Emerging Strategies in the Management of

MULTIPLE MYELOMA

A CME/CE-certified **Oncology Exchange** *Activity*

PROGRAM SYLLABUS

CONTENTS

Jointly sponsored by: pcme, ROCKPOINTE Oncology

Co-provided by: global EDUCATION GROUP | UMA

Supported by an educational grant from: Bristol-Myers Squibb, Celgene, Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

PROGRAM OVERVIEW

In the past decade, the treatment landscape for multiple myeloma (MM) has significantly improved with the introduction of several novel treatment regimens. Community clinicians are constantly challenged to stay up to date with these recent advances in the management of MM.

Emerging Strategies in the Management of Multiple Myeloma will provide guidance on optimal disease management strategies in MM using clinical case scenarios, while exploring issues faced by community clinicians involved in the treatment of patients with MM.

TARGET AUDIENCE

This activity is intended for community-based oncologists and hematologists, oncology nursing professionals, as well as other clinicians involved in the care of patients with multiple myeloma.

EDUCATIONAL OBJECTIVES

This program is designed to address the following IOM competencies: provide patient-centered care and employ evidence-based practice.

At the conclusion of this activity, participants should be able to demonstrate the ability to:

- Assess the prognosis of patients based on risk stratification and patient- and disease-related characteristics that influence the selection of optimal treatment in frontline, maintenance, and relapsed/refractory settings
- Review current and emerging maintenance therapy options considered for MM
- Review treatment options for patients with relapsed/refractory MM
- Identify and manage common treatment-related toxicities in MM
- Evaluate clinical trial opportunities for patients with relapsed/refractory MM

Jointly sponsored by: **Potomac Center for Medical Education** and **Rockpointe**

Co-provided by: **Global Education Group**

Supported by an unrestricted educational grant from:
Bristol-Myers Squibb, Celgene, and **Millennium**

ACCREDITATION

Physicians – This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Potomac Center for Medical Education and Rockpointe Oncology. The Potomac Center for Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

Nurses – Global Education Group is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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Physicians – The Potomac Center for Medical Education designates this live activity for a maximum of 1.0 *AMA PRA Category I credit(s)*^{TM}. Physicians should claim only the credit commensurate with the extent of their participation in the activity. For information about the accreditation of this program, please email contact@potomacme.org.

Nurses – This educational activity for 1.0 contact hours is provided by Global Education Group. Nurses should claim only the credit commensurate with the extent of their participation in the activity. For information about the nursing accreditation of this program, please contact Global at inquire@globaleducationgroup.com or 303-395-1782

SPECIAL SERVICES

Event staff will be glad to assist you with any special needs (e.g. physical, dietary, etc.).

FEE AND RECEIVING CME CREDIT

There is no fee for this educational activity. To receive CME/CE credit the participant must:

- Participate in this one-hour-long program in its entirety;
- Sign in / sign out on the sheet provided by the host coordinator;
- Complete and sign the registration and evaluation form; and
- Return the registration and evaluation form to the host coordinator.

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The content of this activity was vetted by an external medical reviewer to assure objectivity and that the activity is free of commercial bias.

PROGRAM DISCLOSURES

Steering Committee:

The steering committee reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Rafael Fonseca, MD: *Consultant:* Amgen, Binding Site, Bristol-Myers Squibb, Celgene, Genzyme, Lilly, Medtronic, Millennium, Onyx, Otsuka; *Research:* Cylene, Onyx Medical Systems

Sergio Giralt, MD: *Consultant/Advisory Board:* Bioline, Celgene, Janssen, Onyx, Sanofi, Seattle Genetics, Skyline Diagnostics, Spectrum Pharmaceuticals; Speaker: Celgene

Non-faculty Content Contributors:

Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Latha Shivakumar, PhD; Blair St. Amand; Jay Katz, CCMEP; CME Peer Review:
Nothing to disclose

FDA DISCLOSURE

The contents of some CME/CE activities may contain discussions of non-approved or off-label uses of some agents mentioned. Please consult the prescribing information for full disclosure of approved uses.

STEERING COMMITTEE

RAFAEL FONSECA, MD
Getz Family Professor of Cancer
Chair of Internal Medicine
Mayo Clinic in Arizona
Scottsdale, AZ

Rafael Fonseca, MD is a consultant in the Division of Hematology/Oncology at Mayo Clinic Arizona, and is the Chair of the Department of Internal Medicine. He holds the academic rank of Professor of Medicine and is also the recipient of a named professorship, Getz Family Professor of Cancer. He holds the distinction of Mayo Clinic Distinguished Investigator. Dr. Fonseca earned his medical doctorate at Universidad Anahuac in Mexico. He completed a residency in internal medicine at the University of Miami and a fellowship in hematology and medical oncology at Mayo Graduate School of Medicine in Rochester, MN. He is a Clinical Investigator of the Damon Runyon Cancer Research Fund.

During his training and career, Dr. Fonseca has received numerous awards and honors, including the Young Investigator Award in Hematology, Damon-Runyon Walter Winchell Clinical Investigator Award, and the International Waldenström Macroglobulinemia Research Award. Dr. Fonseca is a member and serves in positions for several organizations, such as American Society of Clinical Oncology, American Society of Hematology, American Association for Cancer Research, and the International Myeloma Society. He is an active member of several oncology clinical trial cooperative groups, and holds positions on several Mayo Clinic committees, including the Executive Operations Team. He is a founding member of the Multiple Myeloma Research Consortium and Chairs its Tissue Banking Core. He has an adjunct academic appointment at the Translational Genomics Research Institute and his research has been funded by the National Cancer Institute, among other organizations.

Dr. Fonseca serves as a reviewer for several medical publications, including *Blood, Cancer Cell, Lancet, Nature Medicine, Cancer Cell, Leukemia,* and the *New England Journal of Medicine.* He has given many national and international presentations as a visiting professor, and has authored more than 200 book chapters, editorials, abstracts, and letters.

Dr. Fonseca's practice has focused on the diagnosis and treatment of plasma cell disorders and on leading the multiple myeloma team in its effort to develop a better understanding of the disease and its impact on patients. In his laboratory, Dr. Fonseca has led his team of researchers in concentrating on the genetic and cytogenetic nature of the clonal cells of plasma cell disorders.

STEERING COMMITTEE

SERGIO GIRALT, MD
Chief, Adult Bone Marrow Transplant Service
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, NY

Sergio Giralt, MD is the Chief of the Adult Bone Marrow Transplant Service in the Division of Hematologic Oncology at Memorial Sloan-Kettering Cancer Center in New York, NY. He is also affiliated with Weill Cornell Medical College as a Professor of Medicine. He received his medical degree from Universidad Central de Venezuela in Caracas, Venezuela, and completed his postgraduate internship at the University Hospital of Caracas. He also completed an internal medicine residency at Good Samaritan Hospital in Cincinnati, OH and a postdoctoral fellowship in hematology and oncology at the University of Texas MD Anderson Cancer Center.

Board-certified in internal medicine, hematology, and medical oncology, Dr. Giralt holds membership in several professional societies, including the American Society of Hematology, American Society of Clinical Oncology, North American Society of Blood and Bone Marrow Transplantation, and International Society of Haematology. He holds key positions with several organizations, including the International Bone Marrow Transplant Registry Executive Committee, the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) Steering Committee, the National Marrow Donor Program Board of Directors, and the Clinical Advisory Board of the Website Managing Myeloma.

Dr. Giralt is the President-Elect of the American Society for Blood and Marrow Transplantation, as well as the Past Chair of the BMTCTN and of the Center for International Blood and Marrow Transplant Research.

Dr. Giralt has published more than 400 articles and abstracts in the peer-reviewed literature and has written chapters for several books. In addition, Dr. Giralt is a reviewer and editorial board member for several journals.

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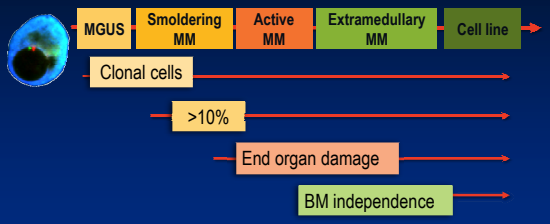
Multiple Myeloma: *Epidemiology*

- Approximately 22,400 new cases in 2013
  - 10,800 associated deaths
- African Americans >2x
- Hispanics 1.7x
- Median age 66 years
  - Age <50 years: 10%
  - Age <40 years: 2%

Cancer Facts and Figures. American Cancer Society. 2013.

Progression of the Disease



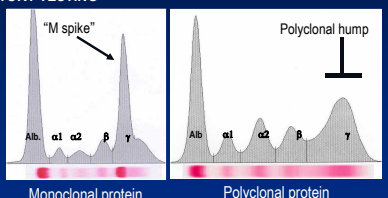
Kuehl WM, Bergsagel PL. *Nat Rev Cancer.* 2002;2:175-187.

Diagnosis of Myeloma

CLINICAL CRITERIA

- Evidence of plasma cell clone
- Usually >10%, but not always
- Any level of protein
- Difference between SMM and MM is CRAB

LABORATORY TESTING

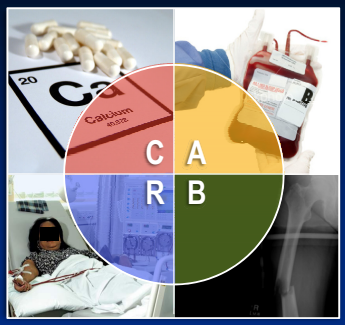


Picture courtesy of Drs. R. Kyle and J. Katzmann. Mayo Clinic; NCCN Clinical Practice Guidelines v2.2013.

Importance of Progression Events

CRAB CRITERIA

- Calcium elevation
- Renal disease
- Anemia
- Bone disease



Durie BG et al. *Leukemia.* 2006;20:1467-1473.

Multiple Myeloma: *Prognosis*

- Survival statistics unknown now
  - If not high risk, many survive 10 years
  - High risk = 3 years
- Some 10%-20% of patients have long-term control with SCT
- Prognosis dictated by host features and genetics
  - High risk – 17p13, t(4;14), and t(14;16)
  - Gene expression profiling
- Other markers: high LDH, hypodiploidy, IgA, plasmablastic
- International Staging System (ISS) is useful to compare trials, not individually
- ISS has replaced the Durie-Salmon staging system

Fonseca R et al. *Leukemia*. 2009;23:2210-2221.

Case Discussions

Myeloma Tales of Two Cases

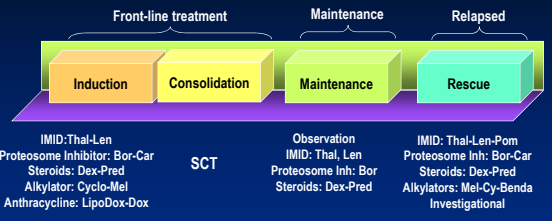
Case 1

- 55-year-old female presents with asymptomatic anemia of 10 g/dL and total serum protein 10 g/L
- Work-up reveals
  - 30% plasma cells
  - Cytogenetic diploid
  - IgA kappa peak of 3.2
  - Beta 2 microglobulin of 3.0/Albumin 2.0 g/dL
  - Survey no lytic lesions
- *What induction therapy should she receive?*

Case 2

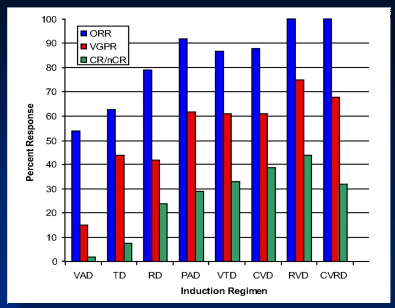
- 55-year-old female presents with asymptomatic anemia of 10 g/dL and total serum protein 10 g/L
- Work-up reveals
  - 30% plasma cells
  - Cytogenetic t 4,14
  - IgA kappa peak of 3.2
  - Beta 2 microglobulin of 5.0
  - Survey multiple lytic lesions
- *What induction therapy should she receive?*

Multiple Myeloma Treatment Lines[a]



[a]Transplant eligible patients.
Bor = bortezomib; Dex = dexamethasone; Dox = doxorubicin; Thal = thalidomide; Len = lenalidomide; SCT = stem-cell transplant; Pred = prednsione; Lipo/Dox = liposomal doxorubicin.
NCCN Clinical Practice Guidelines v2.2013.

Combinations in the Upfront Treatment of MM



Combination therapy incorporating novel agents results in near 100% ORRs

Stewart AK et al. *Blood*. 2009;115:4006.

Lenalidomide/Dexamethasone Efficacy

Objective Response	Whole Cohort (n = 34), %	Len/Dex as 1° Therapy (n = 21), %
Overall response	91	90
CR	18	24
VGPR	38	43
PR	35	24

CR + VGPR = 67%

Survival	Patients, %
2-yr PFS	
Transplant	83
No transplant	59
2-yr OS	90

Rajkumar SV et al. *Blood*. 2005;106:4050.
Lacy MQ et al. *Mayo Clinic Proc*. 2007;82:1179-1184.

Lenalidomide/Bortezomib-based Rx

Response	RVD[1] (n = 66)	RVDD[2] (n = 70)	VDCR[3] (n = 41)
CR + nCR	39%	33%	32%
≥VGPR	67%	59%	59%
≥PR	100%	97%	93%

- Hematologic toxicity is more severe with addition of chemo, but not cumulative
- Risk of DVT does not appear to be increased over lenalidomide alone
- Risk of PN does not appear to be increased over bortezomib alone
- Generally well tolerated, although TRM with VDCR (2 patients in Evolution Study)

RVD = lenalidomide/bortezomib/dexamethasone; RVDD = RVD with pegylated liposomal doxorubicin; VDCR = RVD plus cyclophosphamide; VTD = bortezomib/thalidomide/dexamethasone

1. Richardson PG et al. *Blood*. 2010;116:679-686.
2. Jakubowiak AJ et al. *Blood*. 2011;118:535-543.
3. Kumar S et al. *Blood*. 2009;114:1729-1735.

Frontline Therapy for MM with RVD Regimen

- RVD is highly effective for previously untreated MM
  - The first regimen to result in a 100% response rate (≥PR) without ASCT
  - Remarkably high rates of CR/nCR and ≥VGPR
- Promising outcomes data; estimated 24-month PFS of 68% and OS of 95% with RVD ± ASCT
- Favorable tolerability over a lengthy treatment period
  - Manageable toxicities
  - Only 2% G3 sensory PN, 6% DVT; no treatment-related mortality
  - All-grade PN 80%, but mainly G1/2 and reversible
  - Stem cell mobilization feasible and successful in almost all patients

Richardson et al. *Blood 116: 2010 (679-686);* Anderson, et al. *J Clin Oncol 28:15s, 2010 (suppl; abstr 8016)*

What Toxicities Should You Monitor in These Patients?
IMID-associated Deep Venous Thrombosis

- Pathophysiology unclear
  - MM, unlike solid tumor does not express tissue factor
  - Platelet activation via cathepsin G
- Prevention is key
  - Low risk aspirin
  - High risk anticoagulation
    - High dose dex, immobility, prior DVT, comorbidity
- Pearls
  - Continue until at least 1-2 months post completion
  - Do not forget to bridge for surgical procedures
  - Not a reason to abandon treatment

Palumbo A et al. *Blood Rev*. 2011;25:181-191.
Richardon PG et al. *Leukemia*. 2012;26:595-608.

Other Toxicities: *Peripheral Neuropathy*

- Peripheral neuropathy (PN) – one of the most important complications of MM treatment
- PN can be caused by MM itself, and particularly by certain therapies, including bortezomib, thalidomide, vinca alkaloids, and cisplatin
- Up to 20% of MM patients have PN at diagnosis, and as many as 75% may experience treatment-emergent PN during therapy
- Bortezomib causes any grade PN in 31% to 47% patients
- Lower-than-expected rates of severe PN with bortezomib plus lenalidomide combinations, with grade 3 PN rates of 3% and 2% with bortezomib, lenalidomide, and dexamethasone (RVD) in frontline and relapsed/refractory patients, respectively

Palumbo A et al. *Blood Rev*. 2011;25:181-191.
Richardon PG et al. *Leukemia*. 2012;26:595-608.

Autologous vs Allogeneic

AUTOLOGOUS
- High-dose therapy with reinfusion of own cryopreserved cells
- Safer, TRM <5%
- Possible contamination with malignant cells
- No graft-vs-malignancy effect
- Higher risk of relapse

ALLOGENEIC
- Immunosuppressive Rx with infusion of cells from another person
- Risk of rejection, GVHD
- Higher risk, TRM 10%-40%
- Graft-vs-malignancy occurs
- Lower risk of relapse
- Can perform in diseases in which blood and BM involved

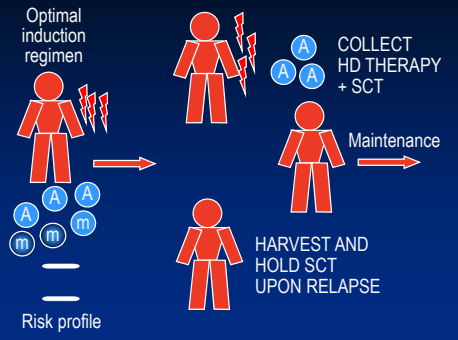
Autologous Transplantation vs Conventional Chemotherapy for Newly Diagnosed Myeloma

		Pts (n)	CR (%)	EFS (mos)	OS (mos)
Barlogie et al	Conventional*	116	–	22	48
	HDT	123	40	49	62
Lenhoff et al	Conventional*	274	–		46% @ 48
	HDT	274	34	27	61% @ 48
Attal et al	Conventional	100	5	18	37
	HDT	100	22	27	52% @ 60
Fermand et al	Conventional	96	–	19	50
	HDT	94	–	24	55
Blade et al	Conventional	83	11	34	67
	HDT	81	30	43	67
Child et al	Conventional	200	9	20	42
	HDT	201	44	32	55

* Historical controls

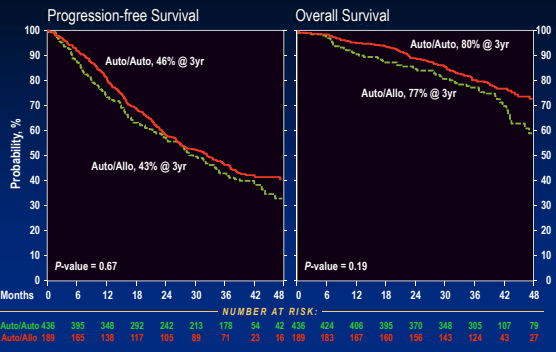
Fermand J. *Blood*. 1998;92:3131.
Blade J. *Blood*. 2001;98:815a.
Barlogie B. *Blood*. 1997;89:789.
Lenhoff S. *Blood*. 2000;95:7.
Attal M. *N Eng J Med*. 1996;335:91.

Is It Time for a New Early-vs-Late SCT Study?



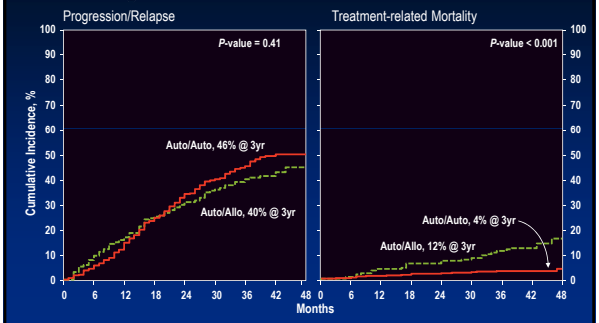
BMT-CTN 0102 Trial: Survival Outcomes after the First Transplant

Auto-Auto vs Auto-Allo: Intent-to-treat Analysis (n=710)



Krishnan et al. *Lancet Oncol.* 2011;12:1195-1203.

BMT-CTN 0102 Trial: Cumulative Incidence of Disease Progression/Relapse and Treatment-related Mortality after First Transplant



Krishnan et al. *Lancet Oncol.* 2011;12:1195-1203.

Lenalidomide Maintenance After Transplantation

Comparisons	CALGB 100104	IFM 2005-02
Induction	Thal- and Len-containing regimens (74%)	VAD (~52%) and VD (~44%)
Pre-AHSCT consolidation	None	DCEP (~25%)
Number of AHSCT	One	One (79%), Two (21%)
Post-AHSCT consolidation before randomization	None	Lenalidomide: 25 mg daily, 3 of 4 wks x 2 pre day ~100
Median F/U at un-blinding	~18 months	~33 months
Median F/U from randomization	31 months	45 months
Dosing schedule	10 mg (between 5 to 15 mg)	10 mg (between 5 to 15 mg)
Time from first patient enrolled	78 months	62 months
Placebo patients crossed over to lenalidomide at un-blinding	Yes (86 of 128 eligible patients)	No
Second primary malignancies	~3 fold increase	~2.6 fold increase
Increase in AML/MDS	Yes	No
Increase in ALL/HL	No	Yes
Maintenance stopped	No	Yes at a median of ~32 months

McCarthy PL. *J Natl Compr Canc Netw.* 2013;11:35-42.

MPR vs MEL200 vs MPR-R vs MEL200-R

Response, PFS, and OS

	R maint. (N=198)	No maint (N=204)	P value
CR	23%	19%	.25
≥ VGPR	48%	48%	.93
≥ PR	78%	77%	.75

FROM DIAGNOSIS	FIRST RANDOMIZATION			SECOND RANDOMIZATION		
	MPR	MEL200	HR (95%CI; *P* value)	MAINT	No MAINT	HR (95%CI; *P* value)
Median PFS (mos)	25	39	1.66 (1.27-2.18; 0.0002)	37.5	25.7	0.63 (0.48-0.83; 0.0008)
4-ys OS	71	72	1.08 (0.72-1.63; 0.71)	76	68	0.68 (0.45-1.04; 0.08)
START OF MAINTENANCE	**FIRST RANDOMIZATION**			**SECOND RANDOMIZATION**		
	MPR	MEL200	HR (95%CI; *P* value)	MAINT	No MAINT	HR (95%CI; *P* value)
Median PFS (mos)	18	41	2.01 (1.45-2.79; <0.0001)	41	18	0.50 (0.36-0.69; <0.0001)
3-ys OS	77	76	0.98 (0.61-1.58; 0.94)	81	72	0.60 (0.37-0.97; 0.04)

Palumbo. Presented at: ASCO 2013.

Myeloma Tales of Two Cases

CASE 1

- 55-year-old female presents with asymptomatic anemia of 10 g/dL and total serum protein 10 g/L
- Receives RVD x 4 followed by autologous SCT and lenalidomide maintenance
- Achieves a CR
- 3 years later has reemergence of SPEP at 0.5 mg/dL
- *What should next step be?*

CASE 2

- 55-year-old female presents with asymptomatic anemia of 10 g/dL and total serum protein 10 g/L
- Receives RVD x 4 followed by autologous SCT and lenalidomide maintenance
- Achieves a CR
- 1 year later has reemergence of SPEP at 0.5 mg/dL
- *What should next step be?*

Types of Relapse

Clinical Patterns of Relapses after Autologous PBSC Transplantation

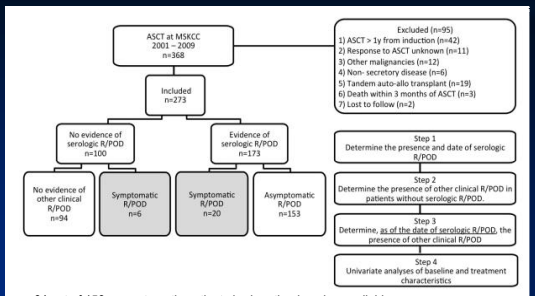
Pattern of relapse	*N (%)*
Insidious form Increase of MC protein in serum or urine without other clinical manifestations.	51 (18 %)
Classical form Progressive increase of MC, medullary plasmacytic infiltration, clinical myeloma symptoms and new osteolytic lesions	183 (66%)
Plasmacytoma form Extramedullary manifestations with single or multiple plasmacytomas	40 (14%)
Leukemia form Plasmacytic leukemia	6 (2%)

Treatment Administered for Relapse of Progression after Autologous PBSCT

Treatment	*N (%)*
No treatment (observation)	23 (20.5%)
Corticosteroids	15 (7%)
Chemotherapy + corticosteroids	15 (7%)
Chemotherapy	88 (37%)
Radiotherapy	8 (4%)
Chemotherapy + radiotherapy	10(5%)
New autologous PBSCT	35(15%)
Allogeneic transplantation	6 (3%)

Alegre A et al. *Haematologica*. 2002;87:609-614.

New Patterns of Relapse



- 64 out of 153 asymptomatic patients had routine imaging available.
- Twenty-five (40%) had new bone lesions by SS (n = 12), PET/CT (n = 11), or MRI (n = 2) despite absence of any prior suspicion.

Zamarin D et al. *Bone Marrow Transplant*. 2013;48:419-424.

Case 3

- A 72-year-old male is diagnosed with MM. He started with back pain which lead to the discovery of anemia (Hgb 9.1) and 3 compression fractures
- A BM showed 60% kappa plasma cells
- His IgG is 4200 mg/dL, kappa FLC is 79 mg/dL, beta 2 microglobulin 8, creatinine 1.0, calcium is normal
- FISH shows hyperdiploidy and no -17 or -13
- He has a complicated PMH
  - CAD with stent 2 years previous
  - Depression
  - Type 2 diabetes, diet controlled
  - HTN
  - Obesity
  - Atrial fibrillation
- He is retired and recently widowed

Case 3 *(continued)*

- He is started on len-dex
- His creatinine has worsened and is now 1.7 mg/dL
  - The patient self-reports poor PO fluid intake
- Len-dex is poorly tolerated – fatigue and insomnia
- After only one month the patient requests treatment discontinuation or change
- He states he is interested only "in quality of life not quantity"

Case 3: Second-line Treatment

- The patient is treated with CyBORD with lower doses of dexamethasone (20 mg weekly)
  - Bortezomib is given IV weekly
- He tolerates well the first cycles
- By cycle 3 he reports signs of early peripheral neuropathy on his feet
- He also complains "his shoes don't fit him anymore"
- He complains of mild SOB

SQ Administration of Bortezomib

- Randomized Phase III study
- 1-3 previous lines of therapy
- Up to eight 21-day cycles of bortezomib
- Primary response was non-inferiority (4 cy)
- 222 patients assigned to receive Rx
  - 145 SQ and 73 IV
- ORR same (42% vs 42%)
  - After 8 cycles 52% vs 52%

Moreau P et al. *Lancet Oncol*. 2011;12:431-440.

Results SQ Bortezomib

- Median FU 11.8 mos, no difference in TTP
  - 10.4 vs 9.4 mos
- One year OS 72% vs 76%
- Grade 3/4 events favored SQ (57% vs 70%)
- PN less common with SQ 38% vs 53% (*P*=0.04)
  - Grade 2 or worse 24% vs 41% (*P*=0.012)
  - Grade 3 or worse 6% vs 16% (*P*=0.026)

Moreau P et al. *Lancet Oncol.* 2011;12:431-440.

Case 3: Second-line Treatment

- Bortezomib is changed to weekly SQ
- Dexamethasone is lowered to 8 mg weekly
- You continue on treatment and have provided 7 cycles
- The patient returns for cycle 8 and is complaining of left chest wall pain; No SOB
  - EKG, TnT, and CxRay are fine
  - A day later a vesicular rash develops
  - You forgot to add a medication!

Carfilzomib PX-171-003-A1: *Best Overall Responses*

Response category, n(%)	All patients (n=257)	Patients with unfavorable cytogenetic/FISH marker (n=71)
CR	1 (0.4)	0 (0)
VGPR	13 (5.1)	3 (4.2)
PR	47 (18.3)	18 (25.4)
MR	34 (13.2)	3 (4.2)
SD	81 (31.5)	28 (39.4)
PD	69 (26.8)	15 (21.1)
Not evaluable	12 (4.7)	4 (5.6)
Overall Response, n(%)	**61 (23.7)**	**21 (29.6)**
95% CI	18.7 – 29.4)	19.3 - 41.6
Clinical benefit rate, n(%)	**95 (37.0)**	**24(33.8)**
95% CI	31.1 – 43.2	23.0 – 46.0
PFS, median (95% CI), mo	**3.7 (2.8 – 4.6)**	**3.6 (2.3-4.6)**
Median DoR, mo (95% CI)	**7.8 (5.6 – 9.2)**	**6.9 (3.7-8.5)**
Mean treatment duration, mo (range)	**3.0 (0.03 – 16.9)**	**3.6 (0-11.1)**

Key Inclusion Criteria: Relapsed MM; ≥2 prior therapies (including bortezomib and thalidomide and/or lenalidomide); ≤25% response to the most recent therapy or disease progression during or within 60 days of the most recent therapy

KYPROLIS [package insert]. Onyx Pharmaceuticals, Inc; 2012.
Siegel D et al. *Blood.* 2012;120:2817-2825.

Pomalidomide + Low-dose Dex for Relapsed MM

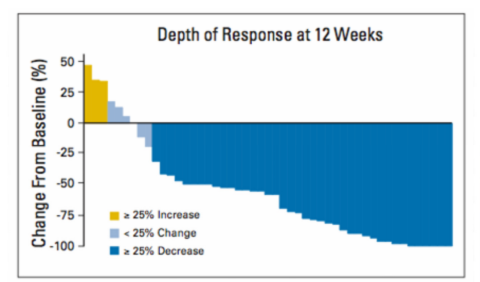
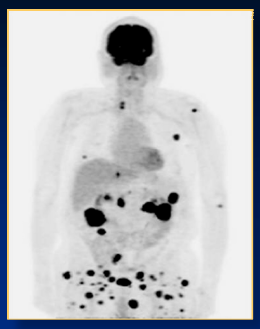


Fig 1. Each bar represents the percent change in the measurable parameter, whether serum, urine, or bone marrow as a percent change from baseline at 12 weeks.

Lacy M et al. *J Clin Oncol.* 2009;27:5008-5014.

Pomalidomide

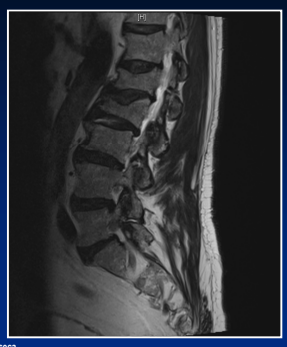


Lacy M et al. *J Clin Oncol.* 2009;27:5008-5014.

Post-transplant Course

- Post-transplant course: thrombocytopenia, but fully recovers
- Maintenance: Len 10-15 mg daily and monthly pamidronate for 2 years, then reduced to every 3 months thereafter
- Develops lower back pain Dec 2011
- Restaging revealed extensive bone marrow involvement
- MRI of the spine positive for recurrent disease and revealed extensive bony progression

MRI of the Spine



Picture Courtesy of Dr. Fonseca.

Post-transplant Course

- 80% plasmacytosis
- IgA kappa markedly elevated: 2.5 g/dL
- WBC 2.5, Hb 9, hematocrit 28, and platelets 60,000
- PFI (progression-free interval from initial therapy): 38 months
- The patient's bisphosphonates are increased to every 4 weeks

Debulking of disease is urgently required, and salvage therapy should also be considered.

Elotuzumab + Len/Dex Study

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein 1,2
- CS1 is highly expressed on >95% of MM cells 1–3
  - Lower expression on NK cells
  - Little to no expression on normal tissues
- Results look very good for this patient population and justify phase III studies
  - ORR 84% (92% in elotuzumab 10 mg/kg group)
  - ORR 91% if 1 line of therapy
  - PFS NR for 10 mg/kg and 18.6 months for 20 mg/kg

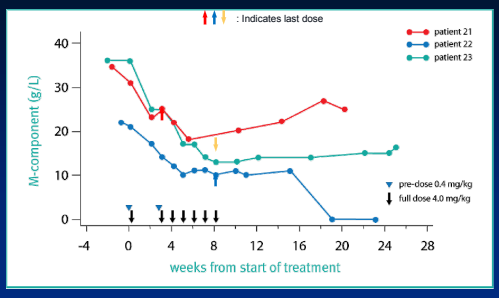
Lonial et al., ASCO 2012, Abstract 8020; Richardson et al., ASH 2012, Abstract 202.

Next Steps for Elotuzumab + Len/Dex

- **Two ongoing Len/Dex +/- Elotuzumab studies**
- **Bor/Dex +/- Elotuzumab phase II study initiated (abstract #92855)**
- **Can we do even better by combining elotuzumab with 3-drug regimens or other agents?**
  - **Is cost going to be a concern?**
- **How to use elotuzumab in LEN-refractory patients may need to be addressed**
- **Lower PFS in high-risk patients is disappointing**
  - **There is a potential for relative benefit**

Lonial et al., ASCO 2012, Abstract 8020; Richardson et al., ASH 2012, Abstract 202.

M-Component in Patients Treated with Daratumumab 4 mg/kg



Slides courtesy of Dr. Torben.
Presented at: ASCO 2012, Abstract 8019.

MLN9708 (Ixazomib, a Novel Proteasome Inhibitor) in Combination with len + dex in Previously Untreated MM: Evaluation of Weekly and Twice-weekly Dosing

Preliminary response in weekly dosing study: pts treated with ≥4 cycles

Response, n (%)*	Phase 1 (n=13)	Phase 2 (n=33)	Total (n=46)
Median number of cycles	6 (4–15)	5 (4–5)	5 (4–15)
Overall response (≥PR)	13 (100)	32 (97)†	45 (98)†
CR+VGPR	8 (62)	13 (39)	21 (46)
CR	5 (38)	7 (21)	12 (26)
VGPR	3 (23)	6 (18)	9 (20)

*Response assessed using IMWG uniform response criteria
†Only 1 pt did not reach the criteria for PR, but achieved a 46% reduction in M-protein by cycle 4 at the data cut-off

Preliminary response in twice-weekly dosing study

Response, n (%)	Overall (n=10)*	Patients treated with ≥4 cycles (n=6)
Median number of cycles	4 (1–8)	6 (4–8)
Overall response (≥PR)	9 (90)†	6 (100)
CR+VGPR	6 (60)	5 (83)
CR	1 (10)	1 (17)
VGPR	5 (50)	4 (67)

*1 pt was not response-evaluable at data cut-off
†Only 1 pt did not reach the criteria for PR, but achieved a 32% reduction in M-protein after cycle 1 at the data cut-off

Response appears to get better with time on treatment

Slides courtesy of Dr. Richardson
Presented at: ASCO 2012, Abstract 8033.