NCCN 10th Annual Congress:
Hematologic Malignancies™

Management of Multiple Myeloma

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Seattle Cancer Care Alliance

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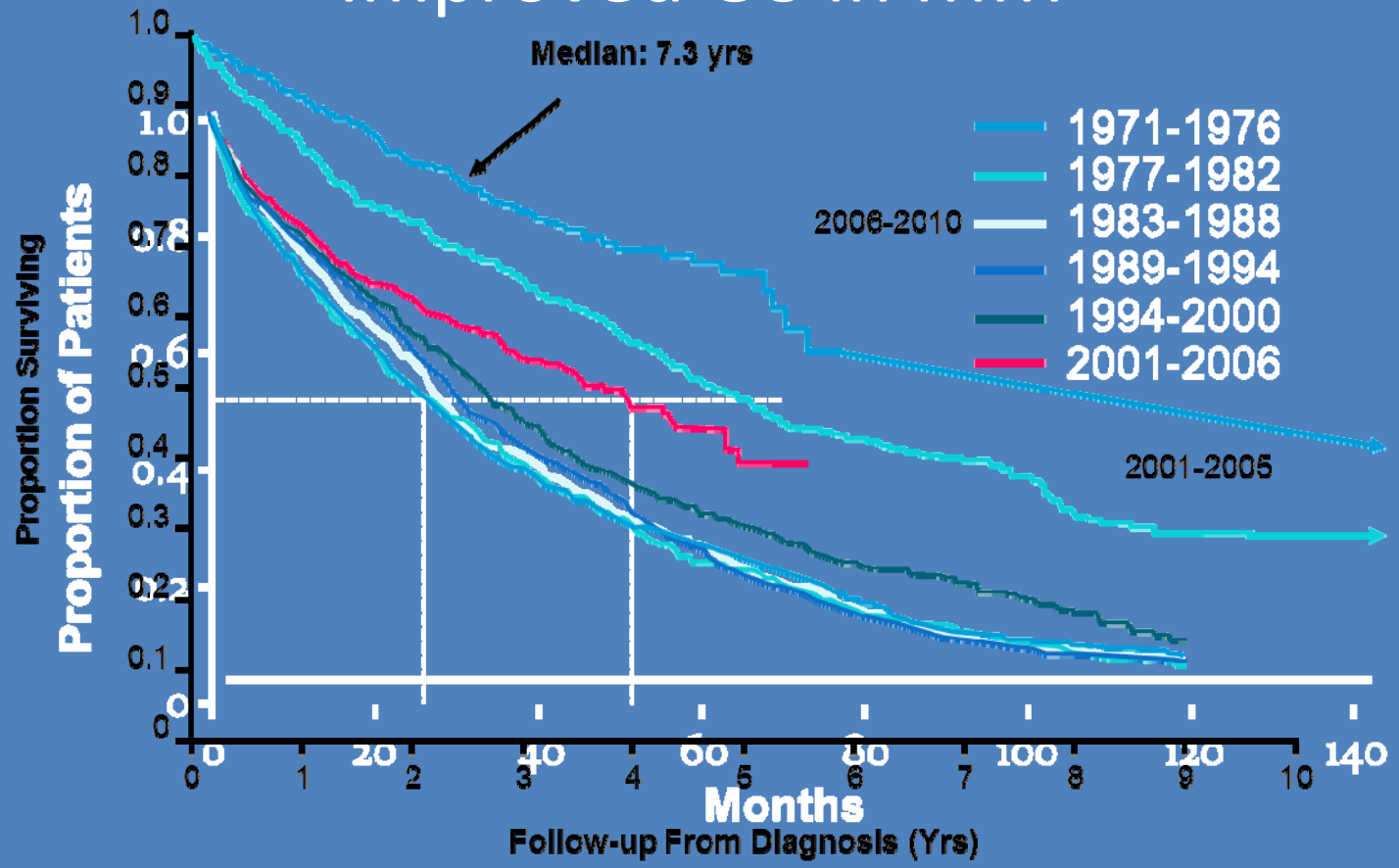
New Treatment Options Have Improved OS in MM



Kumar SK, et al. Blood. 2008;111:2516-2520.

Kumar SK, et al. ASH 2012. Abstract 3972.

The speed of change:

"If everything seems under control, you are not going fast enough"
-Mario Andretti

- Terms: CR → stringent CR → MRD negative CR
- Risk adapted therapy
- CRAB → I'M A CRAB
- The role of functional imaging in staging and response
- Clonal evolution of disease
- Staging criteria

Initial Evaluation

- Physical Exam
- BM
  - Conventional metaphase karyotype and MM FISH
- Imaging
  - Skeletal Survey
  - MRI (smoldering/active)
  - DEXA- axial skeleton
- CBC with differential
- Chem + Ca^{2+}
- SPEP with IFE
- β 2 microglobulin + Albumen + LDH
- FLC
- Quantitative Immunoglobulins
- 24 hour urine with total protein, UPEP + IFE Bence Jones quantitation
- LDH

Based on NCCN Clinical Practice Guidelines for Multiple Myeloma

New Criteria for MM Defining Events

- Bone marrow plasma cells ≥ 60%
- Serum Free light chain ratio ≥ 100
- Skeletal MRI/CT >1 focal lesion
  - MRI lesion > 5 mm
  - PET –FDG avidity alone insufficient

- Creatinine clearance <40 ml/min
- Only cast nephropathy, (amyloid and light chain deposition are not MM defining events)

Lancet Oncology November 2014

Old Diagnostic Criteria

MGUS
<3 gram M-spike &
<10% PC*

Smoldering MM
≥3 gram M-spike
Or ≥10% PC*

And

No anemia, normal calcium and kidney function; no bone lesions

Active MM
≥10% PC*
M-spike

And

Hyper**C**alcemia *or* **R**enal *or* **A**nemia *or* **B**one involvement

"**CRAB** Criteria"

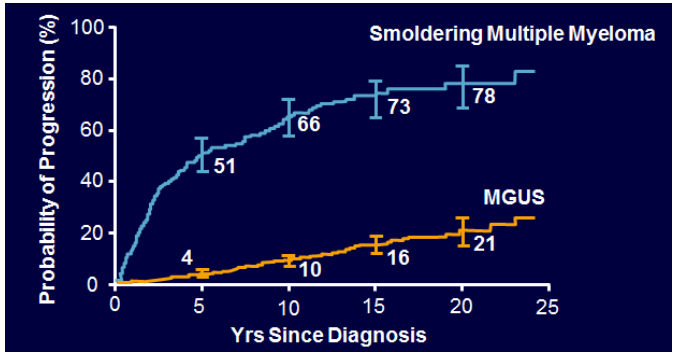
* By morphology (not flow)

CRAB → → → I'M A CRAB
Imaging, Marrow, Abnormal ratio, Calcium, Renal, Anemia, Bone

Epidemiology

SMM Epidemiology is going to change!!

- MGUS
  - Progression is 1% per year
  - F/U annually, bone marrow if M-spike >1.5 or non IgG, abnl FLC ratio or any other concern for possible MM or Amyloid
- SMM
  - Rate of progression is 10% per year in first 5 years
  - 3% per year for next 5 years
  - 1-2% per year for next 10 years
  - F/U with labs q 3 months
  - Annual skeletal survey



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Vaccinate MGUS patients for pneumococci, influenza, H. flu, hep A &B

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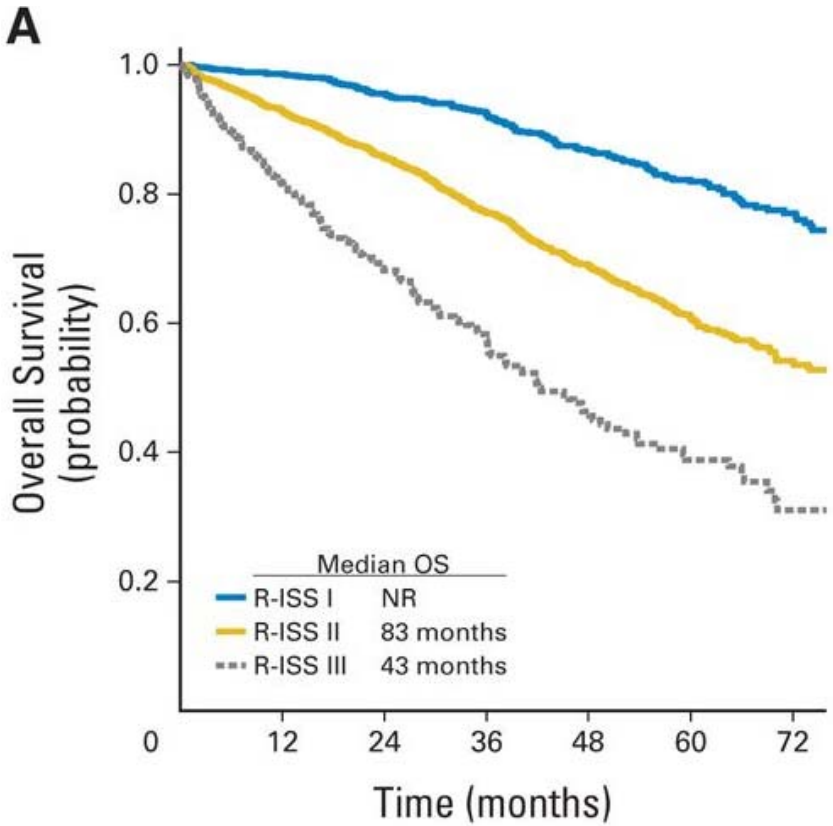
NCCN Guidelines Version 2.2016 Multiple Myeloma

STAGING SYSTEMS FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria[1]	ISS Criteria[2]
I	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or ≤12 mg/dL • Bone x-ray, normal bone structure) or solitary bone plasmacytoma only • Low M-component production rate ➤ IgG value <5 g/dL; ➤ IgA value <3 g/dL ➤ Bence Jones protein <4 g/24 h	Serum beta-2 microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions • High M-component production rate ➤ IgG value >7 g/dL; ➤ IgA value >5 g/dL ➤ Bence Jones protein >12 g/24 h	Serum beta-2 microglobulin ≥5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine level <2.0 mg/dL) B Abnormal renal function (serum creatinine level ≥2.0 mg/dL)		

[1] From Durie BGM, Salmon SE: A clinical staging system for multiple myeloma. Cancer 1975;36(9):842-854. Copyright © (1975) American Cancer Society. Reproduced with permission of John Wiley & Sons, Inc.
[2] Greipp P, San Miquel J, Durie B et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-3420.

(A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm.



Old ISS I + no high Risk cytogenetics* + nl LDH

All others

Old ISS III + high Risk cytogenetics +/or Elevated LDH

*High risk cytogenetics defined as 17p-; t(4;14) or t(14;16)

Palumbo et al. JCO 2015;33:2863-2869

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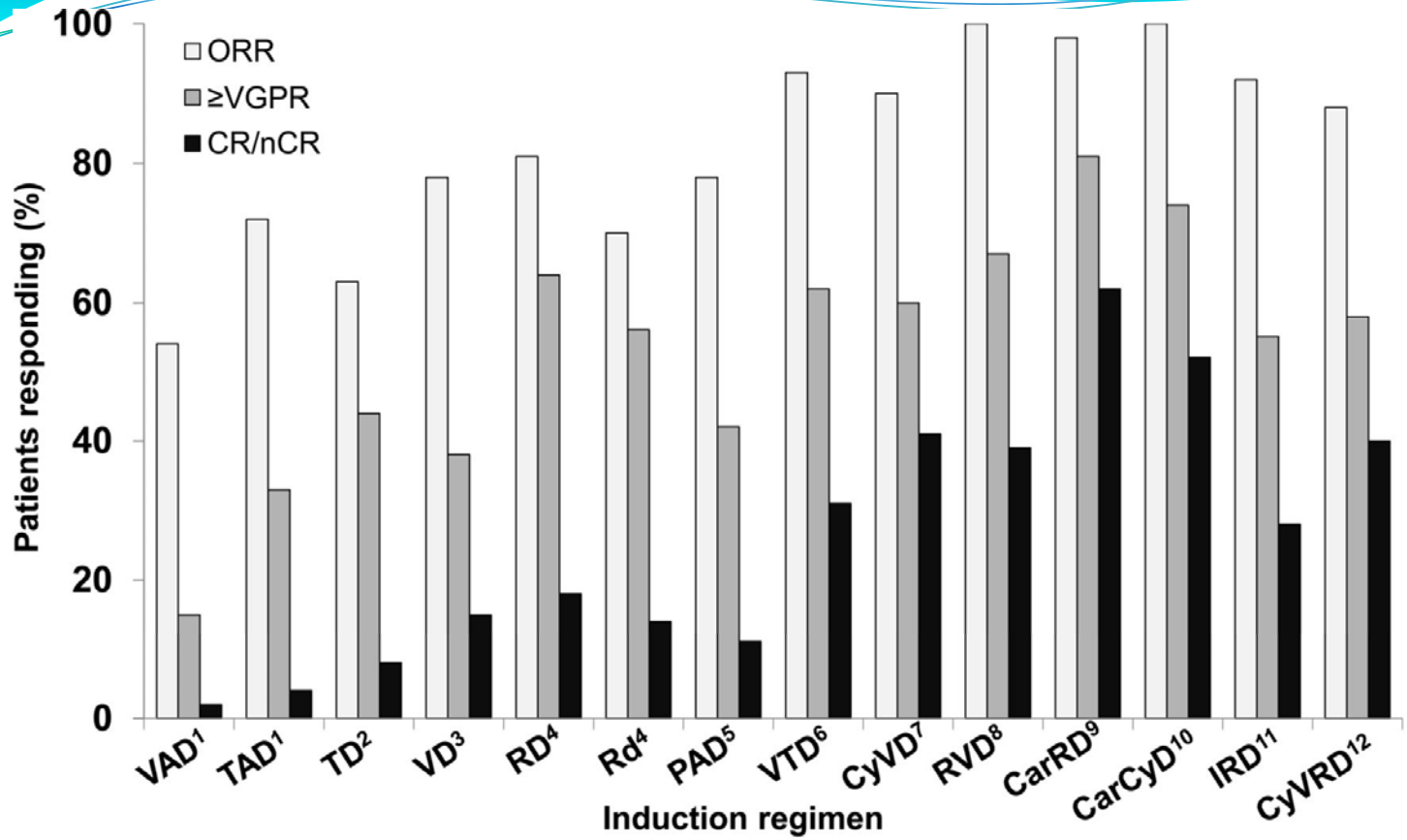
Multiple Myeloma

MYELOMA THERAPY

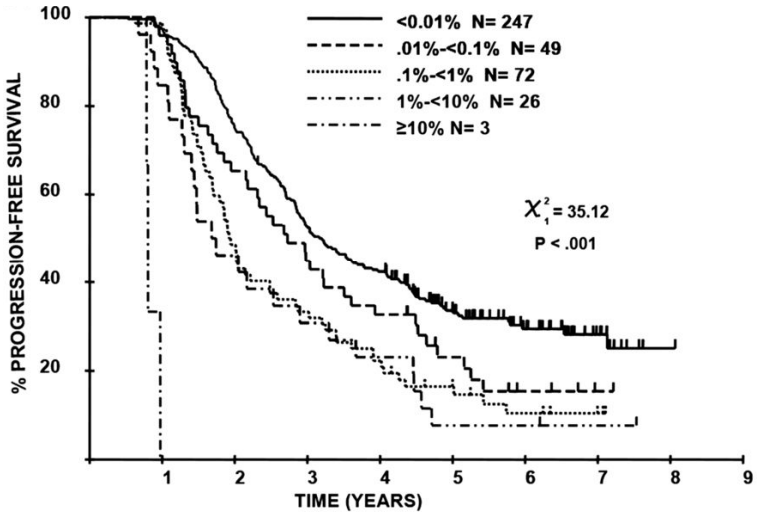
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	
Preferred Regimens	**Other Regimens**
• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dex • Bortezomib/doxorubicin/dex (category 1) • Bortezomib/lenalidomide/dexamethasone • Bortezomib/thalidomide/dex (category 1) • Lenalidomide/dexamethasone (category 1)	• Carfilzomib/lenalidomide/dex • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/ dexamethasone (category 2B) • Thalidomide/dex (category 2B)

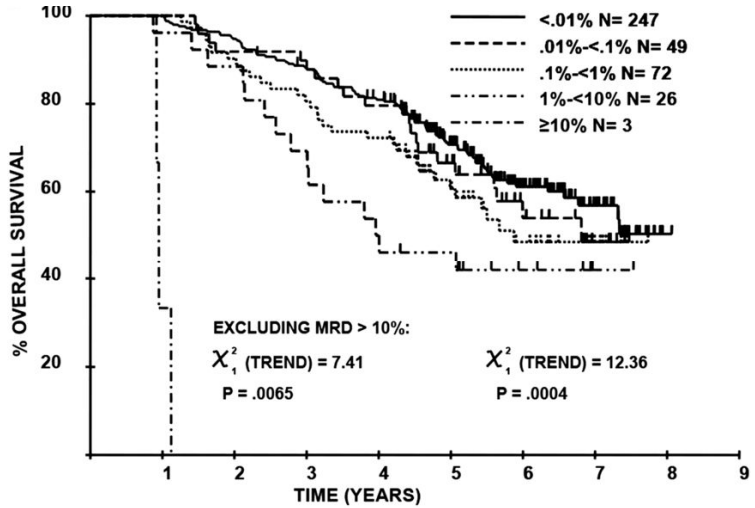
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	
Preferred Regimens	**Other Regimens**
• Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dex • Bortezomib/lenalidomide/dexamethasone • Lenalidomide/low-dose dex (category 1) • Melphalan/prednisone/bortezomib (category 1) • Melphalan/prednisone/lenalidomide (category 1) • Melphalan/prednisone/thalidomide (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/ dexamethasone (category 2B) • Melphalan/prednisone • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (category 2B)



1. Lokhorst HM, et al. Haematologica. 2008;93:124-7. 2. Rajkumar SV, et al 2008 J Clin Oncol 26:2171-77. 3. Harousseau JL, et al 2010 J Clin Oncol 28:4621-4629. 4. Rajkumar SV, et al Lancet Oncol 2010; 11: 29–37. 5. Sonneveld P, et al J Clin Oncol 2012; 30:2946-55. 6. Cavo M, et al Lancet 2010; 376: 2075–85. 7. Reeder CB, et al. Blood. 2010; 115:3416-7. 8. Richardson et al. Blood 2010;116:679-686. 9. Jakubowiak AJ, et al Blood. 2012 30;120:1801-9. 10. Palumbo A, et al. Blood. 2012;120:[abstract 730]. 11. Kumar S, et al . Blood. 2012;120:[abstract 332]. 12. Kumar S, et al. Blood 2012 119: 4375-82.

Sequential improvements in PFS and OS for each log depletion in MRD level, as assessed by multiparameter flow cytometry.

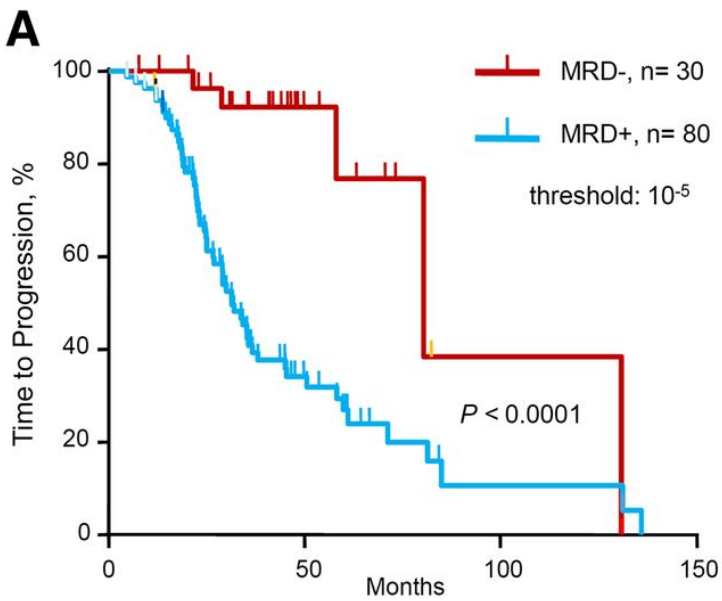


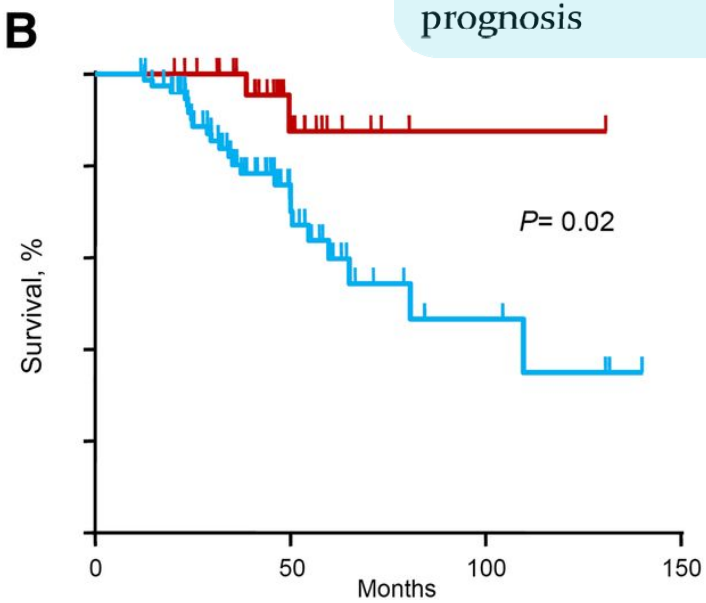


Andy C. Rawstron et al. Blood 2015;125:1932-1935

Depth of CR Matters:

MRD stratifies the CR population into 2 groups with strikingly different prognosis





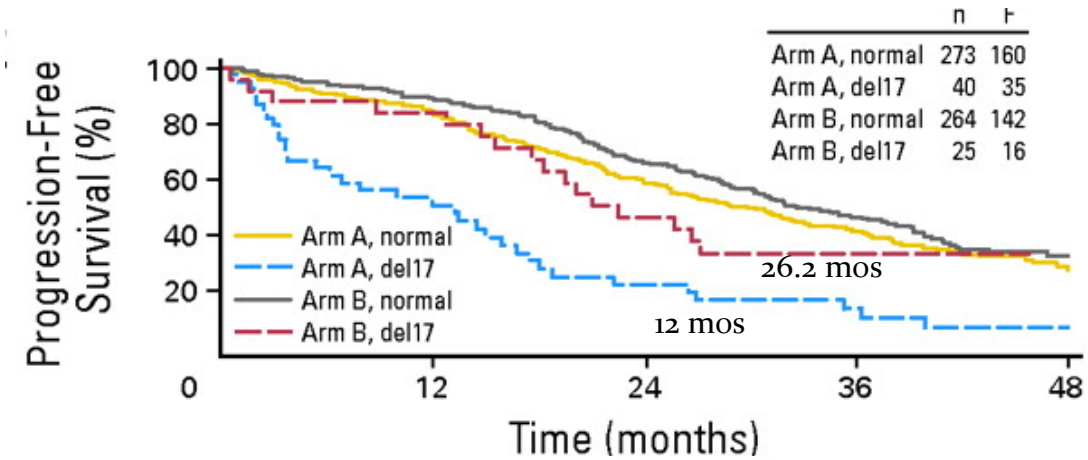
Martinez-Lopez, et al. Blood. 2014;123:3073-3079.

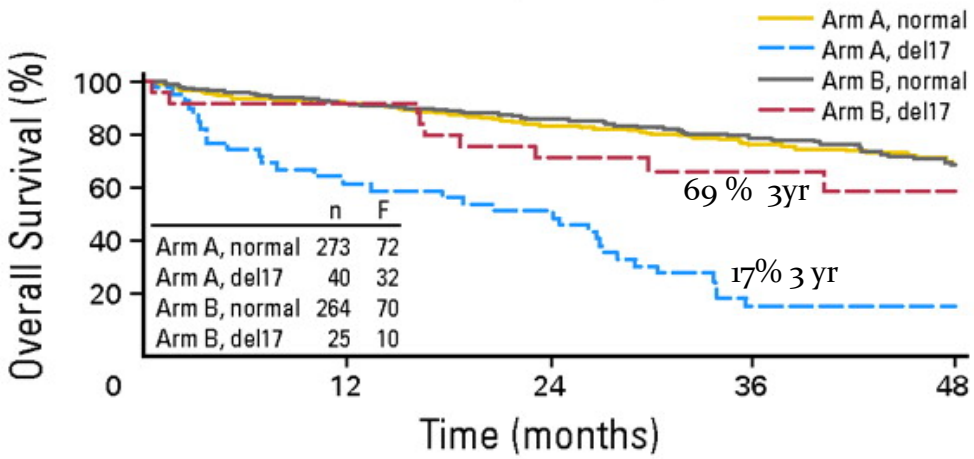
Detects to 10^{-6}

Risk adapted therapy?

STANDARD RISK	Intermediate Risk	HIGH RISK
•Normal conventional cytogenetics and FISH •Trisomies •t(11;14) •t(6;14)	•t(4;14)* •1 q amplification •Complex karyotype •Metaphase del (13) ? •Hypodiploidy	•t(4;14)* •t(14;16) •t(14;20) •del(17p-) •del(1p-) •GEP- high risk signature

Role of Proteasome Inhibition in del 17 Disease





Arm A:
VAD→ HDT→ Thal (maint)

Arm B:
PAD→ HDT→ bort (maint)

Sonneveld P et al. JCO 2012;30:2946-2955

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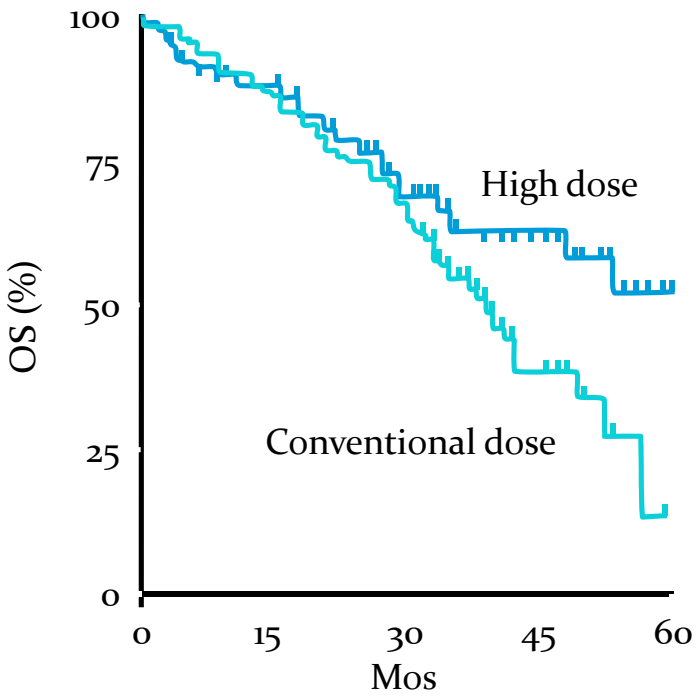
Primary Therapy for Non-Transplant Candidates	(Assess for response after 2 cycles)
Preferred Regimens	**Other Regimens**
• Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dex • Bortezomib/lenalidomide/dexamethasone • Lenalidomide/low-dose dex (category 1) • Melphalan/prednisone/bortezomib (category 1) • Melphalan/prednisone/lenalidomide (category 1) • Melphalan/prednisone/thalidomide (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/ dexamethasone (category 2B) • Melphalan/prednisone • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (category 2B)

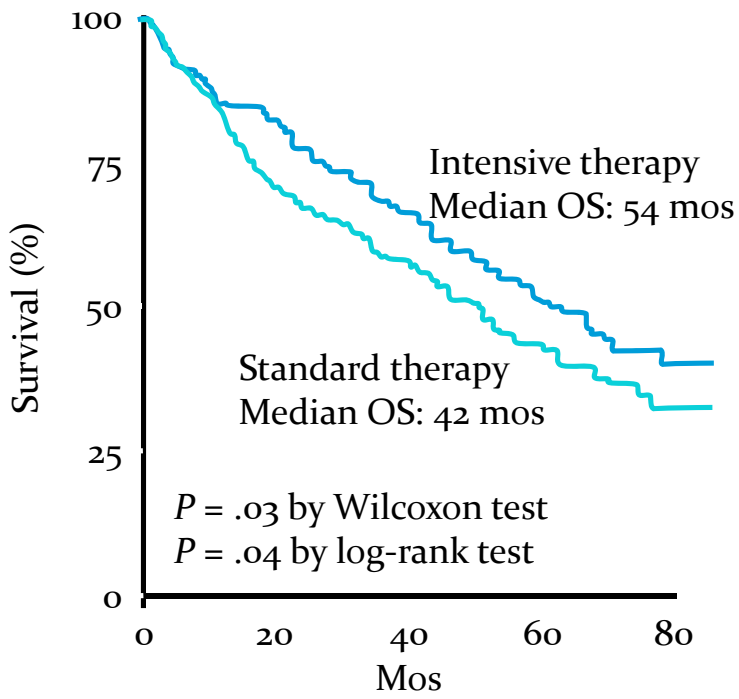
MYELOMA THERAPY

Maintenance Therapy	
Preferred Regimens	**Other Regimens**
• Bortezomib • Lenalidomide (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

Role of Auto Transplant



IFM-90



MRC-7

Attal M, et al. N Engl J Med. 1996;335:91-97. Child JA, et al. N Engl J Med. 2003;348:1875-1883.

Maintenance Lenalidomide

	Initial Tx	N	Time of Randomiz.	Median PFS (months)	OS after randomiz.
Attal	SCT	614	3 m post SCT	41 vs 23	4-year OS 73% vs 75%
McCarthy	SCT	460	SCT	39 vs 21	3-year OS **88% vs 80%**
Palumbo	MPR	305	Diagnosis	31 vs 14	3-year OS 70% vs 62%

Attal et al NEJM 2012; McCarthy et al. NEJM 2012; Palumbo et al. NEJM 2012

RELAPSE

- Defined as 1 or more of the following:
  - New soft tissue plasmacytoma or bone lesions
  - Plasmacytomas or bone lesions increasing in size (50% increase & at least 1 cm)
  - Hypercalcemia
  - Progressive anemia
  - New or recurrent renal dysfunction

Presented at the 2011 International Myeloma Workshop in Paris, France. Available at: http://www.myeloma-paris2011.com/files/files/ConsensusPanel2TheFinal.pdf. Accessed April 2012.

RELAPSE

- Paraprotein
  - Doubling of M-spike on two consecutive measurements

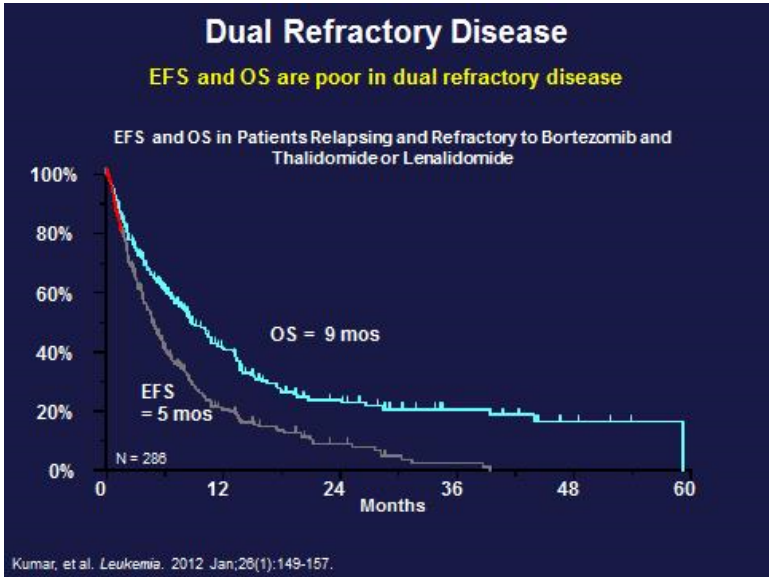
  OR

  - Absolute M-protein ≥ 1 g/dl
  - Urine M-protein ≥ 500 mg/24 hr
  - Involved FLC ≥ 20 mg/dl(with abnormal FLC ratio or >25% increase)

Presented at the 2011 International Myeloma Workshop in Paris, France. Available at: http://www.myeloma-paris2011.com/files/files/ConsensusPanel2TheFinal.pdf. Accessed April 2012.

Deciding on Salvage?

- Cytogenetics
- Duration of initial response
- Prior transplant
- Age
- Neuropathy
- Coagulation issues
- Performance Status
- Route of administration



MM Salvage Regimens

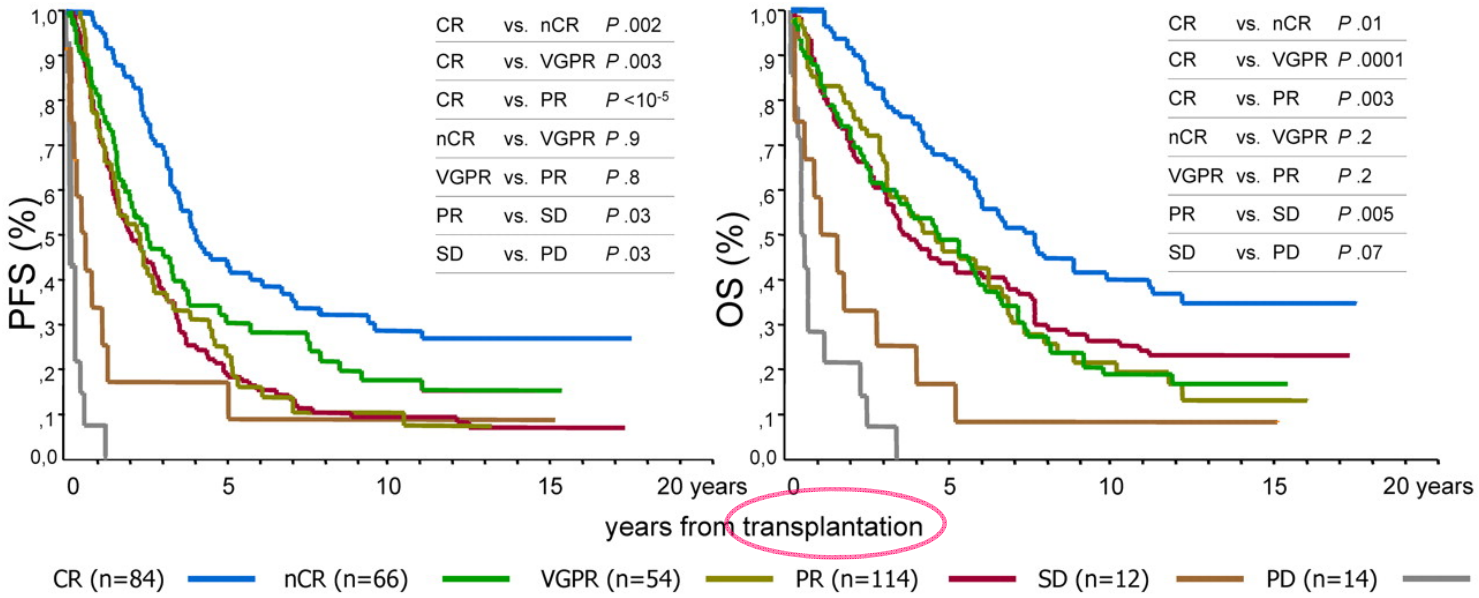
- **CLINICAL TRIAL!!!**
  - **Only 4% of patients enroll; 40% close due to low accrual**
- Consider repeating previously successful agents

- Thalidomide
- Lenalidomide
- Bortezomib
- Bendamustine
- Melphalan
- Carfilzomib
- Panobinostat
- Liposomal doxorubicin
- Doxorubicin
- Vincristine
- Cyclophosphamide
- Steroids
- Pomalidomide

MYELOMA THERAPY

Therapy for Previously Treated Multiple Myeloma	
Preferred Regimens	**Other Regimens**
• Repeat primary induction therapy (if >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dex • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/dex • Carfilzomib/lenalidomide/dex (category 1) • Cyclophosphamide/lenalidomide/dex • Dex/cyclophosphamide/etoposide/cisplatin • Dex/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide ± bortezomib • High-dose cyclophosphamide • Lenalidomide/dexamethasone (category 1) • Panobinostat/bortezomib/dex (category 1) • Pomalidomide/dexamethasone • Thalidomide/dexamethasone	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/ dexamethasone

Can we cure patients with myeloma?



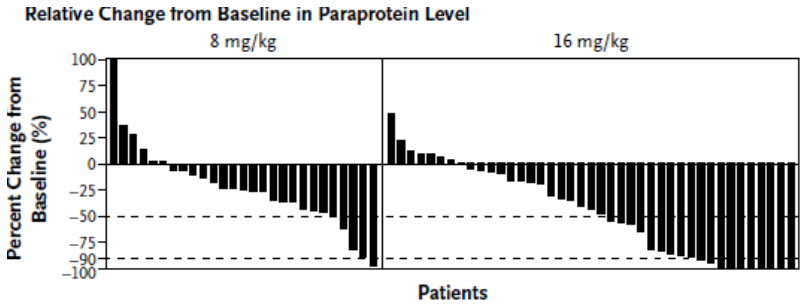
Joaquin Martinez-Lopez et al. Blood 2011;118:529-534

New Myeloma Agents

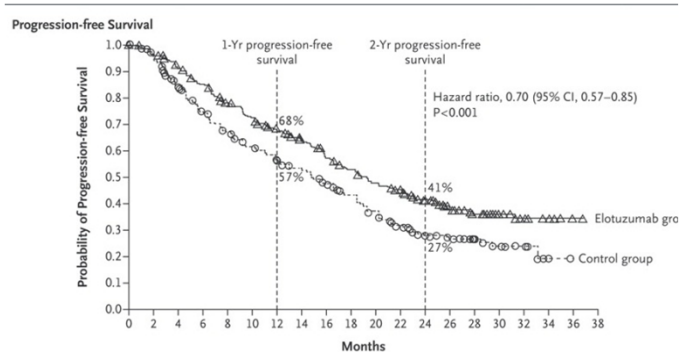
- mAbs (anti-CD38, anti-SLAM-F7, anti-IL-6…)
- HDAC Inhibitors (ACY1125)
- Oprozomib (oral analog of carfilzomib), Ixazomib, Marizomib, Delanzomib
- CAR-T Cell Therapy
- Ibrutinib (Bruton's tyrosine kinase inhibitor)
- Kinesin spindle protein inhibitors
- PD1/PDL-1

Immunotherapy for Myeloma

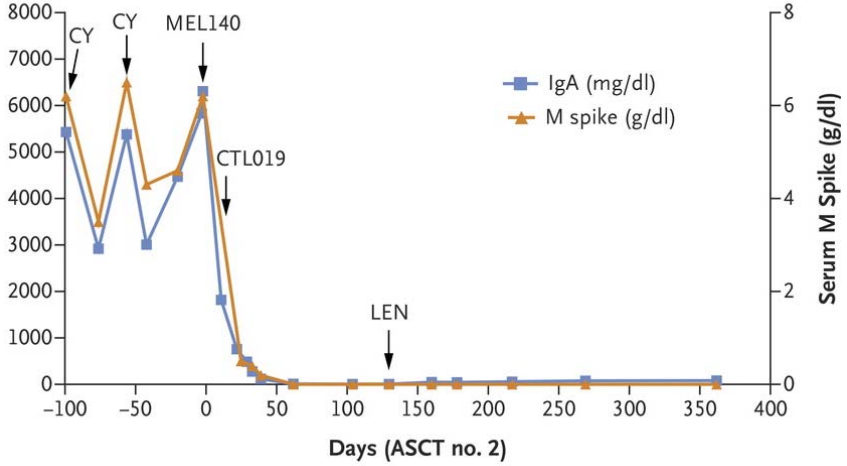
1). Anti-CD38 (Daratumumab)



2). Anti-SLAM F7 (Elotuzumab)



3). Anti-CD19 CAR T Cells



1. Lokhorst, H.M. NEJM, 2015
2. Lonial, S. NEJM, 2015
3. Garfall, A.L., NEJM, 2015

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