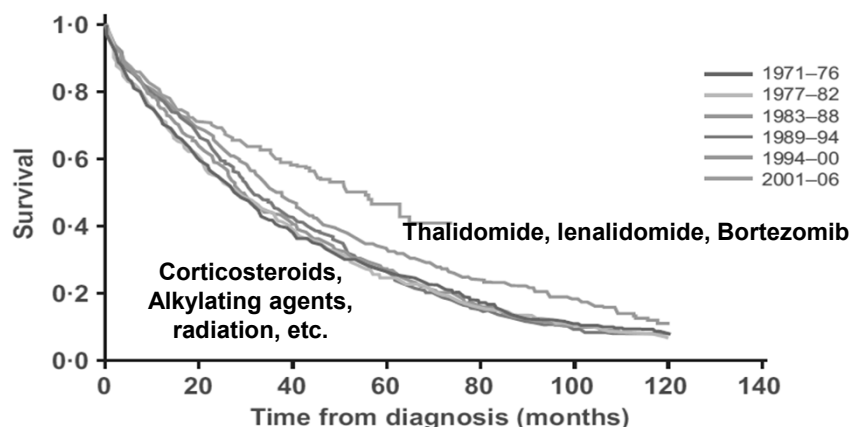
Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. JCO 33, 3-Aug-2015.

History of Multiple Myeloma

- 1844 First reported case of soft, fragile bones, heat soluble substance in urine abnormal cells in bone marrow – Sarah Newbury
- 1873 “Multiple Myeloma” term used
 - 1889 Detailed pathologic description published
 - 1903 Lytic lesions seen on radiographs
- 1939 Serum electrophoresis employed
- 1956 “Bence Jones” proteinuria described
- 1962 First use of melphalan
- 1964 First use of cyclophosphamide
- 1967 First use of corticosteroids
- 1983 First use of autologous stem cell transplantation
- 1990s Thalidomide found to be effective
- 2000s Revlimid and Velcade are FDA approved



Overall Survival from Time of Diagnosis in 6-yr Intervals based on date of Diagnosis



Kumar SK et al, Blood 2008; 111: 2516

2015: A GREAT YEAR for Myeloma

- 4 New drugs approved for relapsed/refractory MM
- Daratumumab: Nov 16, 2015: monoclonal ab, anti-CD38, single agent
- Elotuzumab: Nov 30, 2015: monoclonal ab, SLAMF7 and NK cell activation, in combination with lenalidomide and Dex
- Ixazomib: Nov 20, 2015: oral proteasome inhibitor, in combination with lenalidomide and Dex
- Panobinostat: Feb 28, 2015: HDAC inhibitor, in combination with bortezomib and Dex

Approved Newly Dx MM	Newly Diagnosed Regimen	Approved Relapsed MM
Thalidomide (T) Lenalidomide (R) Bortezomib (V) Dexamethasone (D) Prednisone (P)	VRD VTD CVD (CyborD) CRD RD VD Melphalan based (transplant ineligible)	Pomalidomide (P) Carfilzomib (K) Panobinostat Daratumumab Ixazomib Elotuzumab
Cyclophosphamide (C) Vincristine Doxil Melphalan		

1 Standard Induction treatment for fit patients

Drug (VRD)	Type	Mode	Side Effects
Dexamethasone	Steroid	Pill, weekly	insomnia, weight gain
Revlimid	IMiDs (immune modulating)	Pill, daily	blood clots, diarrhea
Velcade	Proteasome Inhibitors	Shot 2x / wk subcutaneous	tingling numbness in hands or feet

2 Autologous transplant = High dose IV melphalan
(Leads to 30 months of remission on average)

3 Revlimid (pill) maintenance
(Adds 18-23 months of remission on average)

**Supportive Care: Palliative Radiation;
Bisphosphonate-zolidronic acid**

Auto transplant in Eligible patients

- **Melphalan 200 mg/m² autologous transplant improves survival over standard cytotoxic chemotherapy¹⁻⁴**
- **Who can be transplanted safely?**
 - **Age ≤ 75 y.o. (140 mg/m² 71-75 y.o.)**
 - **Functionally able to work at a “desk job”**
 - **Normal functioning liver by enzymes and PT/PTT, low risk PFTs, LVEF > 40%**
 - **No other interfering comorbidity**
 - **Dialysis patients are eligible for auto SCT (140 mg/m²)**

1. Attal M et al, *New England Journal of Medicine*, 1996.
2. Child JA et al, *New England Journal of Medicine*, 2003.
3. Fermand et al, *Journal of Clinical Oncology*, 2005.
4. Barlogie B. et al, *Journal of Clinical Oncology*, 2006.

I F M	Bortezomib, Thalidomide and Dexamethasone (VTD) Is Superior to Bortezomib, Cyclophosphamide and Dexamethasone (VCD) Prior to Autologous Stem Cell Transplantation for Patients with De Novo Multiple Myeloma. Results of the Prospective IFM 2013-04 Trial. Philippe Moreau et al		
	VTD x 4 versus VCD x 4 as induction therapy prior to ASCT Symptomatic de novo MM less than 66 years Primary end-point : VGPR rate after cycle 4 340 patients overall (170 per arm).		
	ISS1 / 2 versus ISS 3 t(4;14) and / or del17p versus others	Arm A : Induction Therapy: 4 cycles VTD Each cycle : 21 days Thalidomide® 100 mg/d, PO D1 to D21 o Velcade® 1.3 mg/m ² /d, SC D1, 4, 8 and 11 o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12 ARM B: Induction Therapy : 4 cycles of VCD Each cycle : 21 days o Cyclophosphamide 500 mg/m ² /d, PO D1, 8, 15 o Velcade® 1.3 mg/m ² /d, SC D1, 4, 8 and 11 o Dexamethasone 40 mg/d, PO D1 to 4, D9 to 12	

I
F
M

Intent-to-treat analysis			
	VTD N = 169	VCD N = 169	P value
≥ CR	13.0%	8.9%	0.22
≥ VGPR	66.3%	56.2%	0.05
≥ PR	92.3%	83.4%	0.01

Per protocol analysis			
	VTD N = 157	VCD N = 154	P value
> = CR	14.0%	9.1%	0.17
> = VGPR	70.7%	60.4%	0.05
> = PR	98.7%	90.3%	0.001

Response: centralized assessment (Dr Dejoie, Nantes), IMWG criteria 2011

<div> <div>I</div> <div>F</div> <div>M</div> <div>Toxicity</div> </div>			
	VTD, n = 169 Grade 3-4 %	VCD, n= 169 Grade 3-4 %	p value
Any Aes	63.9	68.2	0.40
Anemia	4.1	9.5	0.05
Neutropenia	18.9	33.1	0.003
Infection	7.7	10.1	0.45
Thrombocytopenia	4.7	10.6	0.04
Thrombosis	1.8	1.8	0.99
Cardiac disorders	1.2	0	0.16
Cystitis	0	0.6	0.32
GI symptoms	5.3	3.5	0.42
Periph. Neuropathy	7.7	2.9	0.05
PN grade 2-4	21.9	12.9	0.008

Toxicities assessed according to NCI CTCAE, version 4.0.

Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. Cavo et al leukemia:2015 ,2429-2431			
<i>All patients</i>	VTD (n=236)	VCD (n=236)	P
Complete response	44 (19%; 14–24)	13 (6%; 3–8)	<0.001
Very good partial response or better	151 (64%; 58–70)	87 (37%; 31–43)	<0.001
Partial response or better	220 (93%; 90–96)	192 (81%; 76–86)	<0.001
Stable disease	16 (7%; 4–10)	38 (16%; 11–21)	0.001
Progressive disease	0 (0%)	6 (3%; 1–5)	0.015
<i>Patients with ISS 2-3</i>	VTD (n=129)	VCD (n=129)	
Complete response	26 (20%; 13–27)	5 (4%; 1–7)	<0.001
Very good partial response or better	86 (67%; 59–75)	45 (35%; 27–43)	<0.001
<i>Patients with t(4;14) and/or del(17p)</i>	VTD (n=53)	VCD (n=53)	
Complete response	12 (23%; 11–34)	4 (8%; 0–15)	0.030
Very good partial response or better	44 (83%; 73–93)	25 (47%; 34–61)	<0.001

Dose and schedule same as Moreau et al. except- V and C given IV, 3 cycles each before SCT

Toxicity

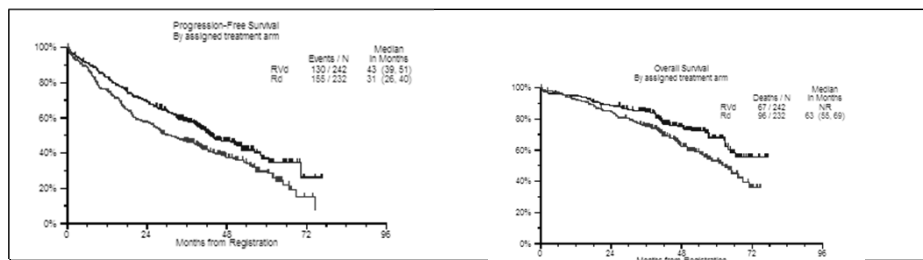
	VTD (n=236)	VCD (n=236)	P
Any grade 3 or 4 adverse event	64 (27%)	61 (26%)	0.754
<i>Any grade 3 or 4 non-hematological adverse event</i>			
Skin rash	19 (8%)	2 (1%)	<0.001
Peripheral neuropathy	17 (7%)	5 (2%)	0.009
Gastrointestinal events	15 (6%)	8 (3%)	0.135
Liver toxicity	5 (2%)	8 (3%)	0.399
<i>Any grade 3 or 4 hematological adverse event</i>			
Neutropenia	5 (2%)	19 (8%)	0.003
Anemia	0	16 (7%)	<0.001
Thrombocytopenia	1 (<1%)	10 (4%)	0.006
<i>Study protocol discontinuation during induction therapy</i>			
Toxic effects	8 (3%)	4 (2%)	0.242
Disease progression	0	3 (1%)	0.124
Early death	1 (<1%)	2 (1%)	0.500

Bortezomib, Lenalidomide and Dexamethasone (Rd) Vs. Lenalidomide and Dexamethasone in Patients (Pts)(VRd) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 Brian Durie, MD et al

- **Randomized phase III: 2008-2012**
- **Stratified to ISS stage (I,II,III), Intent to transplant (Yes, NO)**
- **Lenalidomide/dex (Rd): 232 patients: R 25 mg days 1-21, dex 40 mg/d days 1 8, 15, 22, cycle q 28 days x 6 cycles**
- **Bortezomib/Rd (VRd): 242 patients: R 25 mg days 1-14, dex 20 mg/d days 1-4, 8-12, velcade 1.3 mg/m² IV push days 1,4,8,11. cycle q 21 days x 8 cycles**
- **Maintenance: Rd until progression**
- **DVT prophylaxis: ASA 325 mg/d; HSV prophylaxis with VRd**
- **Differences b/w gps:**
 - **Fewer women VRd(37% vs 47% p=0.033)**
 - **Fewer older pts VRd (≥ 65yrs 38% vs 48% p=0.042)**
- **Primary Endpoint: PFS**

Brian Durie, MD et al

	VRd	Rd	P-value
ORR	71.07%	63.79%	
Median PFS	43 mos	31 mos	0.0066
Median OS	NR	63 mos	0.0114
≥Grade 3 hem tox (%)			
Anemia	13	16	
Neutropenia	19	21	
thrombocytopenia	18	14	
≥Grade 3 non- hem tox (%)			
Neuropathy	24	5	<0.0001
Thrombosis/embolism	8	9	
Second primary malignancy	7 pts (3%)	9(4%)	



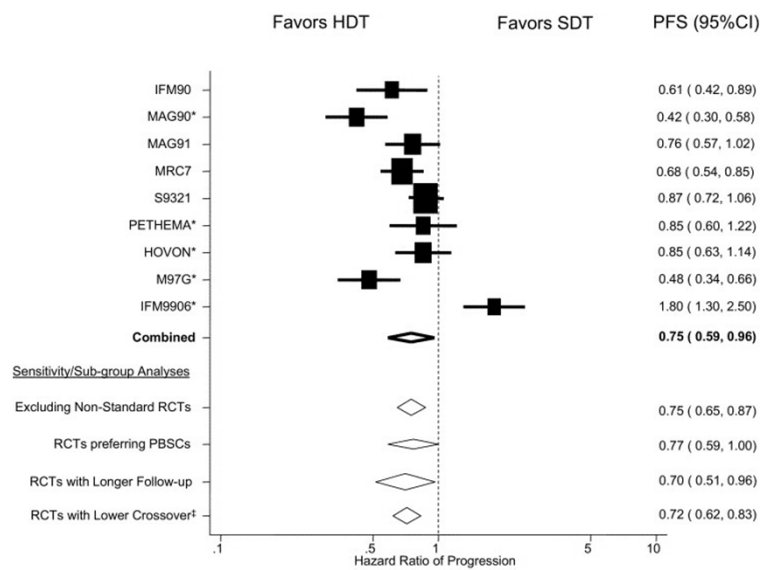
VRd provides meaningful improvement in PFS and OS with acceptable toxicity

Conclusion

- The combination of A proteasome inhibitor (bortezomib) , and an immune modulator(thalidomide, lenalidomide) as induction treatment is a superior regimen
- 3-drug regimen with Novel agents is superior to 2-drug regimen with Novel agent as Induction regimen

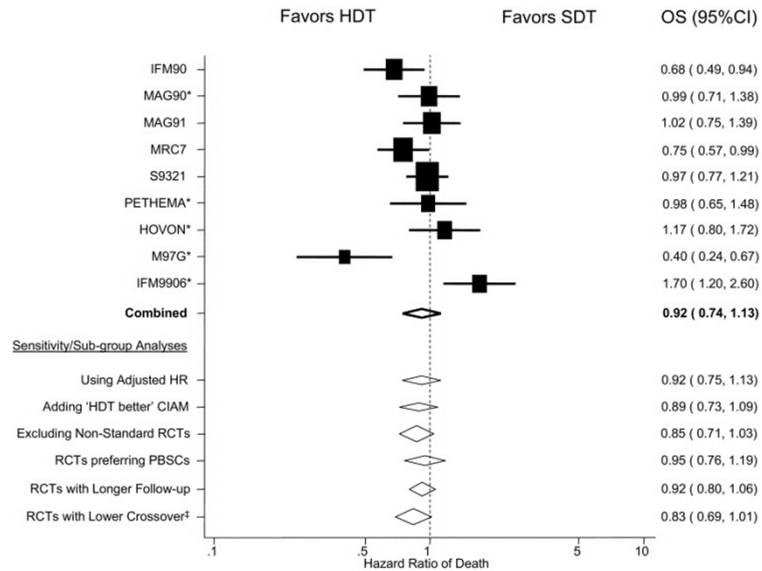
Autologous SCT as consolidation in newly Dx MM vs continuation of Therapy (Early vs delayed SCT) in the ERA of Novel Therapies

Time to disease progression - Using older regimens



Koreth J, BBMT 2007

Overall Survival - Using older regimens



Koreth J, BBMT 2007

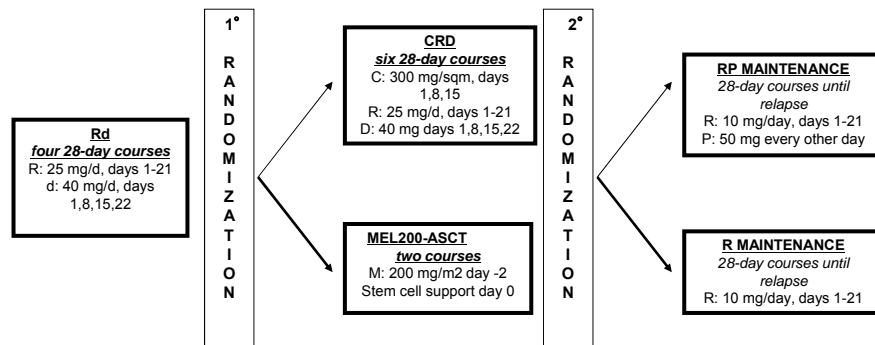
	Old regimen (VAD regimen)	New regimen incorporating Novel agents and maintenance
Overall response rate (ORR)	50-60%	80-100%
Complete response (CR)	16-25%	40-60%
Very good partial response (VGPR)	5-10%	20-30%
5 yr Overall survival (OS)	~30-40%	60-80%
Median time to disease progression (PFS)	15 months	47-53 mos

Palumbo A et al, 2006, Lancet p825; Mateos MV et al, Blood 2010, p 2259; Facon T et al, Lancet 2007, p 1209; Sacchi S, Leuk Lymphoma 2011, p 1942;

Transplant vs. NO Transplant in era of the Novel drugs as part of upfront Therapy? any benefit?

Autologous Transplantation versus cyclophosphamide-lenalidomide-prednisone followed by lenalidomide-prednisone versus lenalidomide maintenance in multiple myeloma: long-term results of a phase III trial. Gay et al- lancet oncology Dec 2015 p1617

- 389 patients (younger than 65 years) randomized from 59 centers
Patients: Symptomatic disease, organ damage (CRAB), measurable disease



R, lenalidomide; D, dexamethasone; C, cyclophosphamide; P, prednisone; Rd, lenalidomide-dexamethasone; CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200-ASCT, melphalan 200 mg/m² followed by autologous stem cell transplantation; RP lenalidomide-prednisone,

CRD vs MEL200-ASCT

Patients Characteristics

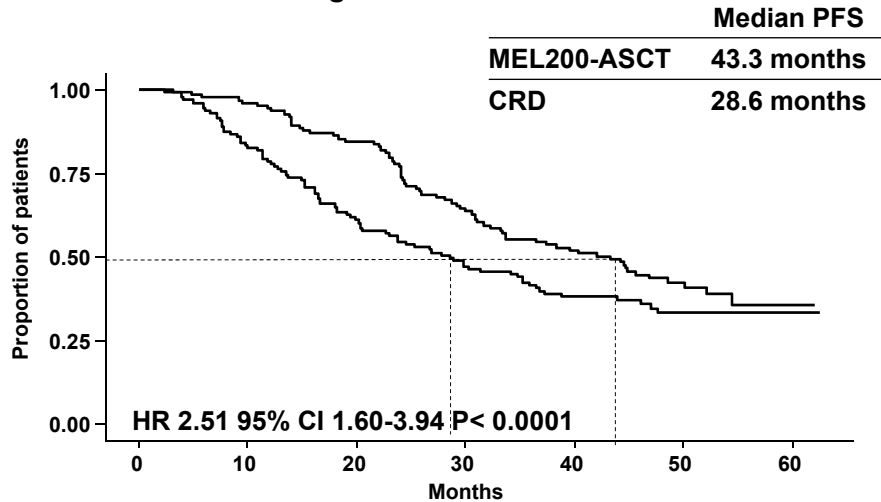
	MEL200-ASCT (n=127)	CRD (n=129)
Age		
median	57	56
>60 years	34	31
ISS Stage		
I	51%	45%
II	36%	50%
III	13%	16%
Chromosomal Abnormalities		
t (4;14)	9%	13%
t (14;16)	5%	5%
del 17	5%	8%
High-risk [t (4;14) or t(14;16) or del17]	18%	23%

CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200-ASCT, melphalan 200 mg/m² followed by autologous stem-cell transplantation; ISS, International Staging System

CRD vs MEL200-ASCT

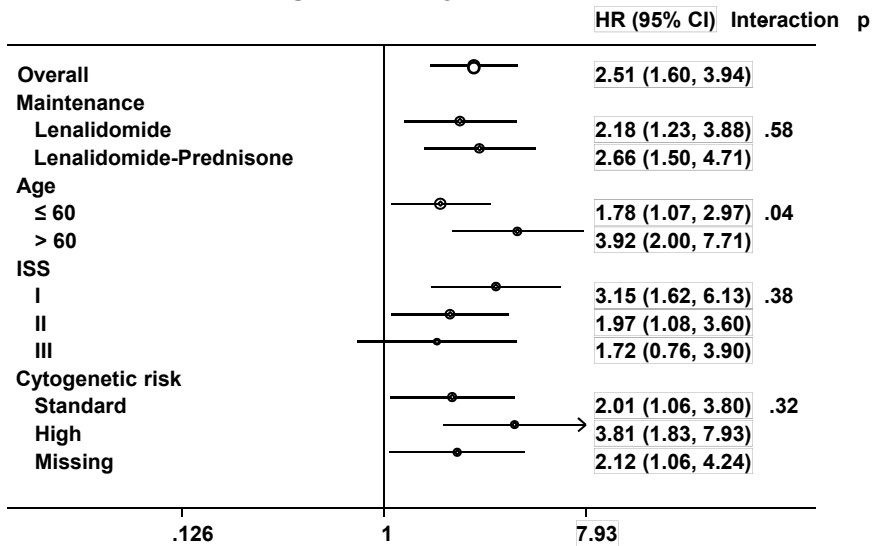
Median follow-up from consolidation : 47 months

Progression-free survival



CRD vs MEL200-ASCT

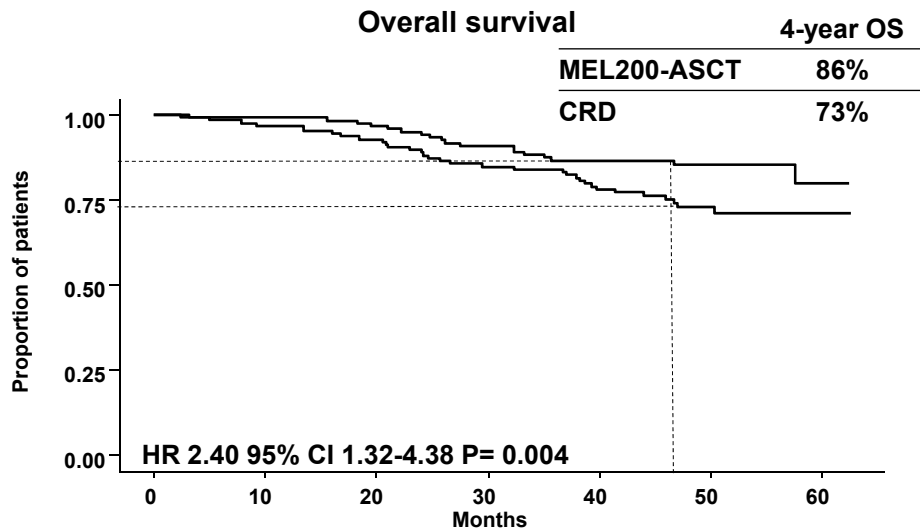
Subgroup Analysis of PFS



MEL200-ASCT, melphalan 200 mg/m² followed by autologous stem cell transplantation; CRD cyclophosphamide lenalidomide dexamethasone; PFS, progression-free survival.

CRD vs MEL200-ASCT

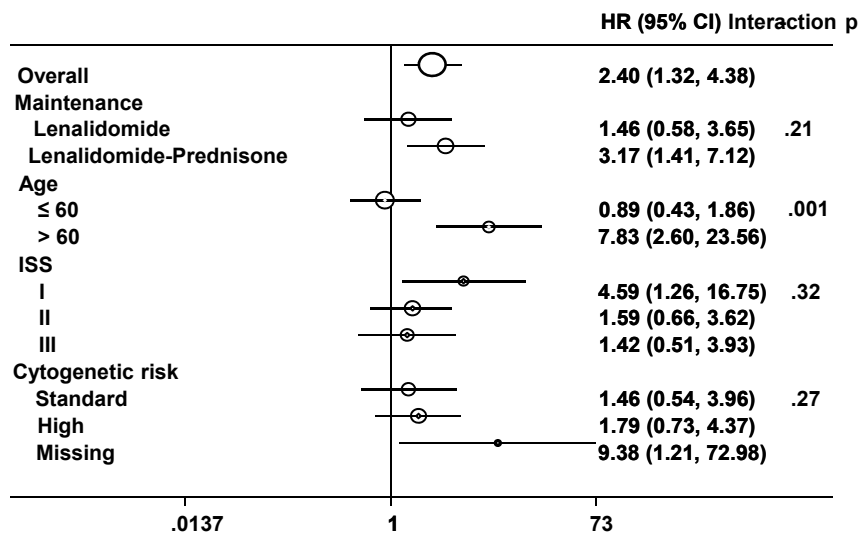
Median follow-up from consolidation : 47 months



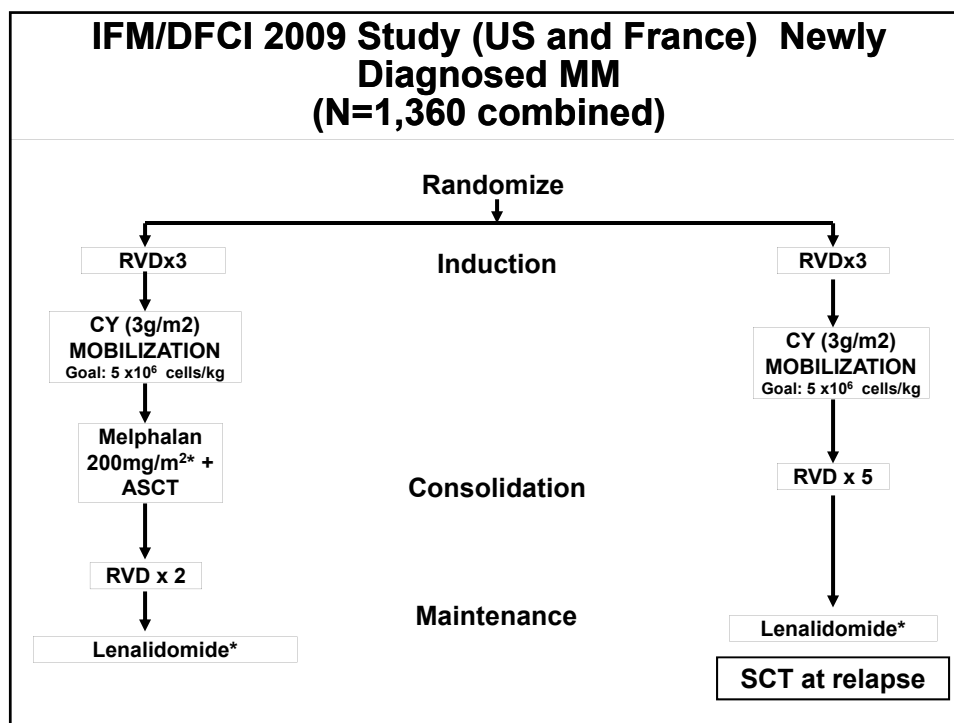
MEL200-ASCT, melphalan 200 mg/m² followed by autologous stem cell transplantation; CRD cyclophosphamide lenalidomide dexamethasone; OS: overall survival

CRD vs MEL200-ASCT

Subgroup Analysis of OS

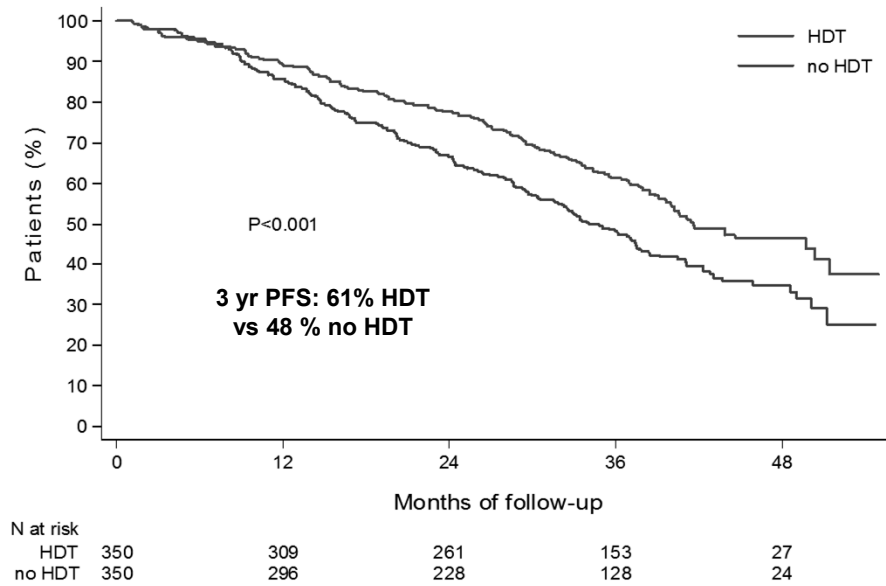


MEL200-ASCT, melphalan 200 mg/m² followed by autologous stem cell transplantation; CRD cyclophosphamide lenalidomide dexamethasone; OS, overall survival.

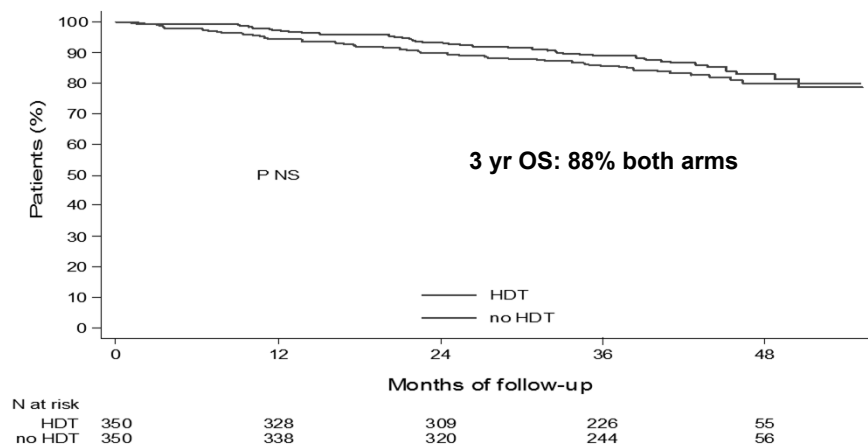


Best Response			
	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	0.02
VGPR	29%	29%	
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

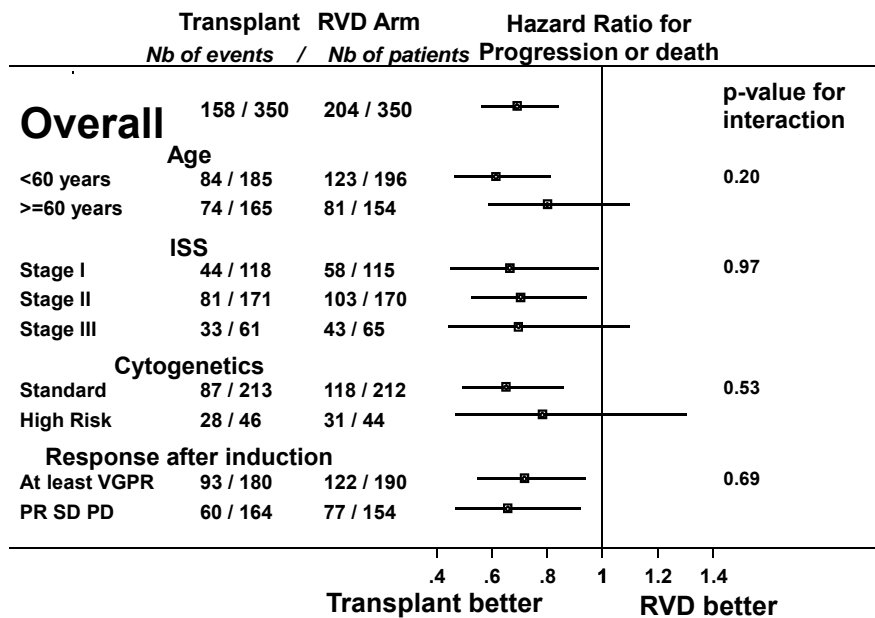
ASH 2015 (Attal et al): IFM 2009: PFS (9/2015)



IFM 2009: OS (9/2015)



IFM 2009: PFS.



ASH 2015: IFM 2009: Causes of Death (9/2015)

	RVD arm N=48	Transplant N=54
Myeloma, n (%)	40/48 (83%)	35/54 (65%)
Toxicity, n (%)	4/48 (8%)	9/54 (16%)
SPM (AML/MDS)	1/48 (2%)	6/54 (11%)
Others	3/48 (6%)	4/54 (7%)

IFM 2009: Conclusions

❖ This second interim analysis demonstrates that transplantation :

- Is feasible: 93%
- Is associated with an acceptable Transplant Related Mortality: 1.4%.
- Is associated with an increased rate of neg MRD (80% vs 65%, $p<0.01$).
- Is associated with an improved 4-year PFS (47% vs 35%, $p<0.001$).
- Is associated with an improved 4-year TTP (49% vs 35%, $p<0.001$).

❖ A longer follow up is required to draw any conclusion concerning OS,

- Since the 4-year survival is high in both arms (80% vs 83%).
- However, transplantation is already associated with a reduced risk of death due to myeloma, but has a higher rate of toxicity (acute and long term)

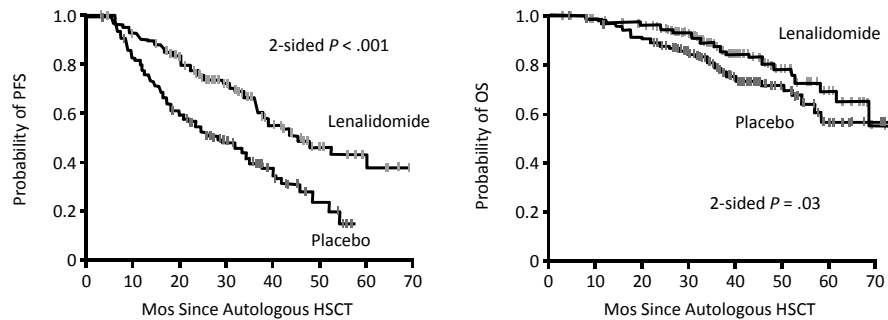
➤ in the era of new drugs, Transplantation is “A Standard of Care” but key questions remain.

Conclusion

- In the era of novel agents, Autologous SCT remains important in the management of newly diagnosed MM- improved PFS and maybe OS
- HOWEVER
- Could this be affected by a longer maintenance ?(indefinite)- the importance of the US study.

Lenalidomide vs Placebo Post auto SCT

CALGB 100104

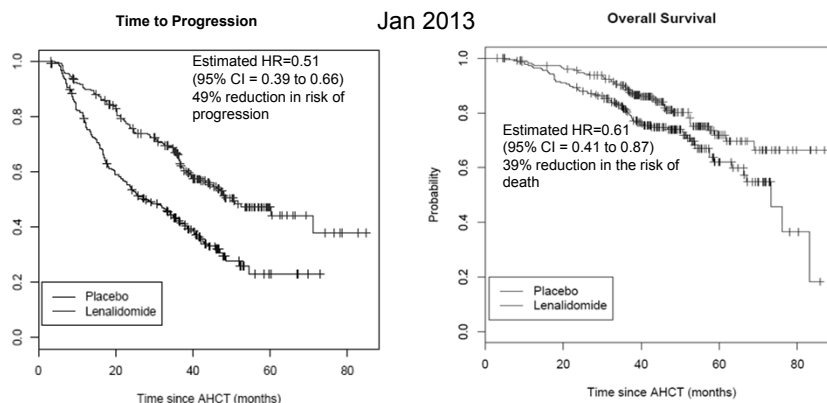


	Len (R)	Placebo	P-value
Med PFS	46 mos	27 mos	<0.001
Med OS	NR	NR	
3 yr OS	88%	80%	0.03
SPM	7.8%	2.6%	

McCarthy PL, et al. *N Engl J Med*. 2012;366:1770-1781.

IMW 2013 Update _ Courtesy Dr. McCarthy

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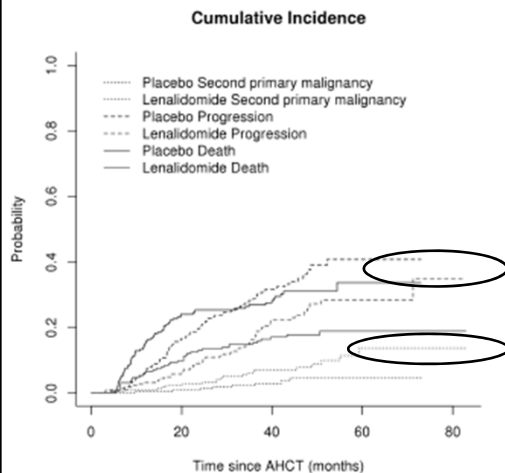


146/229 events (64%) on placebo
104/231 events (45%) on lenalidomide

69/229 (30%) deaths on placebo
47/231 (20%) deaths on lenalidomide

- ITT Analysis; median follow-up from transplant ~48 months
Median TTP: 50 months versus 27 months $p < 0.001$
- Median OS: Not reached versus 73 months $P = 0.008$
- 86 of 128 (67%) non-progressing placebo patients received lenalidomide at study un-blinding in Jan 2010

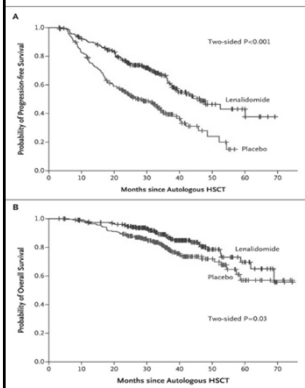
IMW 2013 Update _ Courtesy Dr. McCarthy Jan 2013



The cumulative incidence risks of death ($p<0.001$) progressive disease ($p=0.004$) and were greater in the placebo group. Overall 67% benefit with maintenance

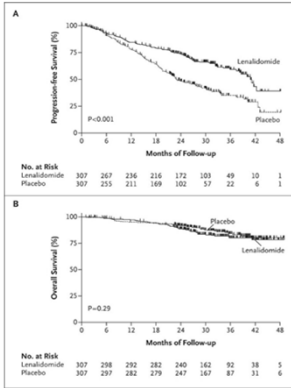
The cumulative incidence risk of second primary cancers was greater in the lenalidomide group ($p=0.034$).

McCarthy, NEJM, 2012, p1770, CALGB 100104



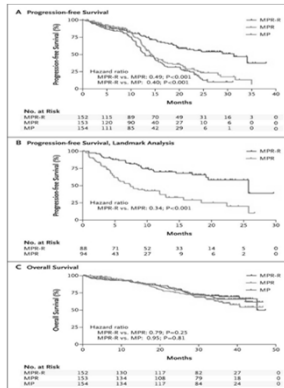
	Len (R)	Placebo	P-value
Med PFS	46 mos	27 mos	<0.001
Med OS	NR	NR	
3 yr OS	88%	80%	0.03

Attal NEJM, 2012, p1782, IFM Investigators



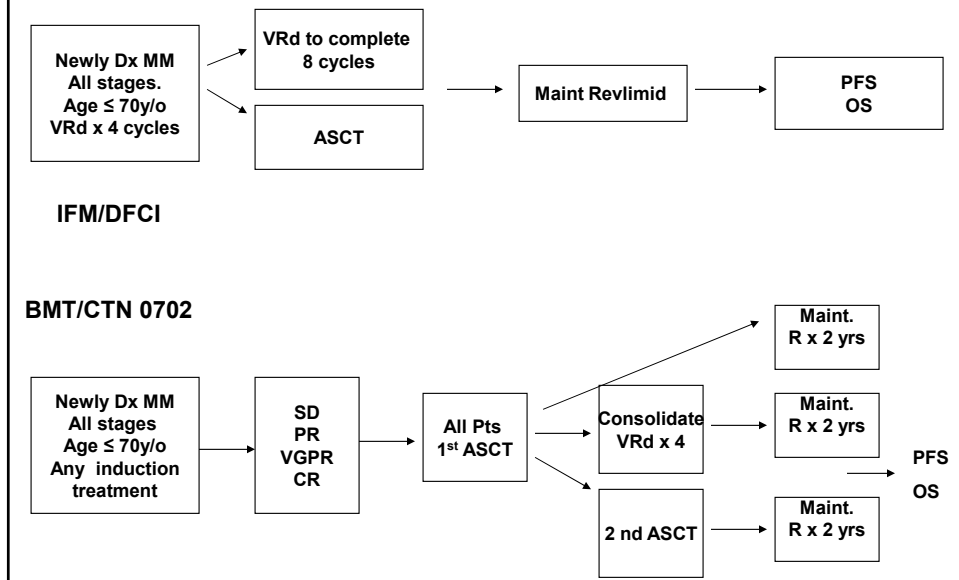
	Len (R)	Placebo	P-value
Med PFS	41 mos	23 mos	<0.001
Med OS	NR	NR	
3 yr OS	88%	84%	0.29

Palumbo NEJM, 2012, p1759, MMO -15 Investigators



	MPR-R	MPR	P-value
Med PFS	31 mos	14 mos	<0.001
Med OS	45.2	NR	0.25
3 yr OS	70%	62%	0.25

Current studies to assess role of SCT



Relapse Patients

- Use any novel drug combinations that have not been used before.
- Repeat drugs that have been used before.
- Participate in clinical trials using other new drugs in development
- Older regimen in Combinations with novel drugs
- Repeat Autologous stem cell transplant
- Allogeneic stem cell transplant in selected patients (always on study)



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