Updates on Diagnostic Criteria and Management of Multiple Myeloma

Kenneth C. Anderson, MD

Dana-Farber Cancer Institute

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | NCCN.org/patients – For Patients

Integration of Novel Therapy Into Myeloma Management

Bortezomib, lenalidomide, thalidomide, bortezomib/doxorubicin, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, elotuzumab

Target MM in the BM microenvironment to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

16 FDA approvals (7 in 2015!) and median patient survival prolonged 3-4 fold

New approaches needed to treat and ultimately prevent relapse

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Criteria for Diagnosis of Multiple Myeloma (MM)

MGUS
- <3 g M spike
  <10% PC

Smoldering MM
- ≥3 g M spike
- OR ≥10% PC

AND

No anemia, bone lesions normal calcium and kidney function

Active MM
- ≥10% PC
- M spike +

AND

Anemia, bone lesions, high calcium or abnormal kidney function

Kyle RA. N Engl J Med 2002; 346: 564

Diagnosis of Active MM In Asymptomatic Patients (IMWG)

Even without CRAB Features, the following define active MM:

Bone marrow plasmacytosis ≥ 60% [1]

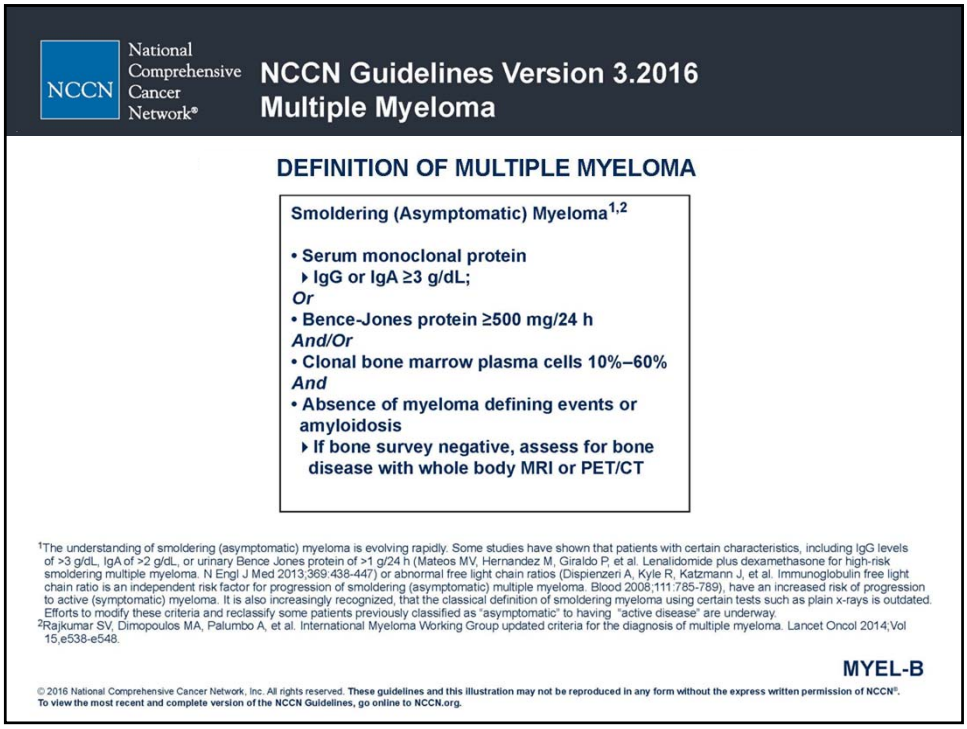
Abnormal FLC ratio ≥ 100 (involved kappa) or <0.01 (involved lambda) [2]

Focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI [3, 4]

1. Rajkumar et al N Eng J Med 2011; 365: 474
2. Larsen et al Leukemia 2013; 27: 941
3. Hillengass et al J Clin Oncol 2010; 28: 1606
4. Hillengass et al Leuk Lymph 2013

Rajkumar et al. *Lancet Oncol* 2015; 12:e538-e548

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.



Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

- **Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses**

Clinical trials (LLS TAP Program):

Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

.

Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Clin Can Res 2012; 17:4850-60.
Bae et al, Leukemia 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Effects of HDACi 241 on MM Specific Cytotoxic T cells (MM CTLs)

Does not affect viability of CD3, CD4, CD8 T cells

Does not induce checkpoint inhibitors on MM CTLs

Increases costimulatory molecules, proliferation, Th-1 cytokine production, and cytotoxicity of MM CTLs

Increases central and effector memory MM CTL cytotoxicity, costimulatory molecules, and proliferation

Decreases regulatory T cells

International Staging System (ISS) for Myeloma

Stage	Criteria	Median Survival (mo)
I	β2m < 3.5 mg/L albumin ≥ 3.5 g/dL	62
II*	Not stage I or III	44
III	β2m > 5.5 mg/L	29

*β2m < 3.5 mg/L and albumin < 3.5 g/dL or β2m 3.5 - < 5.5 mg/dL, any albumin

Greipp et al. J Clin Oncol 2005; 23: 3412-20

Revised ISS (R-ISS) incorporates LDH and high risk FISH abnormalities

Palumbo et all J Clin Oncol 2015: 33: 2863-9.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose theapy:

Nonhyperdiploid worse prognosis than hyperdiploid
t(11;14), hyperdiplody -standard risk
t(4;14), t(14;16),t(14;20), del(17p), del(13q14)- high risk

For novel treatments
Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14)-

del(17p) p53 remains high risk

Increasing Stringency in Defining Complete Response

- **CR …… Negative Immunofixation & < 5% PC in BM**
- **Stringent CR……Normal FLC & no clonal PC by immunohistochemistry** (Low sensitivity $<10^{-2}$)
- **Outside BM ……..Imaging techniques (MRI & CT-PET).**
- **BM Level……...Immunophenotypic remission** (by multiparametric flow)
  Molecular remission (by sequencing) *

** Pitfalls: 1. Pattern of BM infiltration in MM is not uniform… The possibility of residual MM-PC in another territory cannot be excluded (false negative results).*

2. Extramedullary relapses.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

DEFINITION OF MULTIPLE MYELOMA

Active (Symptomatic) Myeloma[2,3]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
And
Any one or more of the following myeloma defining events:
- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or PET-CT**
- **Clonal bone marrow plasma cells ≥60%**
- **Abnormal serum FLC ratio ≥100 (involved kappa) or <0.01 (involved lambda)**
- **>1 focal lesions on MRI studies > 5mm**

[2]Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;Vol 15,e538-e548.
[3]Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

MYEL-B

© 2016 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

Primary Therapy for Transplant Candidates
(Assess for response after 2 cycles)

Preferred Regimens:
- **Bortezomib/dexamethasone (category 1)**
- **Bortezomib/cyclophosphamide/ dexamethasone**
- **Bortezomib/doxorubicin/dexamethasone (category 1)**
- **Bortezomib/lenalidomide/dexamethasone (category 1)**
- **Bortezomib/thalidomide/dexamethasone (category 1)**
- **Lenalidomide/dexamethasone (category 1)**

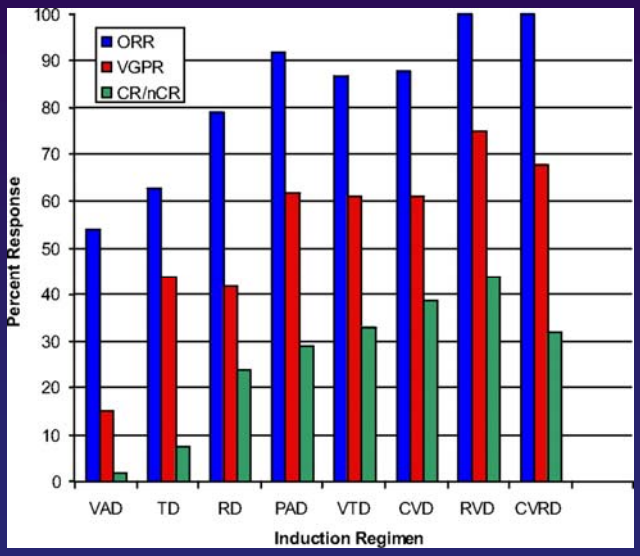
Other Regimens:
- **Carfilzomib/lenalidomide/ dexamethasone**
- **Dexamethasone (category 2B)**
- **Ixazomib/lenalidomide/dexamethasone**
- **Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B)**
- **Thalidomide/dexamethasone (category 2B)**

MYEL-D

© 2016 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.**

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Combinations in the Upfront Treatment of MM



Stewart AK, Richardson PG, San Miguel JF Blood 2009

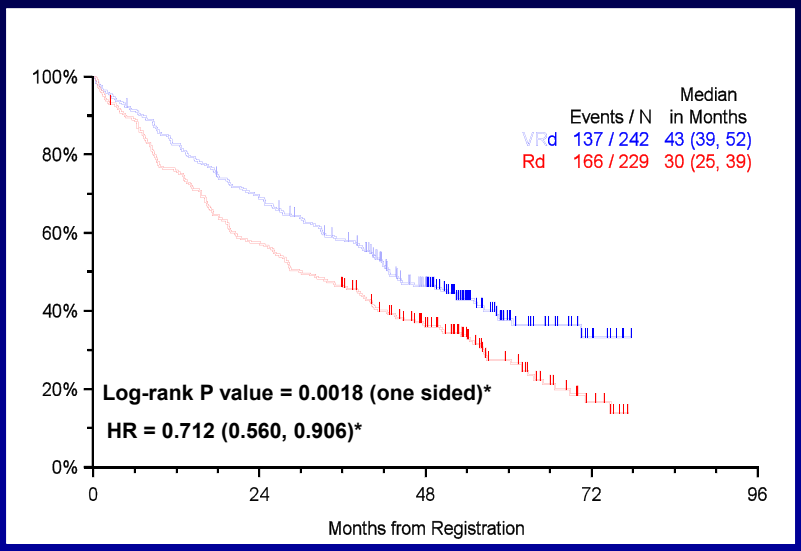
RVd versus Rd for Newly Diagnosed MM

	RVd	Rd
CR	15.7%	8.4%
VGPR	27.8%	23.4%
PR	38%	39.7%
ORR (PR or better)	81.5%	71.5%
SD	15.7%	24.3%
SD or better	97.2%	95.8%
PD or Death	2.8%	4.2%

Durie et al, ASH 2015

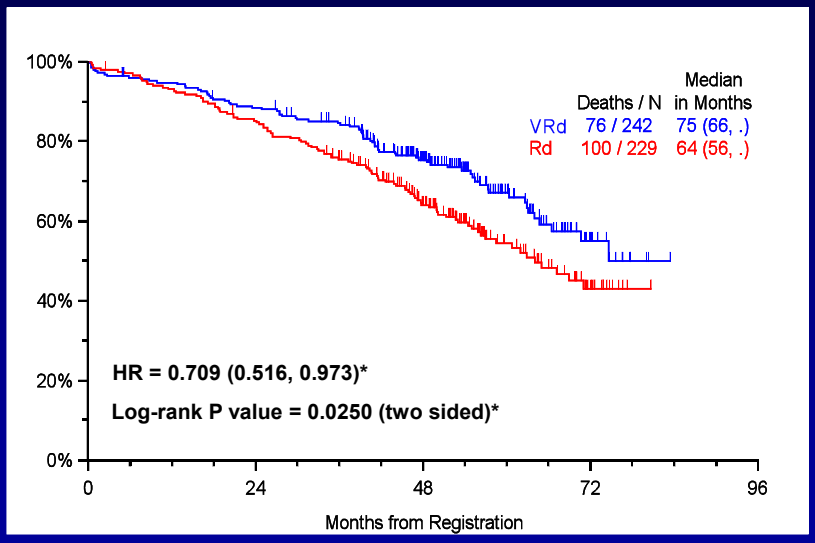
Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone: Progression Free Survival



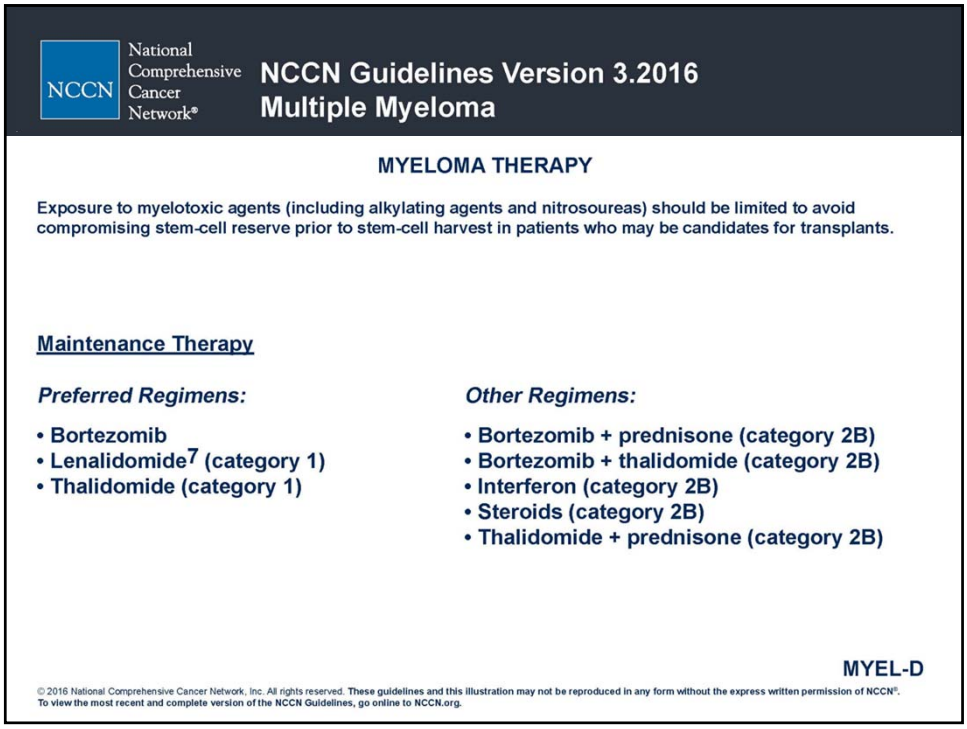
Durie et al, ASH 2015

Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone : Overall Survival



Durie et al, ASH 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.



Phase III Maintenance Studies – Transplant Eligible Patients

Trial	N	Regimen	Outcomes
IFM 2005-02[1]	614	Maintenance lenalidomide vs placebo following first or second ASCT	4-yr PFS: 60% vs 33%
CALGB 100104[2]	460	Maintenance lenalidomide vs placebo after ASCT	Median TTP: 46 vs 27 mos
RV-MM-PI-209[3]	402	MPR + maintenance lenalidomide vs MPR vs MEL200 + maintenance lenalidomide vs MEL200	Median PFS (R vs no R): 37 vs 26 mos 5-Yr OS (R vs no R): 75 vs 58 mos
HOVON-65[4]	827	VAD vs PAD followed by HD melphalan and ASCT, then thalidomide or bortezomib as maintenance	Median PFS: 28 vs 35 mos CR/nCR: 15% vs 31%
Nordic MSG 15[5]	370	Bortezomib x 21 wks vs no maintenance	≥ nCR: 45% vs 35%

1. Attal M, et al. N Engl J Med. 2012;366:1782-1791.
2. McCarthy PL, et al. N Engl J Med. 2012;366:1770-1781.
3. Boccadoro M, et al. ASCO 2013, abstr 8509
4. Sonneveld P, et al. *J Clin Oncol.* 2012;30:2946-2955.
5. Mellqvist UH, et al. *Blood.* 2013;121:4647-4654.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

ASCT and Maintenance Improve Outcome

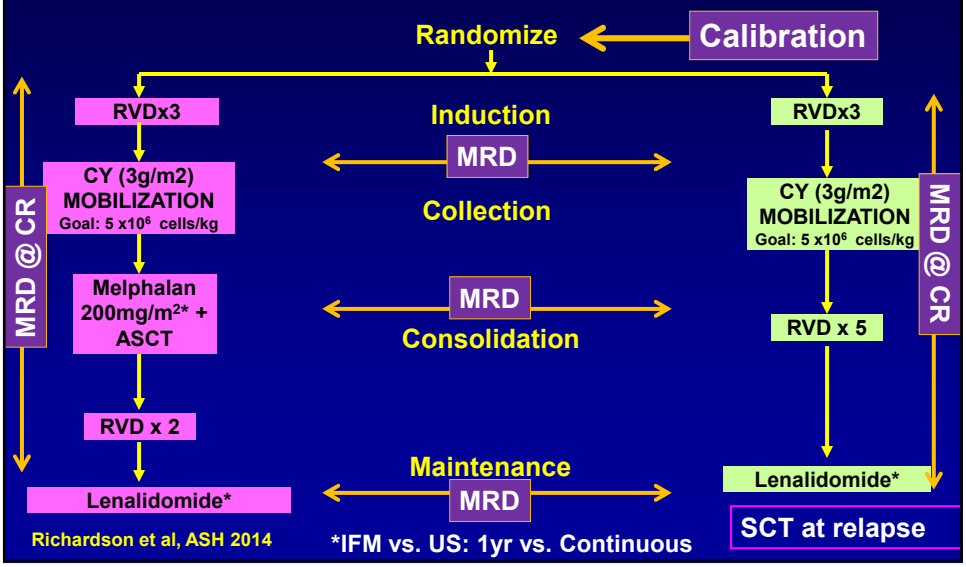
	ASCT	noASCT	p.
• PFS, median	59 mos	42 mos	0.01

	ISS I / II			STANDARD FISH		
	ASCT	noASCT	p.	ASCT	noASCT	
• PFS, median	60 mos	44 mos	0.05	69 mos	49 mos	0.04
• 5-year OS	85%	72%	0.03	84%	72%	0.7

	Maintenance	No maintenance	
ASCT			
• PFS, median	62 mos	41 mos	0.02
noASCT			
• PFS, median	53 mos	21 mos	0.01
• 5-year OS	77%	60%	0.008

Cerrato et al, ASH 2015

IFM/DFCI 2009 Study (US and France)
Newly Diagnosed MM (N=1,360)



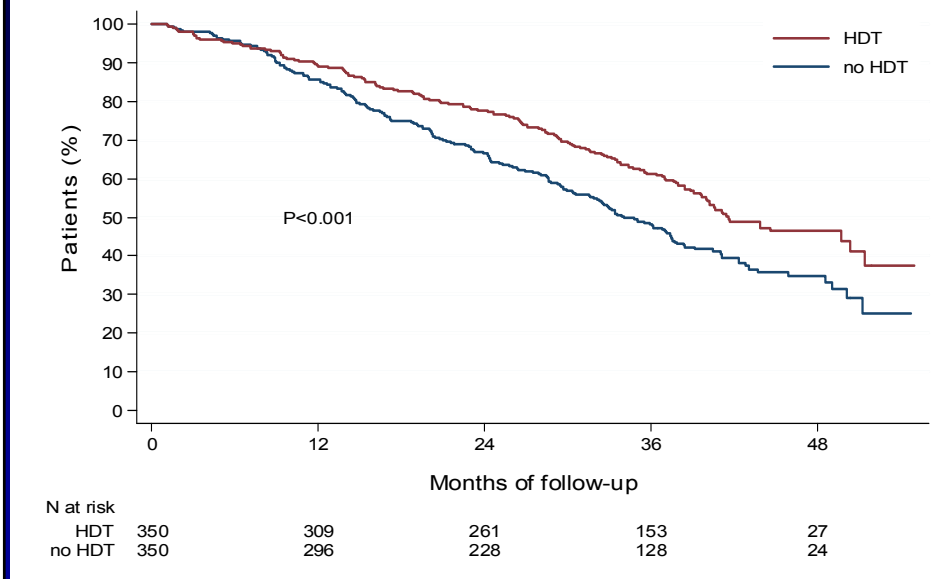
Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

IFM 2009: Best Response

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

Attal et al, ASH 2015

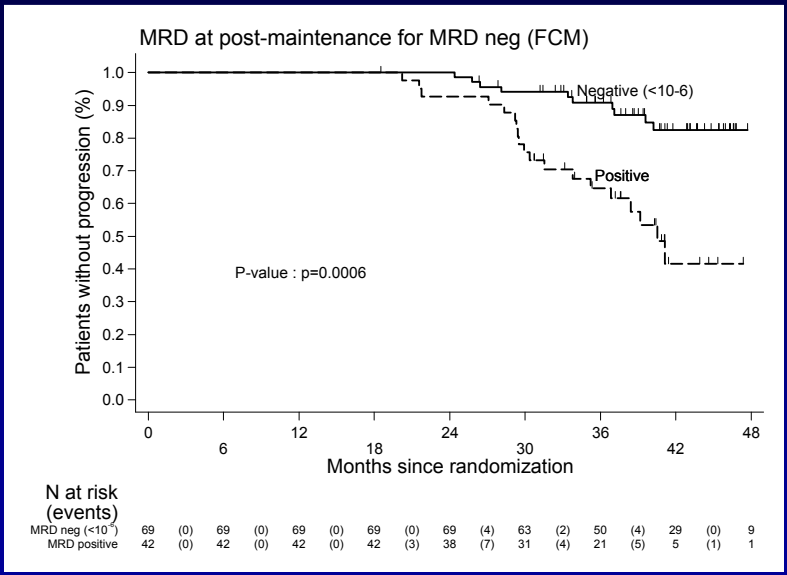
ASH 2015: IFM 2009: PFS (9/2015)



Attal et al, ASH 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Sequencing Distinguishes Outcome in FDM Negative Patients



Avet-Loiseau et al, ASH 2015

Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

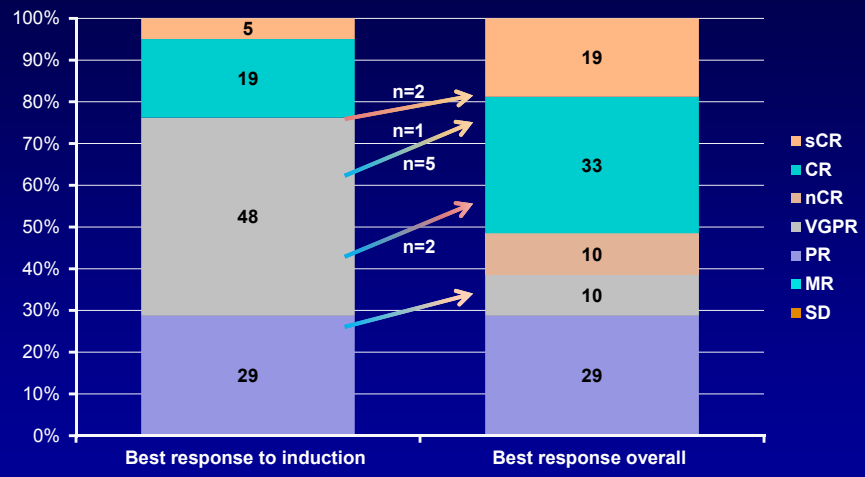
		ISS Stage		Cytogenetics		Carfilzomib Dosage		
Response, %	Overall (n=49)	I (n=20)	II/III (n=29)	Normal or Favorable (n=33)	Unfavorable (n=16)	20 mg/m²	27 mg/m²	36 mg/m²
ORR	98	90	97	91	100	100	100	88
VGPR	65	65	66	61	75	100	100	47
sCR, nCR, or CR	53	50	55	52	56	75	85	38

- Generally well tolerated and manageable side effects
- Grade 3/4 adverse events in ≥10% of pts
  - Hematologic: anemia, neutropenia, thrombocytopenia
  - Non-hematologic: hyperglycemia, dyspnea/CHF, HTN, deep vein thrombosis/ pulmonary embolism, renal dysfunction

Jakubowiak AJ et al. Blood 2012; 120: 1801.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Best Response to Ixazomib Len Dex and Ixazomib maintenance



10 (48%) pts improved their response during maintenance:

- 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR

Kumar et al ASH 2014

Lenalidomide Bortezomib Dexamethasone Panobinostat

- **The combination of lenalidomide 25 mg, subcutaneous bortezomib 1.3 mg/m^2, dexamethasone, and panobinostat 10 mg in newly diagnosed myeloma**

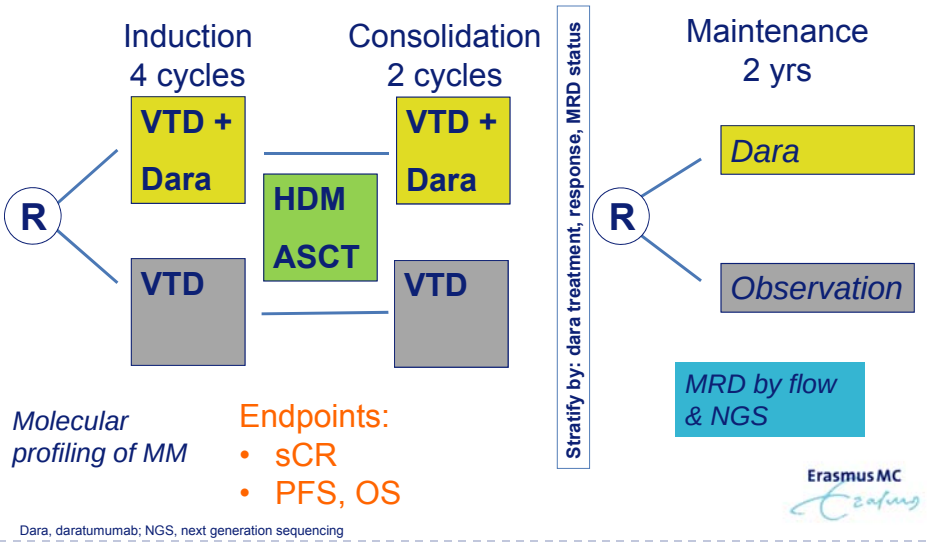
≥ ORR	94%
≥ VGPR	67%
CR/nCR	46%
MRD negative 54% (n=26)	

- **No effect of panobinostat on stem cell collection/mobilization or quality of graft.**
- **Randomized phase II study of RVD +/- panobinostat planned**

Shah et al, ASH 2015

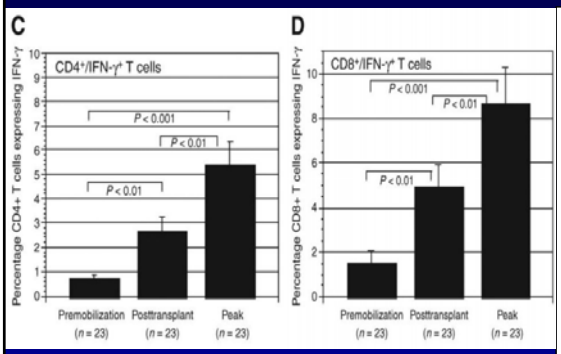
Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

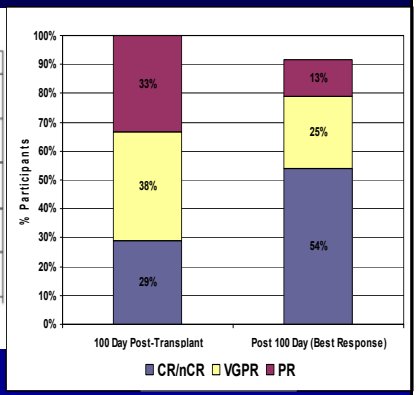
VTD with or without daratumumab in transplant eligible NDMM – IFM2015/HOVON131



Dara, daratumumab; NGS, next generation sequencing

MM/DC Vaccination following Autologous PBSCT for Myeloma

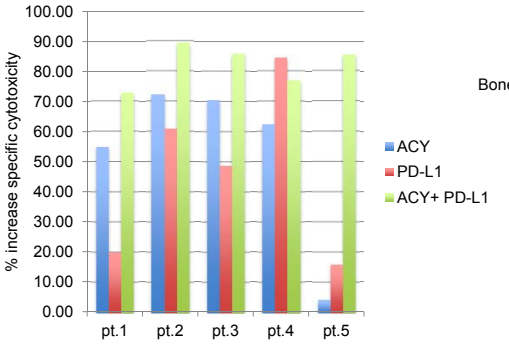




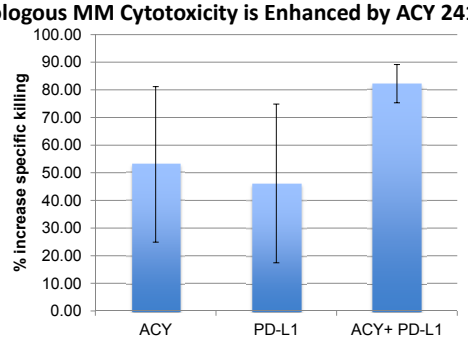
Rosenblatt et al, CCR 2013; 19: 3640-8.

Ongoing CTN randomized trial of lenalidomide with or without vaccine posttransplant Avigan et al

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.



Autologous MM Cytotoxicity is Enhanced by ACY 241 + PD-L1 Ab



Bae et al, 2016

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Multiple Myeloma

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

Primary Therapy for Non-Transplant Candidates
(Assess for response after 2 cycles)

Preferred Regimens:

- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/ dexamethasone
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Melphalan/prednisone/bortezomib (MPB) (category 1)
- Melphalan/prednisone/lenalidomide (MPL) (category 1)
- Melphalan/prednisone/thalidomide (MPT) (category 1)

Other Regimens:

- Dexamethasone (category 2B)
- Ixazomib/lenalidomide/dexamethasone
- Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B)
- Melphalan/prednisone (MP)
- Thalidomide/dexamethasone (category 2B)
- Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)

MYEL-D

© 2016 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®.
To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Impact of Novel Agents in the Treatment of Elderly Patients with Newly Diagnosed MM

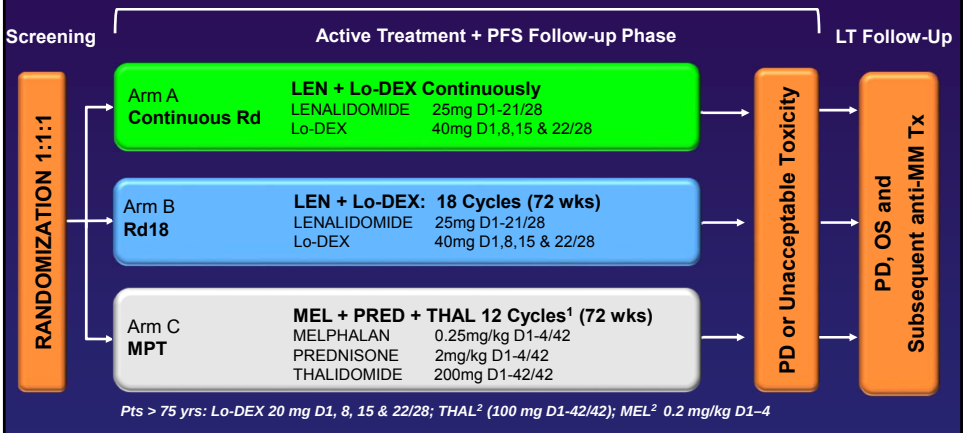
Substantial improvements in PFS and OS

	Median PFS (mos)	Median OS (mos)
MP[1-8]	11–20	29.1–49.4
MPT[1-6]	15–27.5	29–51.6
VMP[7,8,11]	21.7–27.4	68.5% (3-yr OS)*
MPR-R[9]	31	N/A
VMP-VT/VP[10]	34	74% (3-yr OS)*
VMPT-VT[11]	37.2	85% (3-yr OS)*

*Median OS not reached
N/A: not available

[1]Palumbo et al. Blood 2008; 112:3107–3114
[2]Facon et al. Lancet 2007; 370:1209–1218
[3]Hulin et al. J Clin Oncol 2009; 27:3664-70
[4]Waage et al. Blood 2010; 116:1405-12
[5]Wijermans et al. J Clin Oncol 2010; 28:3160-6
[6]Beksac et al. Eur J Haematol 2011;86:16-22
[7]San Miguel et al. N Engl J Med 2008; 359(9): 906–917; Supplementary Appendix
[8]Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266
[9]Palumbo et al. ASH 2010 (Abstract 622)
[10]Mateos et al. Lancet Oncol 2010; 11(10): 934-941
[11]Palumbo et al. ASH 2010 (Abstract 620)

FIRST Trial: Len/Dex versus MPT in Newly Diagnosed Non Transplant Candidates



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

- Stratification: age, country and ISS stage

Benhoubker et al, N Engl J Med 2014; 271: 906-17.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

FIRST Trial: Conclusions

Continuous Rd significantly extended PFS, with an OS benefit vs. MPT

- **PFS:**
  - **HR= 0.72 (*P*= 0.00006)**
  - **Consistent benefit across most subgroups**
  - **Rd better than Rd18 (HR= 0.70, *P*= 0.00001)**
  - **3 yr PFS: 42% Rd vs. 23% Rd18 and MPT**
- **Planned interim OS: HR= 0.78 (*P*= 0.0168)**
- **Rd was superior to MPT across all other efficacy secondary endpoints**

Safety profile with continuous Rd was manageable

- **Hematological and non-hematological AEs were as expected for Rd and MPT**
- **Incidence of hematological SPM was lower with continuous Rd vs. MPT**

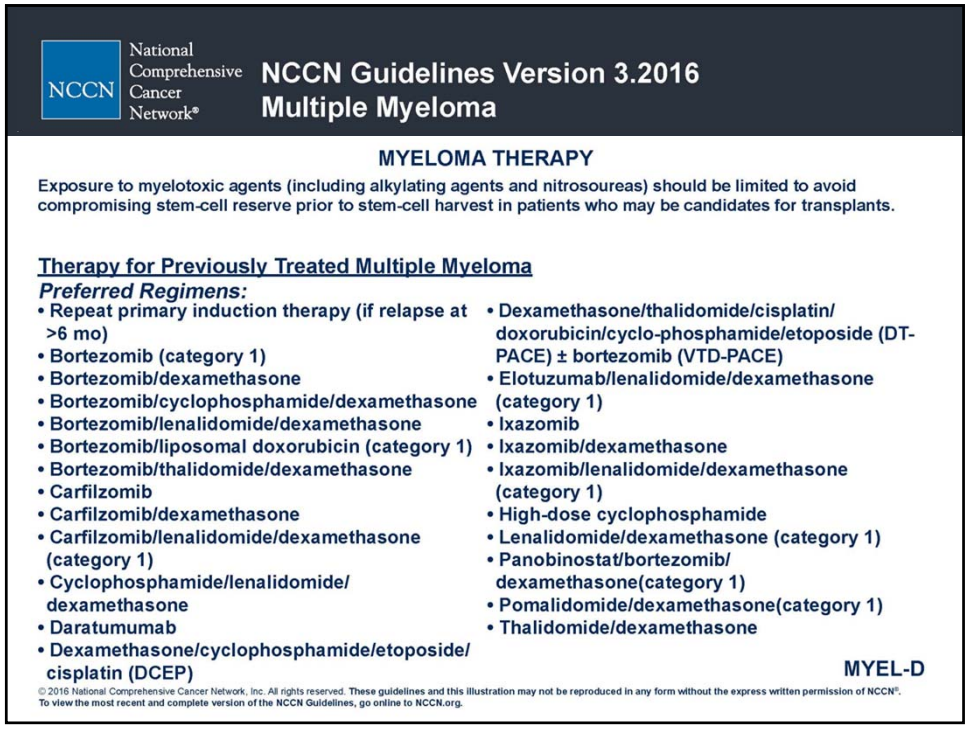
In NDMM transplant-ineligible patients, the FIRST Trial establishes continuous Rd as a new standard of care

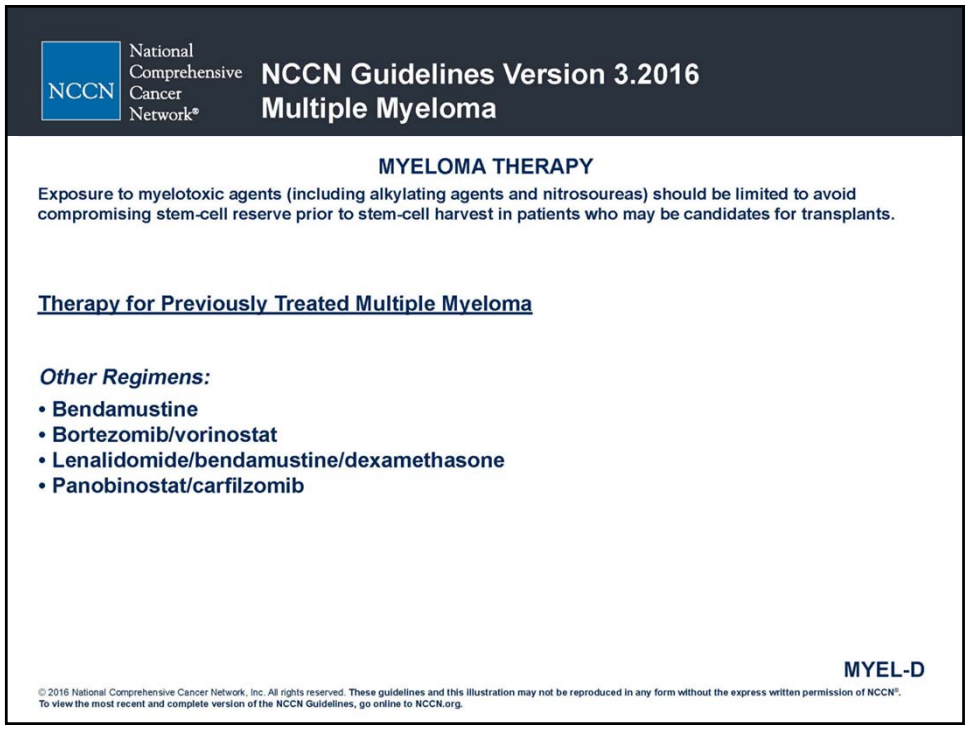
Benhoubker et al, N Engl J Med 2014; 271: 906-17.

When to Consider Retreatment

- **Differences between biochemical relapse and symptomatic relapse need to be considered**
- **Patients with asymptomatic rise in M-protein can be observed to determine the rate of rise and nature of the relapse**
  - **Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse**
- **CRAB criteria are still listed as the indication to treat in the relapsed setting-however, in patients with progression, treatment can avoid CRAB**
  - **C: Calcium elevation (> 11.5 mg/L or ULN)**
    R: Renal dysfunction (serum creatinine > 2 mg/dL)
    A: Anemia (Hb < 10 g/dL or 2 g < normal)
    B: Bone disease (lytic lesions or osteoporosis)

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.





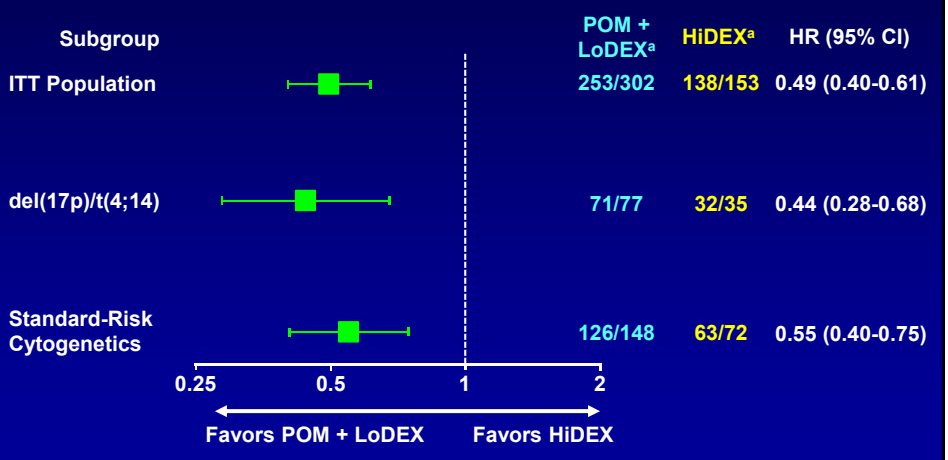
Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Pomalidomide With Low-Dose Dexamethasone Relapsed and Refractory Multiple Myeloma

- POM was effective in heavily pretreated patients who had already received LEN and bortezomib and who progressed on their last line of therapy
- The combination of POM with LoDEX improves the ORR due to synergy between immunomodulatory agents and glucocorticoids
  - POM + LoDEX, 34%; POM alone, 15%
- Response was durable with POM regardless of the addition of LoDEX
  - POM + LoDEX, 8.3 months ; POM alone, 8.8 months
- POM is generally well tolerated, with low rates of discontinuations due to AEs
  - Age had no impact on ORR, DoR, or safety

Richardson et al Blood 2014; 123: 1826-32 .

POM + LoDEX significantly improved PFS vs HiDEX



San Miguel et al Lancet Oncol 2013; 14: 1055-66.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

Characteristic	KRd (n=396)	Rd (n=396)
Presence of neuropathy at baseline, %	36.4	34.6
Number of prior regimens, median (range)	2 (1–3)	2 (1–3)
Prior therapies, %		
Transplant	54.8	57.8
Bortezomib	65.9	65.7
Non-responsive to prior bortezomib*	15.2	14.6
Lenalidomide	19.9	19.7
Any IMiD	58.8	57.8
Refractory to prior IMiD in any prior regimen	21.5	22.2
Bortezomib and IMiD	36.9	35.1
Non-responsive to prior bortezomib* and refractory to prior IMiD	6.1	6.8

Stewart et al NEJM 2015; 372:142-52.

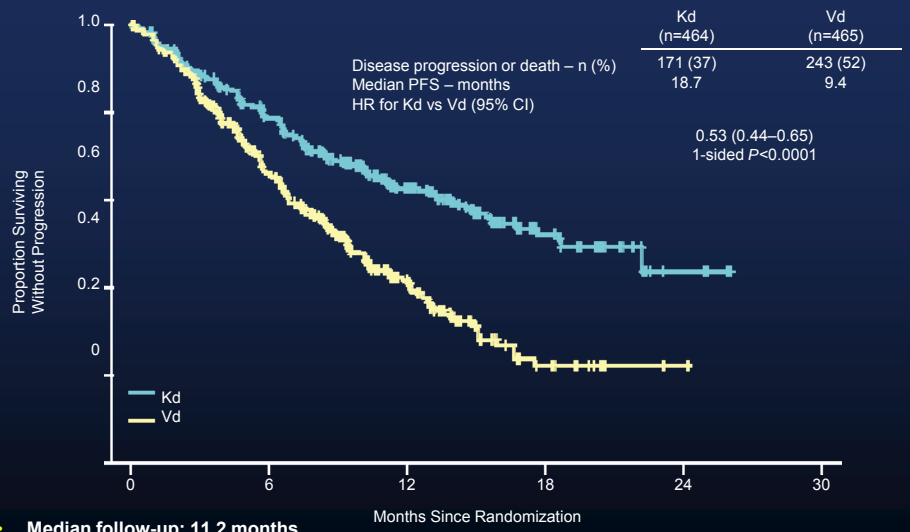
PFS by Risk Group

	KRd (n=396)		Rd (n=396)			
Risk Group by FISH	N	Median, months	N	Median, months	HR	P-value (one-sided)
High	48	23.1	52	13.9	0.70	0.083
Standard	147	29.6	170	19.5	0.66	0.004

Stewart et al NEJM 2015; 372:142-52.

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



- **Median follow-up: 11.2 months**

Dimopoulos et al, ASCO 2015

Carfilzomib Pomalidomide Low dose Dex

- **Median of 5 prior lines of therapy; 49% of patients had high/intermediate risk cytogenetics at baseline**

▪ ≥ VGPR	27%
ORR	70%
CBR	83%
▪ DOR (median)	17.7 months
▪ PFS (median)	9.7 months
▪ OS (median)	> 18 months

- **Response rates, PFS, and OS were preserved independent of FISH/cytogenetic risk status**
- **Well tolerated with no unexpected toxicities**

Shah et al ASH 2013

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

PANORAMA 1: A Randomized, Double-Blind, Phase 3 Study of Panobinostat or Placebo Plus Bortezomib and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma

Improvement in median PFS of 4 mos w/o difference in ORR or OS

Two-fold increase in nCR/CR rate (28% vs 16%)

Higher rate of Grade 3/4 diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leucopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).

Confirms PAN-BTZ-Dex in BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos

FDA approved for relapsed refractory MM exposed to bortezomib and IMiD

Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.

Richardson PG, et al. Blood. 2013;122:2331-2337
San Miguel J, et al. Lancet Oncol. 2014

Ricolinostat (ACY 1215) Selective Histone Deacetylase 6 Inhibitor

Synthesized and validated at DFCI

Angel investor company has advanced to phase II-III clinical trials-LLS TAP Program

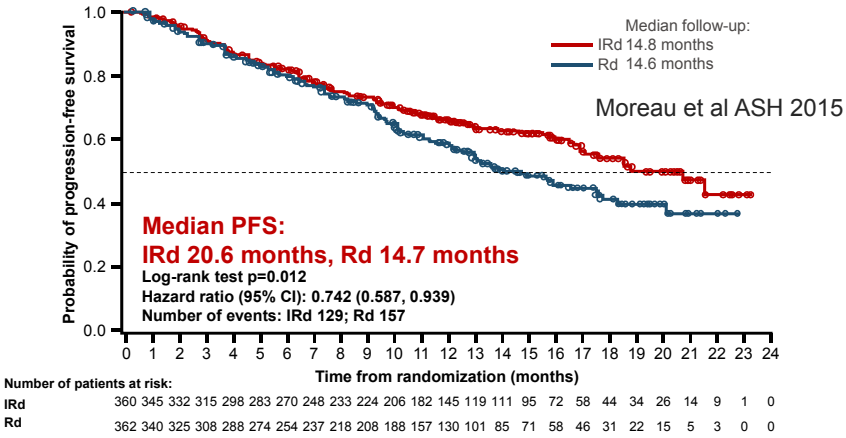
Well tolerated daily oral medication

Achieves 50% responses when combined with either bortezomib, lenalidomide or pomalidomide in relapsed refractory myeloma

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Phase 3 study of weekly oral ixazomib plus lenalidomide-dex: final PFS analysis

- **35% improvement in PFS with IRd vs Rd** (data cut-off 30 October 2014)



- A subsequent exploratory analysis of PFS was conducted (median follow-up 23.3 and 22.9 months in the IRd and Rd arms); median PFS 20 vs 15.9 months

Response rates and TTP improved and responses durable with IRd

Response rates, %	IRd (N=360)	Placebo-Rd (N=362)	p-value
Confirmed ORR (≥PR)	78.3	71.5	p=0.035
CR+VGPR	48.1	39.0	p=0.014
Response categories			
CR	11.7	6.6	p=0.019
PR	66.7	64.9	–
VGPR	36.4	32.3	–
Median time to response, mos*	**1.1**	**1.9**	**–**
Median duration of response, mos	**20.5**	**15.0**	**–**

- Significant improvements in different response categories
  - Conservative assessment of best response – derived up until the end of treatment
  - Independently determined by IRC assessment of blinded central laboratory data, rigorously following IMWG 2011 criteria
- PFS benefit confirmed by time to progression (TTP) analysis: median 21.4 months versus 15.7 months with IRd versus Rd, HR 0.712; p=0.007

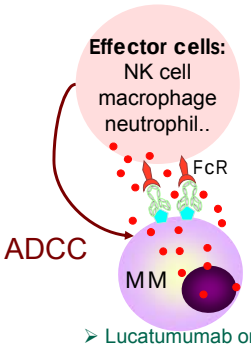
Moreau et al ASH 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

visiting committee

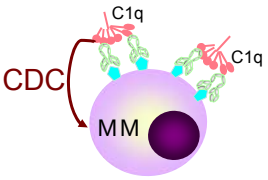
Monoclonal Antibody Based Therapeutic Targeting of Multiple Myeloma

Antibody-dependent Cellular Cytotoxicity (ADCC)



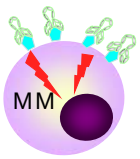
- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (SLAMF7)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **SAR650984 (CD38)**

Complement-dependent Cytotoxicity (CDC)



- **Daratumumab (CD38)**
- **SAR650984 (CD38)**

Apoptosis/growth arrest via intracellular signaling pathways



- **huN901-DM1* (CD56)**
- **nBT062-maytansinoid /DM4* (CD138)**
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- **Daratumumab (CD38)**
- **SAR650984 (CD38)**
- **J6M0-MMAF* (BCMA)**

*** Ab drug conjugate**

Updated from
Tai & Anderson Bone Marrow Research 2011

ELOQUENT-2

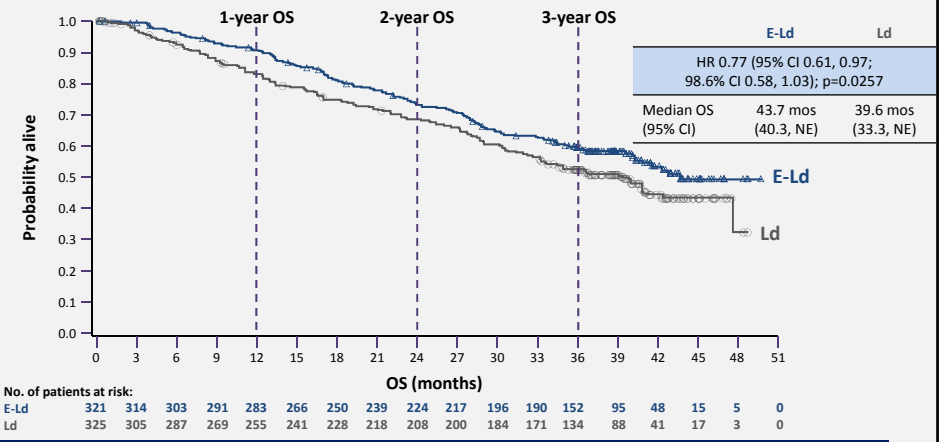
Progression-Free Survival

Parameter	Progression-free survival		
	E-Ld	Ld	Relative difference (%)
Median PFS (months)	**19.4**	**14.9**	
1-year PFS (%)	68	57	19
2-year PFS (%)	41	28	52
3-year PFS (%)	26	18	44
Primary analysis Hazard ratio (95% CI)	0.70 (0.57, 0.85) p=0.0004		
3-year follow-up Hazard ratio (95% CI)	0.73 (0.60, 0.89)		

Dimopoulos et al ASH 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

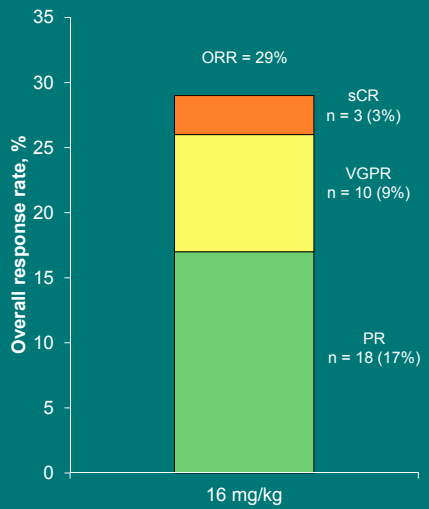
Interim Overall Survival



Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld

Dimopoulos et al ASH 2015

Phase 2 Study of Daratumumab (DARA) in Patients with ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma: 54767414MMY2002 (Sirius)



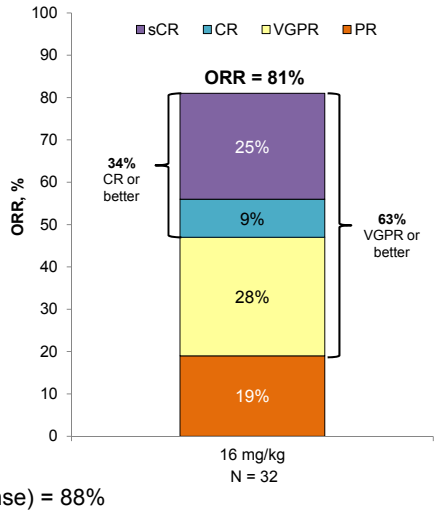
- **ORR was 29% (95% CI, 21–39) in patients receiving 16 mg/kg DARA**
- Stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)
- VGPR or better achieved in 12% (95% CI, 7–20) of patients
- Clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)

Lonial et al ASCO 2015

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Overall Response Rate: Daratumumab + Len/Dex

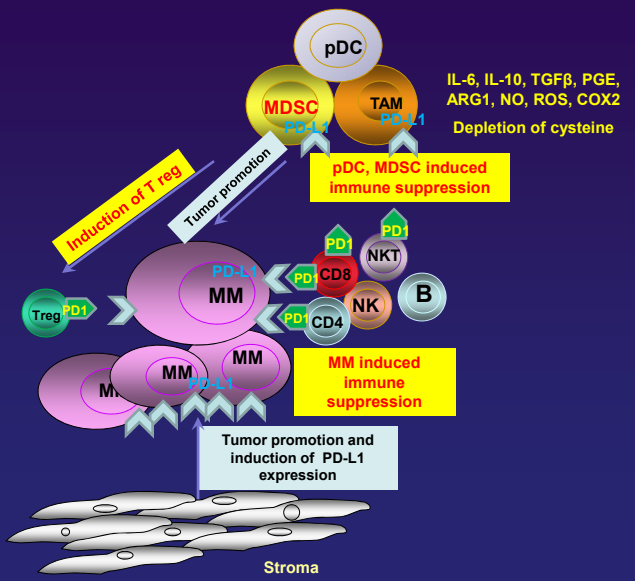
	N = 32	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**26 (81)**	**63.6-92.8**
Best response		
sCR	8 (25)	11.5-43.4
CR	3 (9)	2.0-25.0
VGPR	9 (28)	13.7-46.7
PR	6 (19)	7.2-36.4
VGPR or better (sCR+CR+VGPR)	20 (63)	43.7-78.9
CR or better (sCR+CR)	11 (34)	18.6-53.2



- ORR = 81%
- Clinical benefit rate (ORR + minimal response) = 88%

Plesner et al ASH 2015

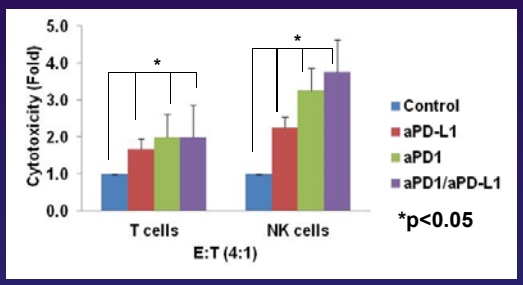
Immune Suppressive Microenvironment in MM



Görgün GT, et al. Blood 2013;121:2975-87

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

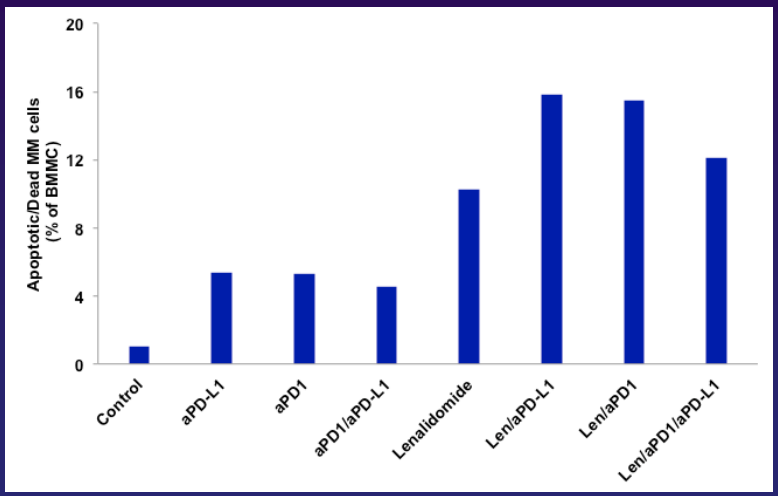


Effector: Autologous effector cells (CD3T cells, NK cells)

Target: CD138+ MM cells from Rel/Ref MM-BM

Görgün G. et al. Clin Cancer Res, in press

Lenalidomide Enhances Checkpoint Blockade Induced Cytotoxicity Against MM cells



Görgün G. et al. Clin Cancer Res, in press

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Phase 1 Trial of Pembrolizumab + Lenalidomide and Low Dose Dexamethasone in RRMM

N (%)	Total N = 17	Len Refractory* N = 9
Overall Response Rate	13 (76)	5 (56)
Very Good Partial Response	4 (24)	2 (22)
Partial Response	9 (53)	3 (33)
Disease Control Rate†	15 (88)	7 (78)
Stable Disease	3 (18)	3 (33)
Progressive Disease	1 (6)	1 (11)

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)
†Disease Control Rate = CR +VGPR + PR + SD >12 weeks.
Data cutoff date: September 22, 2015

San Miguel et al ASH 2015

Immune Effects of HDACi 241 in MM Therapy

Augments PD-L1 expression on MM cells

Augments MM cell line cytotoxicity, which is enhanced with pomalidomide, CD38Ab, and/or PD-1/PD-L1 Abs

Augments and autologous MM cell cytotoxicity, which is enhanced by CD38 Ab and/or PD-1/PD-L1 Abs

Enhances MM cytotoxicity alone and with PD-1/PD-L1Abs, even in the presence of pDCs

Augments NK cell function, alone and with PD-L1 Ab

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

Myeloma CAR therapy

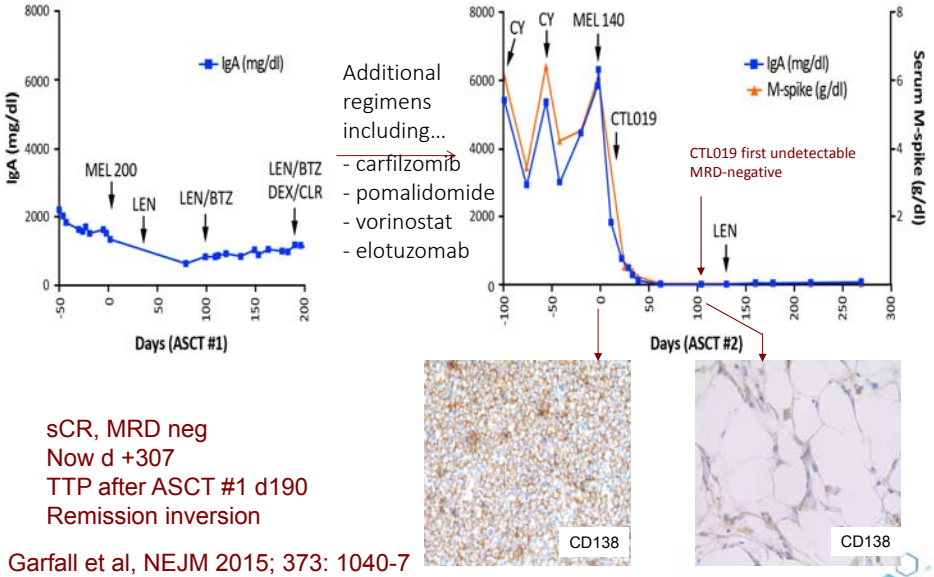
- **Multiple promising targets:**
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1, BCMA
- **Functional CAR T cells can be generated from MM patients**
- **CAR T and NK cells have in vitro and in vivo activity against MM**
- **Clinical trials underway**
  - Anecdotal prolonged responses but no robust efficacy data available yet
- **Many questions remain about CAR design:**
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps 'cocktails' of multiple CARs or CARs + chemotherapy will be required for best outcomes

Stadtmauer et al, 2015

Penn Medicine

the cure is within ABRAMSON CANCER CENTER

MM Patient #1: Response to CD19 CAR Therapy



sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

Garfall et al, NEJM 2015; 373: 1040-7

Penn Medicine

the cure is within ABRAMSON CANCER CENTER

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.

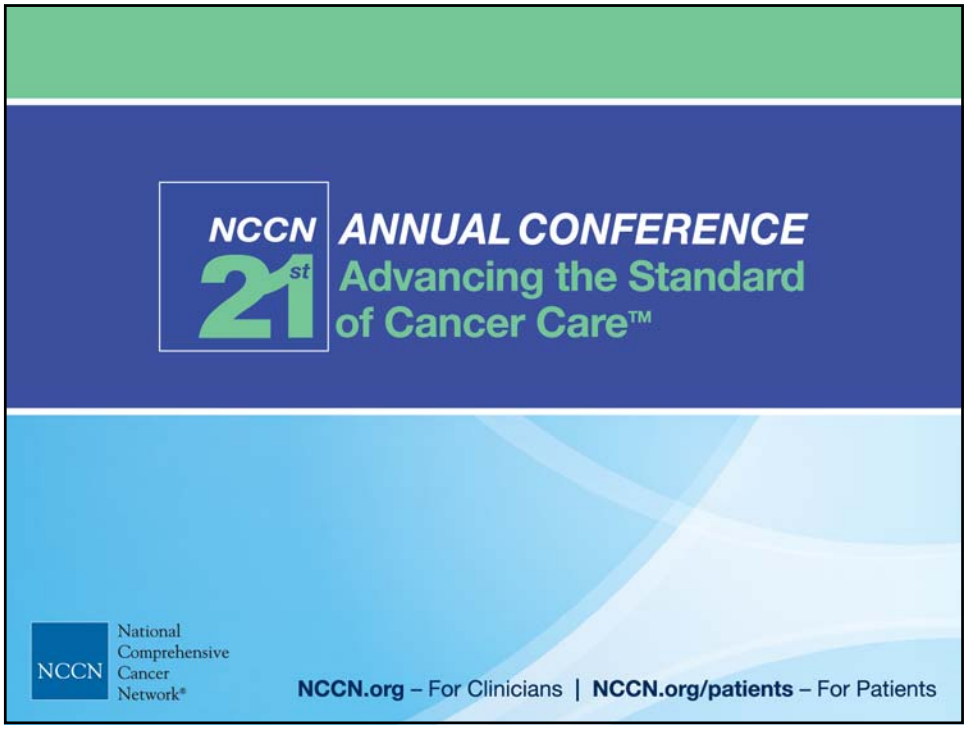
Summary and Conclusions

- Broader population of patients now eligible for therapy: 60% BM plasma cells; kappa:lambda>100; bone disease on MRI or PET/CT
- In newly diagnosed transplant candidates, three drug regimens incorporating immunomodulatory drugs and proteasome inhibitors before and after transplant prolong PFS and OS.
- MRD portends for better patient outcome and is a goal of therapy

Summary and Conclusions

- Relapse therapies now include bortezomib, lenalidomide/dex, bortezomib/pegylated doxorubicin, pomalidomide/dex, carfilzomib, bortezomib/panobinostat, elotuzumab len dex, daratumumab, and ixazomib.
- Novel targeted and immune therapies are showing great promise.
- Incorporation of novel therapies at all stages of disease is further improving patient outcome in MM

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.



Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.