NCCN 11th Annual Congress:
Hematologic Malignancies™

How to Integrate the New Drugs into the Management of Multiple Myeloma

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National Comprehensive Cancer Network®

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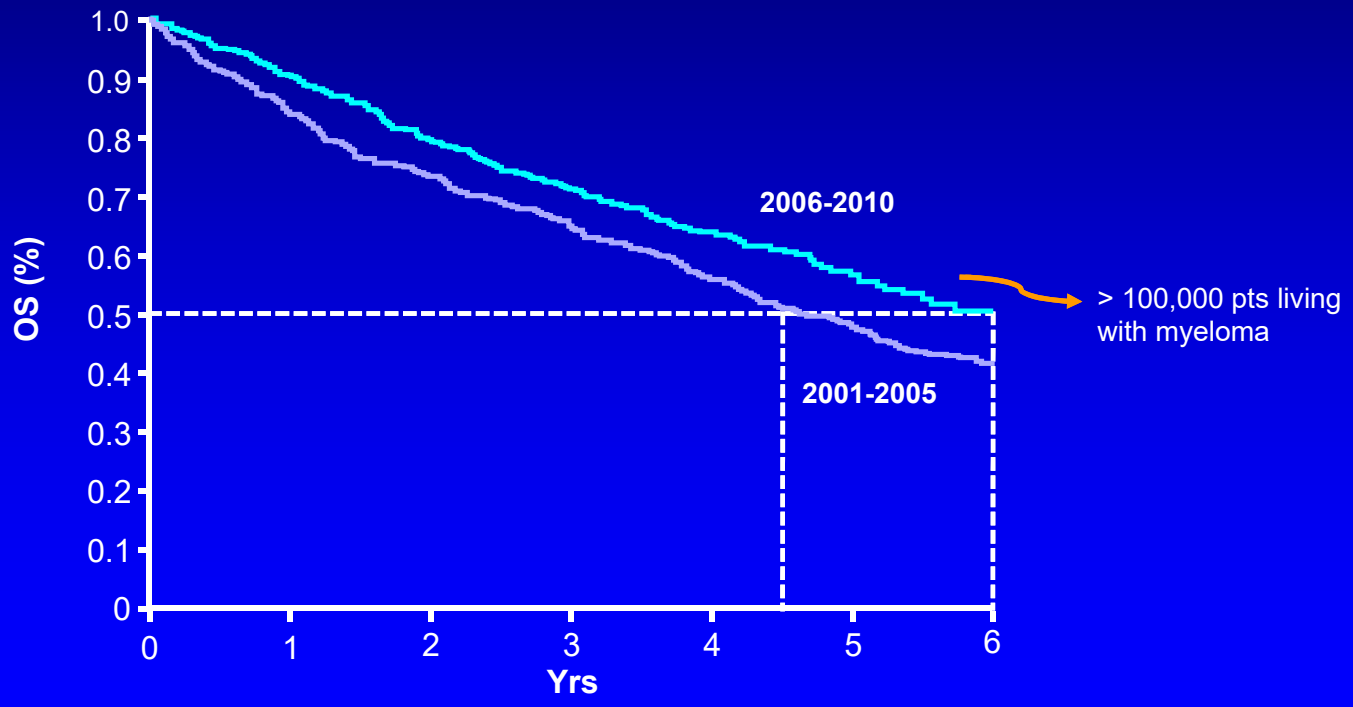
Objective

- Incorporate new regimens in the management of patients with multiple myeloma

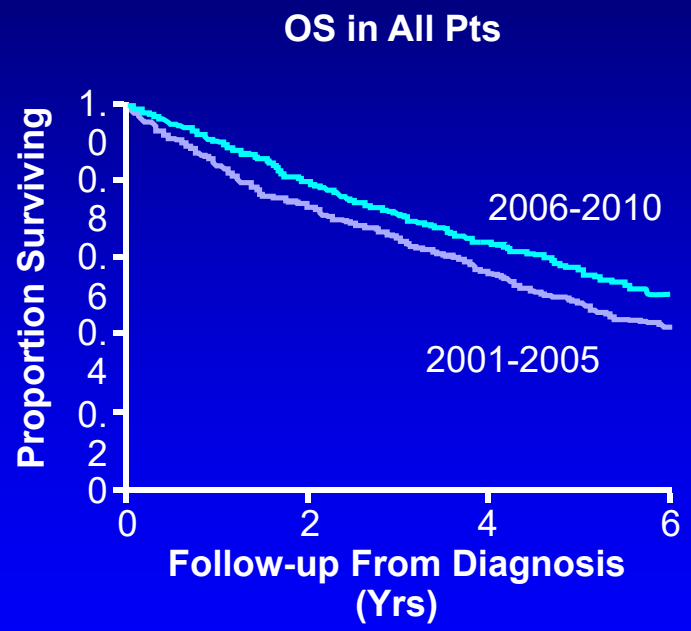
Myeloma: Scope of the Problem

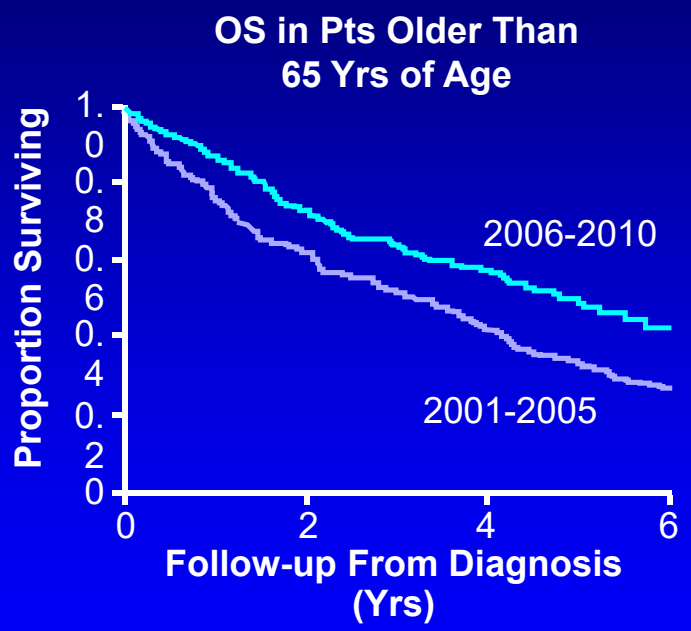
Median time to first relapse with current therapies: 3-4 yrs



Kumar SK, et al. Leukemia. 2014;28:1122-1128.

New Treatment Options Have Improved OS in MM





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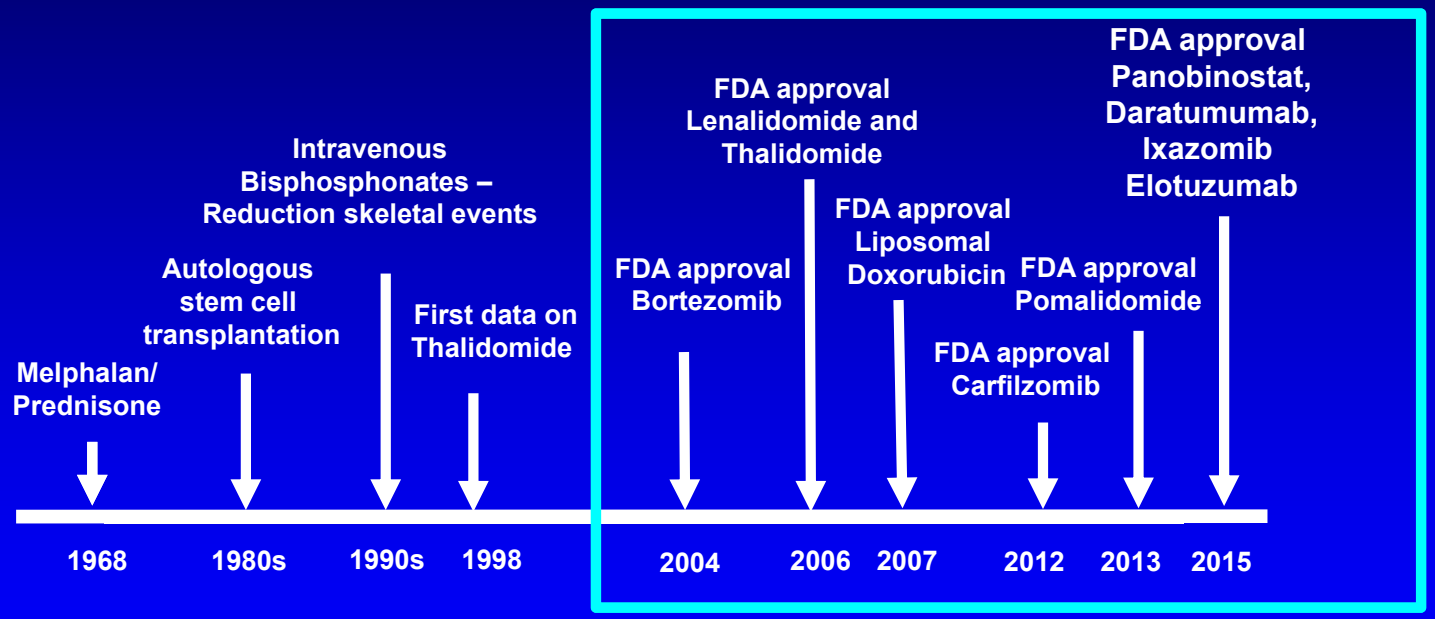
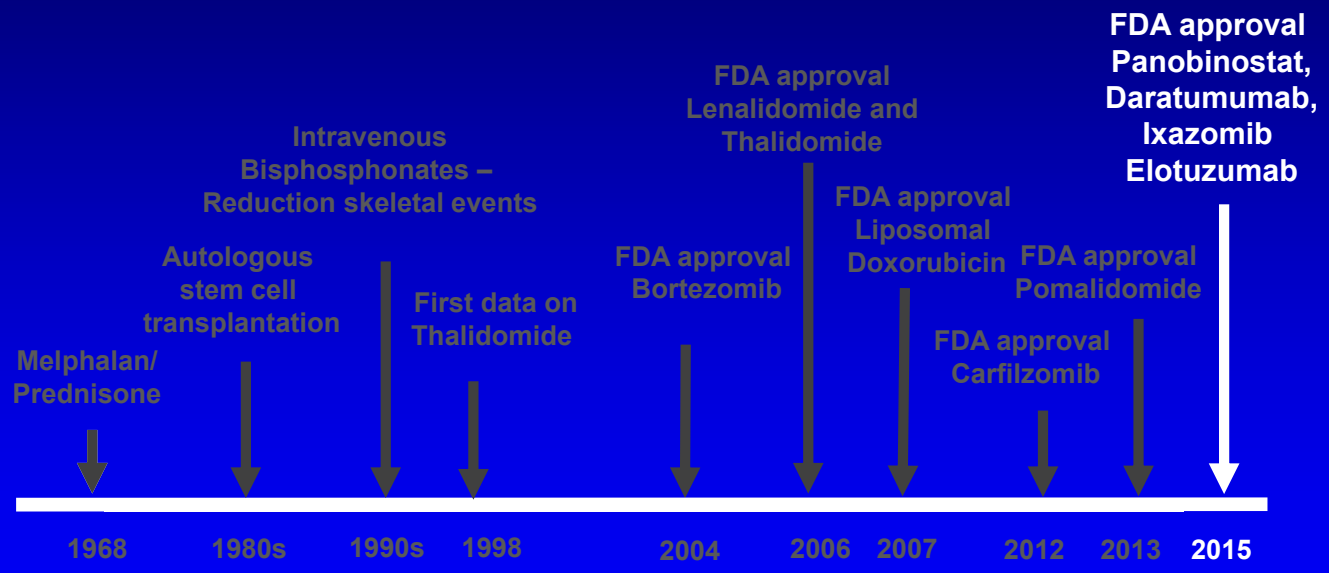
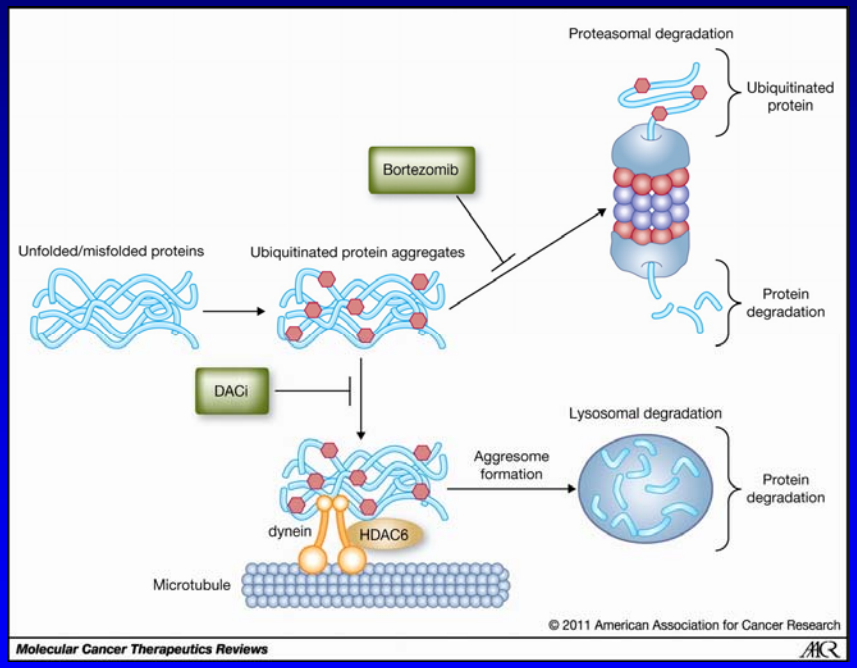
Multiple Myeloma: Evolution of Treatment



Multiple Myeloma: Evolution of Treatment



Combined Proteosome and Histone Deactylase Inhibition

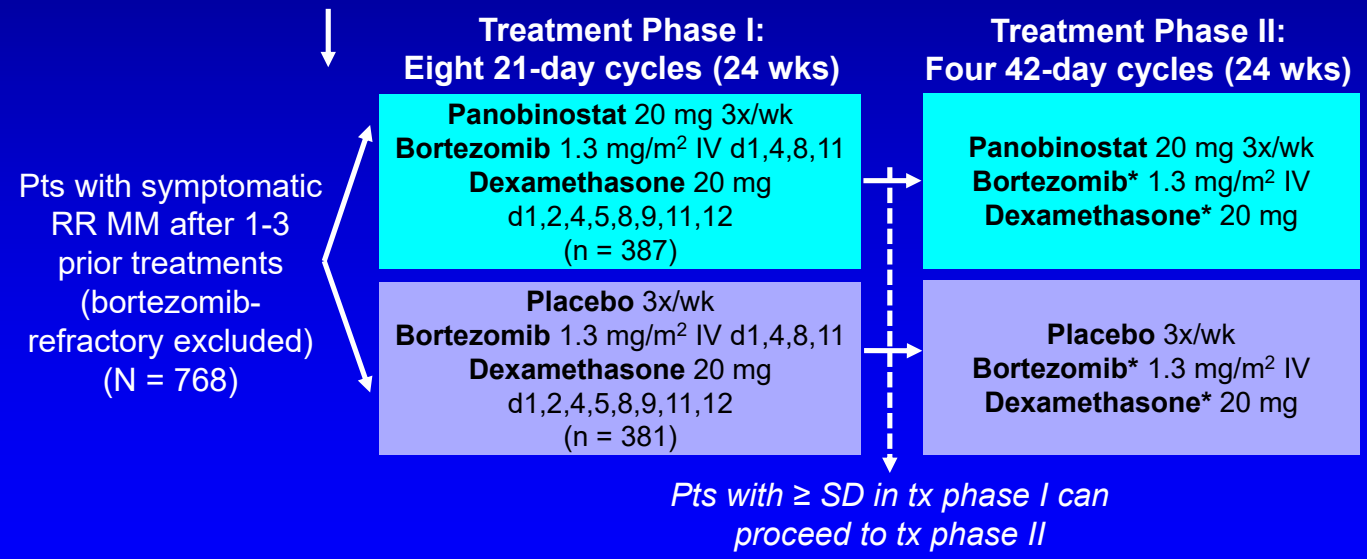


Hideshima, et al. Mol Cancer Ther 2011; 10: 2034- 42

Phase III PANORAMA 1: Bort/Dex ± Panobinostat in RR Myeloma

- **Randomized, double-blind trial**

Stratified by prior lines of therapy and prior bortezomib

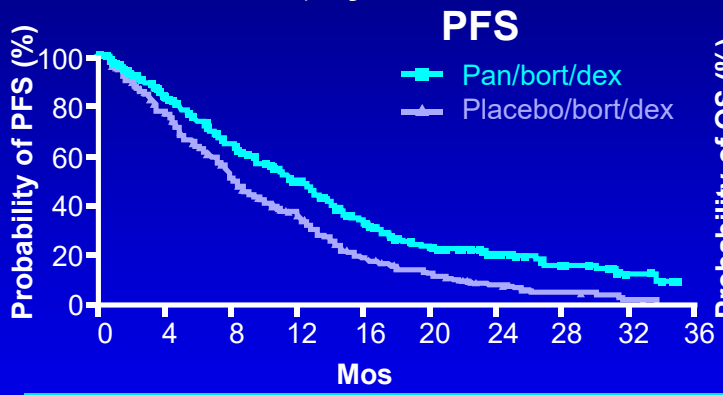


San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.

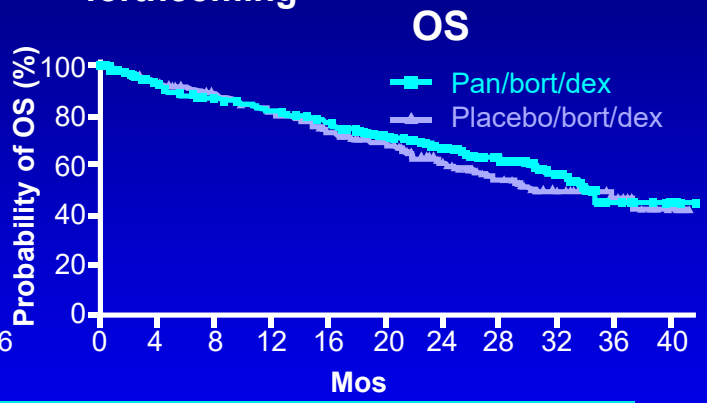
*Reduced frequency.

Bort/Dex ± Panobinostat in RR Myeloma (PANORAMA 1): Overall Population

- **Primary endpoint reached: median PFS ↑ by 3.9 mos**



- **Interim OS analysis; final analysis forthcoming**



Outcome	Pan/Bort/Dex (n = 387)	Bort/Dex (n = 381)	Significance
ORR, %	60.7	59.6	Not significant
Median PFS, mos	12.0	8.1	HR: 0.63
Median OS, mos	33.6	30.4	Not significant

San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206

PANORAMA 1: Subgroup Analysis

- **Subgroup analysis of pts who received ≥ 2 previous treatments, including bortezomib and an IMiD**
  - **FDA approved indication based on subgroup analysis**

Outcome	Pan/Bort/Dex (n = 73)	Bort/Dex (n = 74)	Significance
ORR, %[1]	58.9	39.2	*P* = .017
Median PFS, mo[1]	12.5	4.7	HR: 0.47
Median OS, mo[2]	25.5	19.5	Not significant

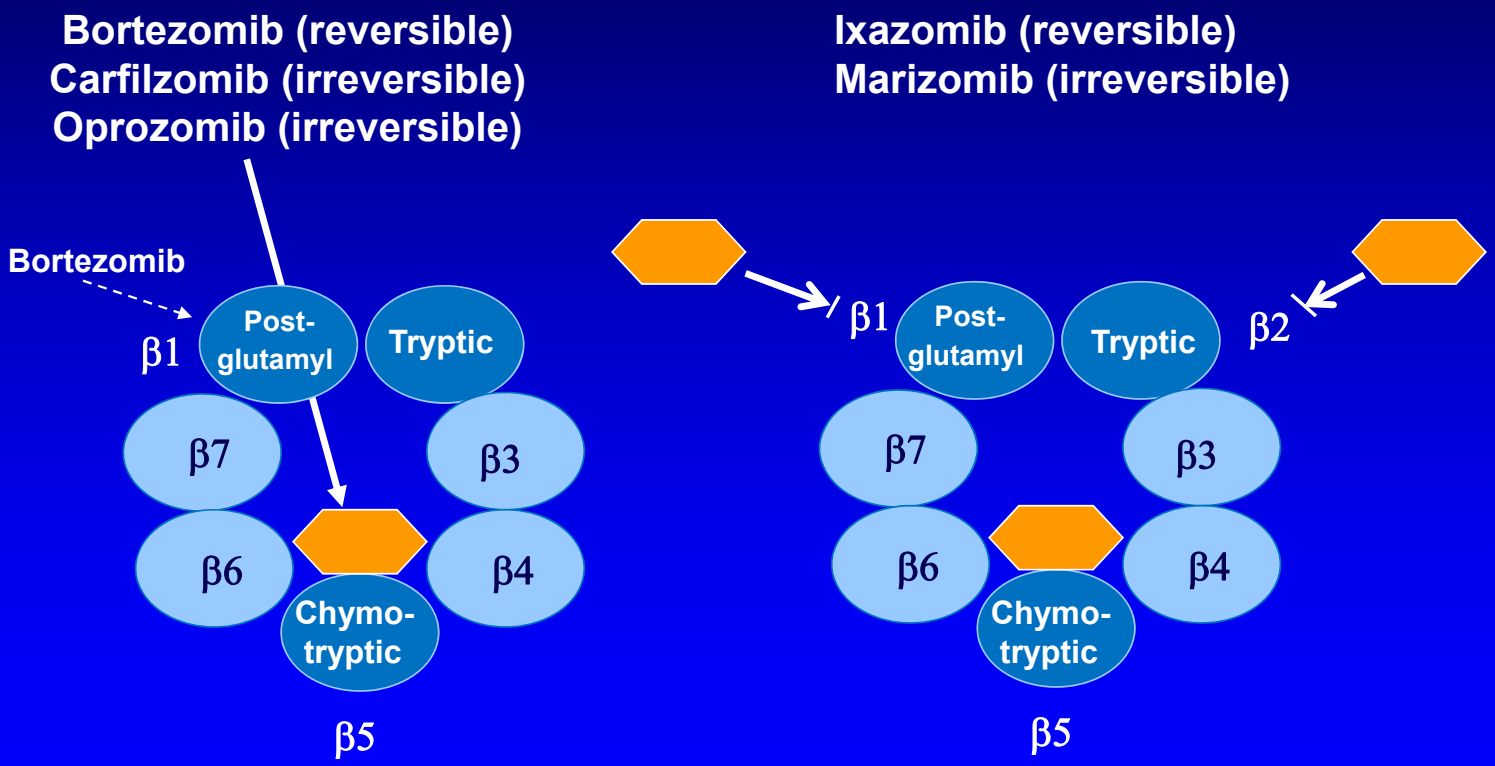
1. Richardson PG, et al. Blood. 2016;127:713-721.
2. San Miguel J, et al. ASH 2015. Abstract 3026.

PANORAMA 1: Safety

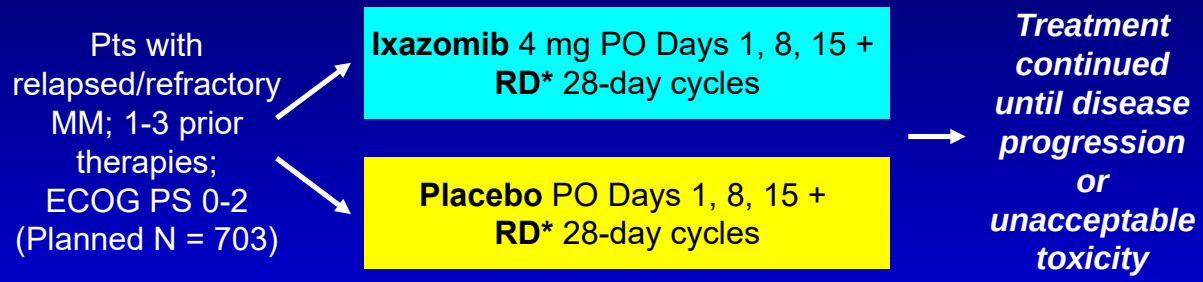
	Select AEs (≥ 10% Incidence and ≥ 5% Greater Incidence With Pan), %	Pan + Bort/Dex (n = 381)		Pbo + Bort/Dex (n = 377)	
		All Grades	Grade 3/4	All Grades	Grade 3/4
Cardiac	Arrhythmia	12	3	5	2
GI	Diarrhea	68	**25**	42	8
GI	Nausea	36	6	21	1
GI	Vomiting	26	7	13	1
Other	Fatigue	60	25	42	12
Other	Peripheral edema	29	2	19	<1
Other	Pyrexia	26	1	15	2
Other	Weight loss	12	2	5	1
Other	Decreased appetite	28	3	12	1
Heme	Thrombocytopenia	97	67	83	31
Heme	Anemia	62	18	52	19
Heme	Neutropenia	75	34	36	11
Heme	Leukopenia	81	23	48	8
Heme	Lymphopenia	82	53	74	40

Richardson P, et al. ASCO 2014. Abstract 8510. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.

Comparison of Proteasome Inhibitors



Phase III TOURMALINE-MM1: IRd vs Rd in Relapsed and/or Refractory MM



*Lenalidomide 25 mg PO Days 1-21; dexamethasone 40 mg PO Days 1, 8, 15, 22

- **Primary endpoint: PFS**
- **Secondary endpoints: OS, OS and PFS in high-risk pts, response (ORR, PR, VGPR, CR, DoR), safety, pain response, global health outcomes, PK analysis, association between response or resistance to ixazomib and cytogenetics**

Moreau et al NEJM 2016: 374: 1626.

Phase III TOURMALINE-MM1: Ixazomib Efficacy

Characteristic	Ixazomib + Rd (n = 360)	Placebo + Rd (n = 362)	*P* Value
Median PFS, mos	20.6	14.7	.012*
ORR, %	78.3	71.5	.035
▪ CR	11.7	6.6	.019
▪ VGPR	36.4	32.3	
▪ PR	66.7	64.9	
Median time to response, mos	1.1	1.9	
Median DoR, mos	20.5	15.0	
Median TTP, mos	21.4	15.7	.007†

*HR: 0.742. †HR: 0.712.

- **PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, PI and IMiD exposed**

Moreau P, et al. ASH 2015. Abstract 727.

Phase III TOURMALINE-MM1: IRD vs RD in Relapsed and/or Refractory MM

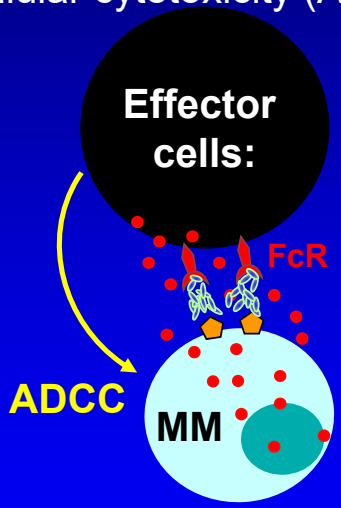
Table 4. Common Adverse Events and Other Adverse Events of Clinical Importance in the Safety Population at the 23-Month Analysis.*

Adverse Event	Ixazomib Group (N=361)			Placebo Group (N=359)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Common hematologic adverse events of any cause†						
Neutropenia‡	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia‡	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Anemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Common nonhematologic adverse events of any cause†						
Diarrhea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Rash§						
Standardized MedDRA query	131 (36)	18 (5)	0	82 (23)	6 (2)	0
High-level term	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Constipation	126 (35)	1 (<1)	0	94 (26)	1 (<1)	0
Fatigue	106 (29)	13 (4)	0	102 (28)	10 (3)	0
Nausea	104 (29)	6 (2)	0	79 (22)	0	0
Peripheral edema	101 (28)	8 (2)	0	73 (20)	4 (1)	0
Peripheral neuropathy‡	97 (27)	9 (2)	0	78 (22)	6 (2)	0
Back pain	87 (24)	3 (<1)	0	62 (17)	9 (3)	0
Vomiting	84 (23)	4 (1)	0	42 (12)	2 (<1)	0
Upper respiratory tract infection	83 (23)	2 (<1)	0	70 (19)	3 (<1)	0
Nasopharyngitis	81 (22)	0	0	73 (20)	0	0
Insomnia	73 (20)	7 (2)	0	98 (27)	11 (3)	0
Muscle spasms	66 (18)	0	0	95 (26)	2 (<1)	0
Other adverse events of clinical interest						
Arrhythmias‡¶	56 (16)	17 (5)	3 (<1)	53 (15)	10 (3)	1 (<1)
Thromboembolism‡¶	29 (8)	9 (2)	2 (<1)	38 (11)	11 (3)	1 (<1)
Liver impairment‡	26 (7)	7 (2)	0	21 (6)	4 (1)	0
Hypertension						
Any	22 (6)	11 (3)	0	18 (5)	4 (1)	0
Hypertensive crisis	1 (<1)	0	0	0	0	0
Hypotension‡¶	22 (6)	4 (1)	0	21 (6)	1 (<1)	0

Moreau et al NEJM 2016: 374: 1626.

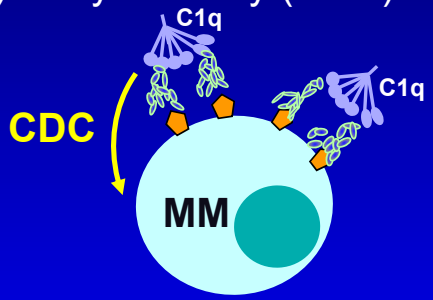
MAb-Based Targeting of Myeloma

Antibody-dependent cellular cytotoxicity (ADCC)



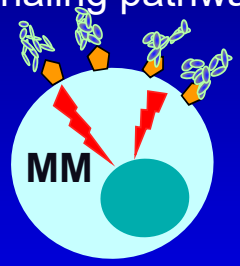
Elotuzumab (SLAMF7)
Daratumumab (CD38)
SAR650984 (CD38)

Complement-dependent cytotoxicity (CDC)



Daratumumab (CD38)
SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways



Daratumumab (CD38)
SAR650984 (CD38)

Tai YT, et al. Bone Marrow Res. 2011;2011:924058.

SIRIUS: Daratumumab in R/R Myeloma

- Phase II trial; patients were heavily pretreated
- Reductions in paraprotein occurred in majority of pts
- Responses observed across subgroups
- Deepening of responses with continued treatment
  - Median time to response: 1 mo

Outcome	Daratumumab (n = 106)	95% CI
ORR, %	29.2	20.8 – 38.9
Median PFS, mo	3.7	2.8 - 4.6
1-year* OS, %	65	51.2 - 75.5
Median DoR, mo	7.4	5.5 - NE

*Median OS not reached

Lonial S, et al. Lancet. 2016;Jan 6:[E-pub ahead of print].

Daratumumab in R/R Myeloma: Adverse Events

	Daratumumab 16 mg/kg (n=106)	
	Any grade	Grade 3 or 4
Fatigue	42 (40%)	3 (3%)
Anaemia	35 (33%)	25 (24%)
Nausea	31 (29%)	0
Thrombocytopenia	27 (25%)	20 (19%)
Neutropenia	24 (23%)	13 (12%)
Back pain	23 (22%)	3 (3%)
Cough	22 (21%)	0 (0%)

Data are number (%).

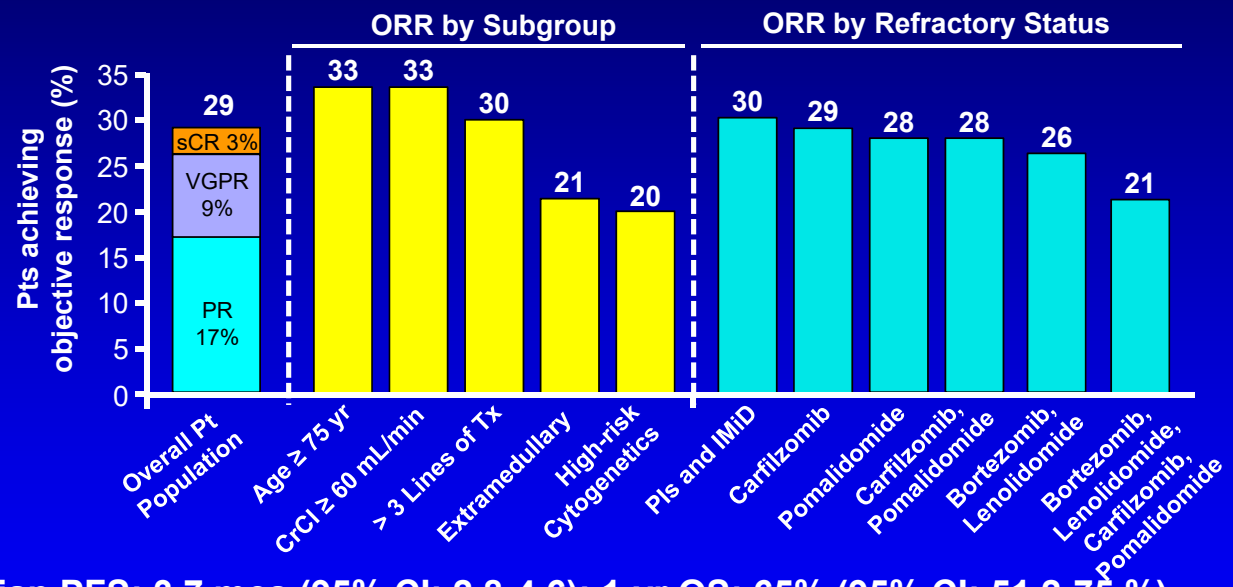
Table 3: Most common (≥20%) treatment-emergent adverse events

Lonial S, et al. Lancet. 2016;Jan 6:[E-pub ahead of print].

Infusion related reactions common: 45 (42%)

- **Predominantly 1st infusion**
- **Grade 3 – 5%**
- **Symptom:**
  - **Nasal congestion 12%**
  - **Throat irritation 7%**
  - **Cough 6%**
  - **Dyspnea 6%**
  - **Chills 6%**
  - **Vomiting 6%**
- **Premedication required**

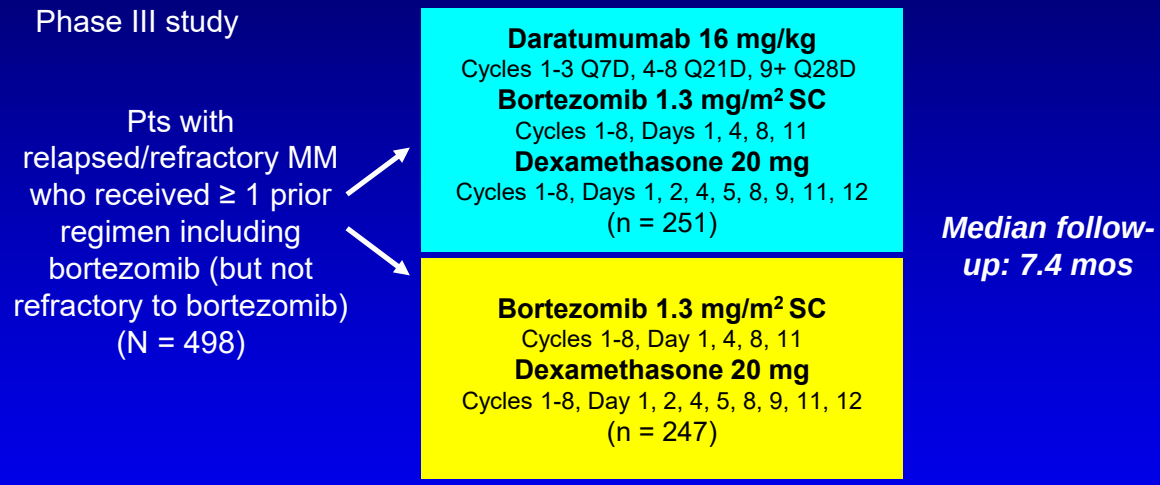
Phase II SIRIUS: Daratumumab Shows Activity in Heavily Pretreated MM



- **Median PFS: 3.7 mos (95% CI: 2.8-4.6); 1-yr OS: 65% (95% CI: 51.2-75.%)**
- **Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%); infusion-related reactions occurred in 43% (most grade 1/2)**

Lonial S, et al. ASCO 2015. Abstract LBA8512.

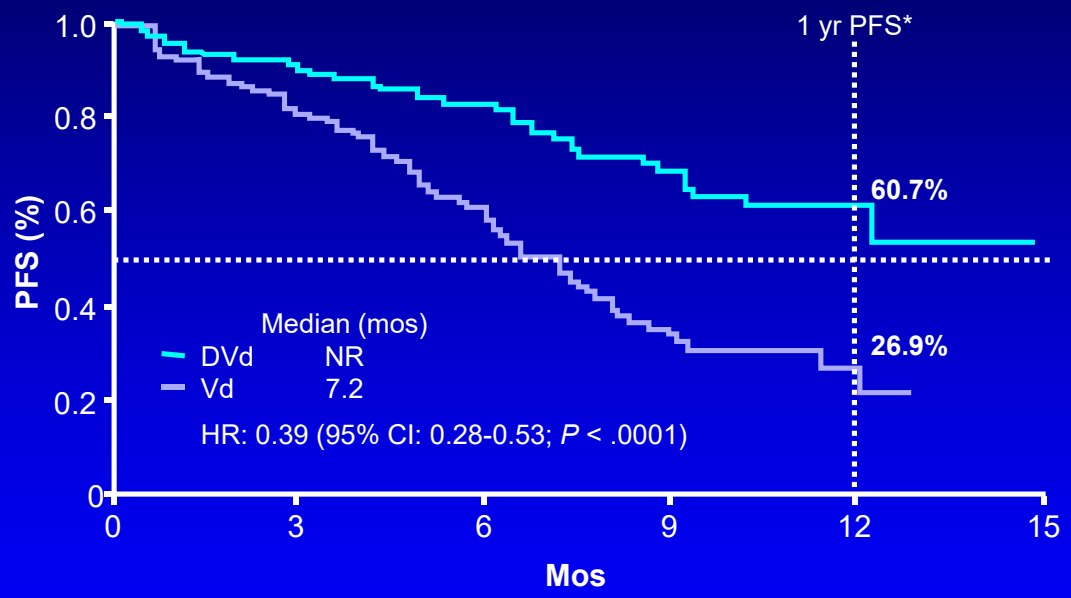
Phase III: Bortezomib / Dex +/- Daratumumab in R/RR MM (CASTOR)



- **Primary endpoint: PFS**
- **Secondary endpoints: TTP, OS, ORR, VGPR, CR, MRD, time to response; DoR**

Palumbo A, et al. NEJM 2016; 375: 357.

CASTOR: Daratumumab Improves PFS



Outcome	Dara + Vid (n = 251)	Vd (n = 247)	HR (95% CE)
ORR, %	83	63	*P<.0001*

Palumbo A, et al. NEJM 2016; 375: 357.

MAb-Based Targeting of Myeloma

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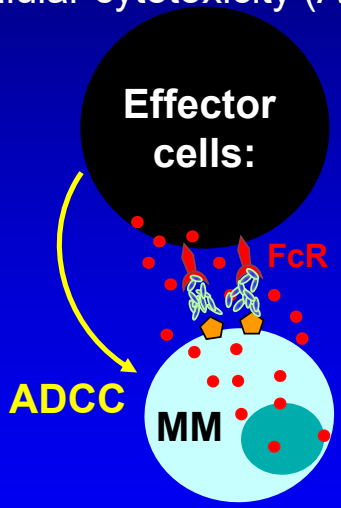

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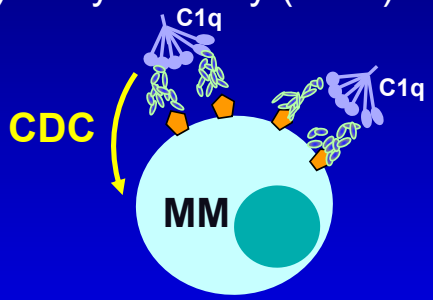

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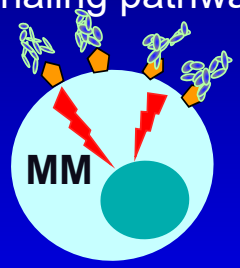

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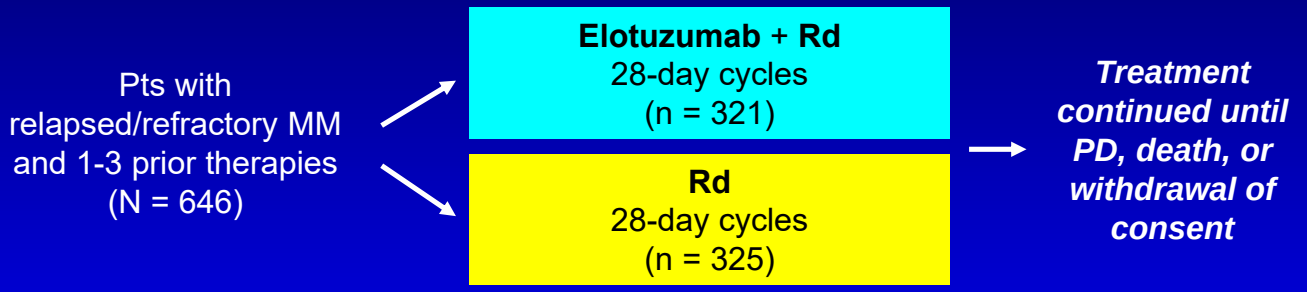
Phase III ELOQUENT-2: Len/dex ± Elotuzumab in RR MM

- **Randomized, open-label, multicenter international phase III trial**



Elotuzumab 10 mg/kg/wk IV Days 1, 8, 15, 22 (cycles 1-2) and Days 1, 15 (cycles 3+) with premedication to prevent infusion reactions; lenalidomide 25 mg PO Days 1-21; dexamethasone 40 mg Days 1,8,15,22 (8 mg IV + 28 mg PO during elotuzumab dosing)

- **Primary endpoints: PFS and ORR**
- **Secondary endpoints: OS, DoR, QoL, safety**
- **Exploratory endpoints: time to response, time to subsequent therapy, PK, and immunogenicity of elotuzumab**

Lonial S, et al. NEJM 2015; 373: 621-31.

ELOQUENT-2: Elotuzumab + Rd vs Rd: Efficacy

Outcome	Elotuzumab + Rd (n = 321)	Rd (n = 325)	HR (95% CI)
PFS			
▪ Median, mos	19.4	14.9	0.73 (0.60-0.89; *P* = .0014)
▪ 1 yr, %	68	57	
▪ 2 yrs, %	41	27	
▪ 3 yrs, %	26	18	
Median time to next treatment, mos	33	21	0.62 (0.50-0.77)
ORR, %	79	66	*P* =.0002
Interim OS, mos	43.7	39.6	0.77 (0.61-0.97; *P* = .0257)

- **PFS benefit seen with elotuzumab in all predefined subgroups** including older pts and pts with high-risk cytogenetics del(17p), t(4;14)

Lonial S, et al. NEJM 2015; 373: 621-31

ELOQUENT-2: Adverse Events

Table 3. Adverse Events.*

Event	Elotuzumab Group (N=318)		Control Group (N=317)	
	Any Grade	Grade 3 to 4	Any Grade	Grade 3 to 4
Common hematologic toxic effect — no. (%)†				
Lymphocytopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Common nonhematologic adverse event — no. (%)				
General disorder				
Fatigue	149 (47)	27 (8)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Peripheral edema	82 (26)	4 (1)	70 (22)	1 (<1)
Nasopharyngitis	78 (25)	0	61 (19)	0
Gastrointestinal disorder				
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (<1)
Musculoskeletal or connective-tissue disorder				
Muscle spasms	95 (30)	1 (<1)	84 (26)	3 (1)
Back pain	90 (28)	16 (5)	89 (28)	14 (4)
Other disorder				
Cough	100 (31)	1 (<1)	57 (18)	0
Insomnia	73 (23)	6 (2)	82 (26)	8 (3)

Infusion related reactions: 10% with elotuzumab

Lonial S, et al. NEJM 2015; 373: 621-31.

Incorporation Into NCCN Guidelines

- Therapy for Previously Treated Multiple Myeloma (MYEL-D)
  - Daratumumab
  - Elotuzumab / Lenalidomide / dexamethasone (category 1)
  - Ixazomib/ Lenalidomide / dexamethasone (category 1)
  - Panobinostat / Lenalidomide / dexamethasone (category 1)

NCCN Guidelines Version 3.2016 Multiple Myeloma

Conclusion

- With FDA approval of panobinostat, daratumumab, ixazomib and elotuzumab,
  - Treatment landscape for myeloma has grown significantly.
  - Rapid incorporation into the NCCN guidelines
- Survival for patients with myeloma is significantly longer
- Ongoing studies looking at these and other treatments in earlier lines of therapy in hopes of even greater benefit.

NCCN Member Institutions