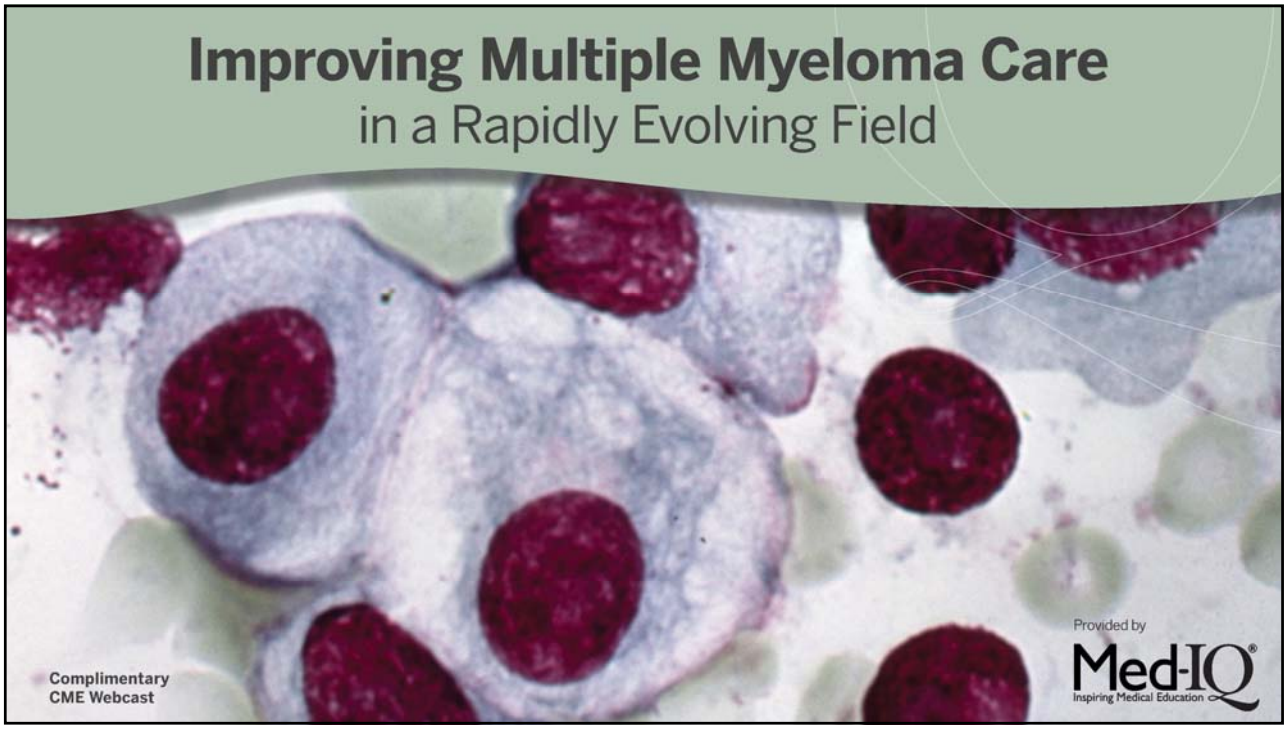

Activity Overview

This CME Webcast explores clinical management strategies for multiple myeloma. Experts in the field use patient cases to discuss current clinical evidence and treatment guidelines for newly diagnosed and relapsed/refractory disease, with a focus on patient-, disease-, and treatment-related factors that guide therapeutic decisions.

Target Audience

This activity is intended for hematologist/oncologists.

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Disclosure Statements

Joseph Mikhael, MD, MEd, FRCPC, FACP
Contracted research: AbbVie Inc., Celgene Corporation, Sanofi-aventis U.S. Inc.

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Learning Objectives

Upon completion, participants should be able to:

- Incorporate safety and efficacy data for various treatment regimens into individualized management strategies for patients with newly diagnosed and relapsed/refractory MM
- Explain patient- and disease-related characteristics that help guide therapeutic decision making for patients with MM in both the frontline and relapsed/refractory settings

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Optimizing MM Care in 2017

- The overall approach must be
  - Evidence based
  - Rational
  - Individualized to patient
- Therapy is based on strategy, not a script
  - Treatment is no longer 1st, 2nd, and 3rd line (and beyond), but a deliberate strategy based on several critical variables

Patient Case

- MS is a 64-year-old man with a 4-month history of persistent lower back and hip pain that radiates down his left leg
- Previous clinical findings include:
  - Medical history: hypertension, no history of cancer
  - Physical examination: normal except for back/hip pain
  - X-ray: lytic bone lesions

Initial Patient Evaluation

CBC with differential

WBC	6.2 x 10^3/mL
Hb	9.8 g/dL
Hematocrit	39%
Platelets	230 x 10^3/mL
Neutrophils	3.9 x 10^3/mL

Comprehensive metabolic panel

BUN	38 mg/dL
Creatinine	1.6 mg/dL
Calcium	9.3 mg/dL
Albumin	3.9 g/dL
LDH	< ULN
β-2 macroglobulin	4.6 μg/mL

SPEP/serum immunofixation

M protein spike 3.8 g/dL

Quantitative IgGs

IgG 5,335 mg/dL; IgA 21 mg/dL; IgM 3 mg/dL

Serum FLC

Kappa FLC	250 mg/L
Lambda FLC	2.4 mg/L
Kappa/lambda FLC ratio	104.2

Skeletal imaging

X-ray: confirm multifocal lesions of left ilium with signs of osteoporosis
MRI: multifocal lesions of the left ilium, 1 lesion > 5 mm

Bone marrow biopsy

Aspirate 69% plasma cells

Flow cytometry

22.4% events CD38, CD56, and CD138 positive

Metaphase cytogenetics and plasma cell FISH

t(11;14)

IMWG Criteria: MM Requiring Therapy

S (≥ 60% plasmacytosis)
Li (≥ 100 light chain ratio; I/U)
M (≥ 2 MRI focal lesions)

C (calcium elevation)
R (renal insufficiency)
A (anemia)
B (bone disease)

Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-48.

Evaluating Risk of Progression

1. Tumor burden
   – Durie-Salmon Staging
   – International Staging System
2. Patient-related factors
   – Comorbidities (eg, heart disease, renal dysfunction, diabetes)
   – Frailty
   – Age
3. Disease biology (cytogenetics)
4. Response to therapy

Rajkumar SV. *Am J Hematol*. 2016;91:719-34;
mSMART guidelines. www.msmart.org/about.html.

Patient Risk: Disease Biology

	mSMART	IMWG
Patient-related factors		**High risk** Serum LDH > ULN **Standard risk** Serum LDH ≤ ULN
Tumor characteristics	**High risk** del 17p, t(14;16), t(14;20), high-risk signature by GEP **Intermediate risk** t(4;14), 1q gain, high PC S-phase **Standard risk** All others including trisomies, t(11,14), t(6,14)	**High risk** del 17p, t(4;14), t(14;16) **Standard risk** No high-risk chromosomal abnormality

mSMART guidelines. www.msmart.org/about.html; Palumbo A, et al. *J Clin Oncol.* 2015;33:2863-9.

Primary Therapy for MM

- Triplets > doublets

Transplant Eligible	Transplant Ineligible
Preferred regimens Bortez/lenalid/dex (category 1) Bortez/doxorub/dex (category 1) Bortez/cyclophos/dex	**Preferred regimens** Bortez/lenalid/dex (category 1) Lenalid/low-dose dex (category 1) Bortez/cyclophos/dex
Other Regimens Lenalid/dex (category 1) Bortez/dex (category 1) Bortez/thalid/dex (category 1) Carfil/lenalid/dex Ixazomib/lenalid/dex	**Other Regimens** Bortez/dex Carfil/lenalid/dex (category 2B) Ixazomib/lenalid/dex

NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2017.

Transplant Eligibility: Patient-Related Factors

- Age
- Frailty
- Performance status
- Comorbidities

Gertz MA, et al. *Blood.* 2014;124:882-92;
Palumbo A, et al. *Blood.* 2015;125:2068-74.

Risk-Adapted Management of MM in Transplant-Eligible Patients

	Front-Line Treatment	Post-Consolidation Treatment[a]
Standard risk	VRd x 4 cycles/SCH/ASCT[1,2]	Lenalidomide ≥ 2 years[1]
		Lenalidomide for < VGPR after induction[2,3]
	VRd x 4 cycles/SCH/VRd 4 cycles for good responders (delayed ASCT)[1]	Rd until PD[1]
	VRd x 4 cycles/SCH/VRd for 8 to 12 cycles for good response (delayed ASCT)[2]	Lenalidomide for < VGPR after induction[2]
	VTd or VCd with plasma exchange for patients with acute renal failure[2]	Lenalidomide for < VGPR after induction[2]
Intermediate risk	VRd x 4 cycles/SCH/ASCT[1,2] (consider tandem ASCT)	Bortezomib-based regimen for 2 years[1,2]
	VTd or VCd with plasma exchange for patients with acute renal failure[2]	
High risk	KRd x 4 cycles/SHC/ASCT[1,2] (consider tandem ASCT)	Carfilzomib- or bortezomib-based regimen for 2 years[1,2]

[a]On February 22, 2017, the US FDA approved lenalidomide as maintenance therapy for patients with MM following ASCT.

1. mSMART guidelines. www.msmart.org/about.html; 2. Rajkumar SV. *Am J Hematol.* 2016;91:719-34; 3. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm542791.htm.

IFM 2013-04 Trial: VTd vs VCd Prior to ASCT

- VTd compared with VCd prior to ASCT led to higher rates of VGPR (66.7% vs 56.2%, *P* = .04) and ORR (92.3% vs 84%, *P* = .02)
- The incidence of grade 3/4 peripheral neuropathy was slightly higher in VTd-treated patients (4% vs 2.2%); the incidence of grade 3/4 neutropenia was higher in VCd-treated patients (11.9% vs 22.5%)

Moreau P, et al. *Blood.* 2015;126:393.

SWOG S0777 Trial: VRd vs Rd With Rd Continuous Maintenance

- VRd led to deeper response and was superior to Rd in terms of mPFS (43 vs 30 months, *P* = .0018) and mOS (75 vs 64 months, *P* = .025)
- VRd treatment was tolerable but associated with higher rates of grade 3/4 neuropathy and GI events

Durie B, et al. *Lancet.* 2017;389:519-27.

IFM/DFCI 2009 Trial: VRd ± ASCT in Newly Diagnosed MM

- ASCT led to a lower risk of progression (HR, 0.69; *P* < .001) and higher rates of VPGR (*P* = .001) and MRD negativity (*P* = .001)
- Grade 5 toxicity occurred in 5 patients receiving ASCT during mobilization or transplantation; SPM developed in 23 patients in the transplant cohort and in 18 of the RVd alone cohort
- ASCT should remain the standard of care for newly diagnosed MM in the era of new treatments

Attal M, et al. ASH 2015. Abstract 391;
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Risk-Adapted Management of MM in Transplant-Ineligible Patients

	Front-Line Treatment	Post-Consolidation Treatment
Standard risk	Rd for 12 months if frail or ≥ 75 years[1]	Rd for year[1]
		Rd until progression[1] for good response or low toxicity[1]
	VRd for approximately 12 months (or x 12-18 cycles)[1,2]	Rd until progression[1]
		Lenalidomide for < VGPR after induction[2]
	Rd until progression if frail or ≥ 75 years[2]	
Intermediate risk	VRd for approximately 12 months (or x 12-18 cycles)[1,2]	Bortezomib-based regimen for 2 years[1,2]
	VCd x 8-12 cycles if frail or ≥ 75 years[2]	
High risk	KRd x 4 cycles/KRd for approximately 12 months (or x 12-18 cycles)[1,2]	(Carfilzomib- or)[2] bortezomib-based regimen for 2 years[1,2]
	KRd (dose reduced) if frail or ≥ 75 years[2]	

1. mSMART guidelines. www.msmart.org/about.html;
2. Rajkumar SV. *Am J Hematol*. 2016;91:719-34.

FIRST (MM-020) Trial: Rd-Continuous vs Rd-18 vs MPT

- Continuous Rd (low-dose dex) for transplant-ineligible patients prolonged PFS (HR, 0.69; *P* < .001) and OS (HR, 0.78; *P* = .02) compared with MPT
- Continuous Rd was associated with fewer cases of grade 3/4 hematologic toxicity, neuropathy, and SPM, but slightly more infections
- Continuous Rd is the standard of care for transplant-ineligible patients of all ages with newly diagnosed MM

Hulin C, et al. *J Clin Oncol*. 2016;34:3609-17;
Benboubker L, et al. *N Engl J Med*. 2014;371:906-17.

Treatment-Associated Safety Considerations

	Select Warnings and Precautions
Thalidomide (IMiD)	**Boxed warning: embryo-fetal toxicity, venous thromboembolism** Ischemic heart disease, somnolence, peripheral neuropathy, dizziness, orthostatic hypotension, neutropenia, increased HIV viral load, hypersensitivity, bradycardia, TLS
Lenalidomide (ImiD)	**Boxed warning: embryo-fetal toxicity, hematologic toxicity, venous thromboembolism** Angioedema, hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, tumor flare reaction, TLS, hepatotoxicity, SPM
Bortezomib (PI)	Peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, posterior reversible encephalopathy syndrome, GI toxicity, thrombocytopenia or neutropenia, TLS, hepatic toxicity, embryo-fetal risk
Carfilzomib (PI)	Heart failure, ischemia, pulmonary hypertension and complications, infusion reactions, TLS, thrombocytopenia, hepatic toxicity and failure, embryo-fetal toxicity

1. Thalidomide [package insert]. Summit, NJ: Celgene Corporation; 2017; 2. Lenalidomide [package insert]. Summit, NJ: Celgene Corporation; 2017; 3. Bortezomib [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2014; 4. Carfilzomib [package insert]. Thousand Oaks, CA: Amgen Inc.; 2016.

Evaluating Response

General
- Updated IMWG criteria
- Assess response prior to each treatment cycle
- Use response to help direct therapeutic decision making
- Designating a response category requires 2 consecutive assessments on therapy

Methods of Measuring Response
- Measure M protein in serum and urine
- FLC assay (ratio required for stringent CR; use in patients with disease with unmeasurable M protein in serum and urine protein)
- Bone marrow (for CR; detects quantitative/qualitative abnormalities of plasma cells, including cytogenetics)
  - Multiparametric flow cytometry: first- and next-generation flow
  - Allele-specific oligonucleotide quantitative polymerase chain reaction
  - Next-generation sequencing
- Renal response (for patients with disease-associated renal impairment; linked to eGFR)
- Imaging (CT/PET; if M protein and FLC not possible)

Lonial S, et al. *Leukemia.* 2014;28:258-68; Kumar S, et al. *Lancet Oncol.* 2016;17:e328-46; NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2017.

Patient Case (cont.)

- MS received VRd plus ASCT front-line therapy and 2 years of lenalidomide maintenance therapy
- He achieved sequencing MRD negativity on VRd; therapy was well tolerated
- MS presented with pain in his ribs and left hip 30 months after the cessation of maintenance therapy; disease progression was confirmed by MRI, SPEP, and creatinine

Therapy for Previously Treated MM

Preferred Regimens
- Repeat primary induction therapy (if relapse at > 6 months)
- Bortez/dex (category 1)
- Bortez/cyclophos/dex
- Bortez/lenalid/dex
- Carfil/dex (category 1)
- Carfil/lenalid/dex (category 1)
- Daratumumab
- Daratumumab/bortez/dex (category 1)
- Daratumumab/lenalid/dex (category 1)
- Elotuzumab/lenalid/dex (category 1)
- Ixazomib/lenalid/dex (category 1)
- Lenalid/dex (category 1)
- Pomalidomide/dex (category 1)
- Pomalid/bortz/dex
- Pomalid/carfil/dex

Other Regimens
- Bendamustine
- Bendamustine/bortez/dex
- Bendamustine/lenalid/dex
- Bortez/liposomal doxorubicin (category 1)
- Cyclophosphamide/lenalid/dex
- Dex/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dex/thalid/cisplatin/doxorubin/cyclophos/etoposide (DT-PACE) ± bortez (VTD-PACE)
- Elotuzumab/bortez/dex
- High-dose cyclophosphamide
- Ixazomib/dex
- Panobinostat/bortez/dex (category 1)
- Panobinostat/carfil
- Pomalidomide/cyclophos/dex

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Considerations for Relapsed/Refractory MM Treatment

1. When to initiate salvage therapy: SLiMCRAB[1]
2. Goals for therapy
   - Durable disease control with minimal toxicity, improve patient QOL
3. Can patient receive previous treatment regimen?
   - Depends on depth (eg, CR, VGPR) and duration of response (> 6 months)
   - Regimen will likely be less effective
   - Bortezomib is FDA approved for the retreatment of MM[2]
4. Use all FDA-approved agents for the treatment of MM
   - PIs (bortezomib, carfilzomib, ixazomib)[2-4]
   - IMiDs (thalidomide, lenalidomide, pomalidomide)[5-7]
   - mAbs (daratumumab, elotuzumab)[8,9]

1 Rajkumar SV, et al. *Lancet Oncology*, 2014; 15:e538-48; 2; Bortezomib [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2014; 3. Carfilzomib [package insert]. Thousand Oaks, CA: Amgen Inc.; 2016; 4. Ixazomib [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2016. 5. Thalidomide [package insert]. Summit, NJ: Celgene Corporation; 2017; 6. Lenalidomide [package insert]. Summit, NJ: Celgene Corporation; 2017; 7. Pomalidomide [package insert]. Summit, NJ: Celgene Corporation; 2016; 8. Daratumumab [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2016; 9. Elotuzumab [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2015.

Considerations for Relapsed/Refractory MM Treatment (cont.)

5. Optimal treatment strategy for the individual
   - Should preferentially involve clinical trials[1]
   - Must take into account
     - Patient-related factors: age, performance status, comorbidities (eg, cardiac, renal failure, diabetes, amyloidosis)[1]
     - Disease-related factors: risk status, rapidity of relapse, previous therapy exposure, response to previous therapy[1,2]
     - Treatment-related factors: mode of administration, single or combination therapy, cost, toxicity, risk of SPM

1. mSMART guidelines. www.msmart.org/about.html; 2. Kumar S, et al. *Lancet Oncol.* 2016;17:e328-46.

Risk-Adapted Treatment

- Cytogenetics should be retested after relapse to assess for mutations acquired over time and after previous therapy
- Risk of relapsed/refractory MM
  - High risk: relapse < 12 months from transplant or progression within first year of diagnosis; FISH del 17p, t(14;16), t(14,20); high-risk GEP
  - Intermediate risk: FISH t(4;14), 1q gain; high PC S-phase
  - Standard risk: all others including trisomies; FISH t(11;14), t(6;14)

mSMART guidelines. www.msmart.org/about.html.

Risk-Adapted Management of MM—First Relapse

	Patient Classification	Treatment	
Relapse during maintenance	Fit patients	Eligible for salvage ASCT? 1) Pts not previously treated with ASCT, or 2) second if > 18 mos no maintenance or > 36 mos maintained response to first ASCT[1,2]	Len-based maintenance: KPd,[1,2] DVd,[1]
			Bortez-based maintenance: DRd,[1] KRd[2]
	Indolent relapse		Len-based maintenance: DVd[1], ICd,[1] Pd[2]
			Bortez-based maintenance: IRd,[1] DRd,[1,2] ERd,[2] Pd[2]
	Frail patients	For len-based maintenance: DVd,[1] ICd,[1] Pd[2]	
		For bortez-based maintenance: DRd,[1] IRd,[2] ERd,[2] Pd[2]	
Relapse off-therapy/ unmaintained	Fit patients[a]	Eligible for salvage ASCT? 1) Pts not previously treated with ASCT or 2) second if > 18 mos no maintenance or > 36 mos maintained response to first ASCT[1,2]	KRd,[1,2] DRd,[1] KPd[2]
	Indolent relapse[a]		IRd,[1,2] ERd,[1,2] Pd[2]
	Frail patients[a]	IRd,[1,2] ERd,[1,2] Pd[2]	

[a]Can retreat with front-line therapy if relapse > 6 months after cessation of treatment.[2]

1. mSMART guidelines. www.msmart.org/about.html;
2. Rajkumar SV. *Am J Hematol*. 2016;91:719-34.

The ASPIRE Trial: KRd vs Rd

- mPFS was prolonged in patients who received carfilzomib (26.3 vs 17.6 months; HR, 0.69; *P* = .0001)
- Patients with previous exposure to bortezomib benefitted from carfilzomib (HR, 0.70)
- Patients treated with carfilzomib had an increased incidence of grade 3/4 toxicities (eg, hypokalemia, cardiac toxicity)

Avet-Loiseau H, et al. *Blood*. 2016;128:1174-80;
Stewart AK, et al. *N Engl J Med*. 2015;372:142-52.

The POLLUX Trial: DRd vs RD

- Approximately 48% of the ITT population received ≥ 2 prior lines of therapy
- Daratumumab treatment was associated with a significant reduction in the relative risk of progression or death (HR, 0.37; *P* < .001)
- Daratumumab was associated with an increased incidence of grade 3 or lower infusion reactions, grade 3/4 neutropenia, and febrile neutropenia

Dimopoulos M, et al. *N Engl J Med.* 2016;375:1319-31;
Moreau P, et al. *Blood*. 2016;124:abstract 489.

The TOURMALINE-MM1 Trial: IRd vs Rd

- 69% of the ITT population received prior treatment with a PI
- Ixazomib treatment was associated with improved mPFS (20.6 vs 14.7 months; HR, 0.74; *P* = .01)
- Rash, GI toxicity, peripheral neuropathy, and grade 3/4 thrombocytopenia occurred more frequently in patients treated with ixazomib

Moreau P, et al. *N Engl J Med*. 2016;374:1621-34.

The ELOQUENT-2 Trial: ERd vs Rd

- Elotuzumab treatment was associated with increased mPFS (19.4 vs 14.9 months; HR, 0.70; *P* < .001)
- The PFS benefit was slightly increased in patients with ≥ 2 prior lines of therapy (HR, 0.65)
- Increased incidences of grade 3/4 lymphocytopenia, any grade GI disorders, and infusion reactions were noted in elotuzumab-treated patients

Lonial S, et al. *N Engl J Med*. 2015;373:621-31.

Lenalidomide-Dexamethasone Combination Studies Experimental Arms

	POLLUX DRd vs Rd[1,2]	ASPIRE KRd vs Rd[3]	ELOQUENT-2 ERd vs Rd[4,5]	TOURMALINE-MM1 IRd vs Rd[6]
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥ VGPR	76%	70%	33%	48%
≥ CR	43%	32%	4%	12%
Duration of response, mos	NE	28.6	21	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

1. Dimopoulos M, et al. *N Engl J Med.* 2016;375:1319-31; 2. Moreau P, et al. *Blood*. 2016;124:abstract 489; 3. Stewart AK, et al. *N Engl J Med*. 2015;372:142-52; 4. Lonial S, et al. *N Engl J Med*. 2015;373:621-31; 5. Dimopoulos MA, et al. *Blood*. 2015;126:abstract 28; 6. Moreau P, et al. *N Engl J Med*. 2016;374:1621-34.

The CASTOR Trial: DVd vs Vd

- Daratumumab treatment was associated with a 61.4% reduction in the risk of disease progression or death (HR, 0.39; *P* < .001)
- The rates of ORR (82.9% vs 63.2%; *P* < .001) and ≥ VGPR (59.2% vs 29.1%; *P* < .001) were higher in daratumumab-treated patients
- Daratumumab-treated patients had an increased incidence of grade 3/4 neutropenia, lymphopenia, and thrombocytopenia; infusion-related reactions reported in 45.3% of patients

Palumbo A, et al. *N Engl J Med.* 2016;375:754-66.

- Pomalidomide/low-dose dexamethasone significantly improved mPFS compared with high-dose dexamethasone (4.0 vs 1.9 months; HR, 0.48; *P* < .0001)
- Pomalidomide/low-dose dexamethasone significantly improved mPFS compared with pomalidomide alone (4.2 vs 2.7 months; HR, 0.68; *P* = .003)

San Miguel J, et al. *Lancet Oncol.* 2013;14:1055-66;
Richardson P, et al. *Blood.* 2014;123:1826-32.

The STRATUS Trial (MM-010): Pomalidomide/Low-Dose Dexamethasone in Relapsed/Refractory MM

- In the ITT population, 93% received > 2 previous regimens, and 80% were bortezomib- and lenalidomide-refractory
- In bortezomib- and lenalidomide-refractory patients, pomalidomide/low-dose dexamethasone led to an ORR of 32.4% with a median duration of 7.4 months
- Frequent grade 3/4 treatment-emergent toxicities included neutropenia, anemia, and thrombocytopenia

Dimopoulos M, et al. *Blood*. 2016;128:497-503.

Treatment-Associated Safety Considerations

	Select Warnings and Precautions
Ixazomib (PI)[1]	Thrombocytopenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy
Pomalidomide (IMiD)[2]	**Boxed warning: embryo-fetal toxicity, venous thromboembolism** Hematologic toxicity, especially neutropenia
Daratumumab (anti-CD38 mAb)[3]	Infusion reactions, interference with cross-matching and red blood cell antibody screening
Elotuzumab (anti-SLAMF7 mAb)[4]	Infusion reactions (requires premedication), infections, SPM, hepatotoxicity, interference with determination of complete response (M protein)

1. Ixazomib [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2016;
2. Pomalidomide [package insert]. Summit, NJ: Celgene Corporation; 2016;
3. Daratumumab [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2016;
4. Elotuzumab [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2015.

Patient Case (cont.)

- MS was treated with DVd; he initially achieved a VGPR and tolerated therapy, but he developed grade 2 peripheral neuropathy after 6 months
- During the 11th month of treatment, progressive disease was confirmed by routine response evaluation
- Bone marrow aspiration and cytogenetic/FISH analysis indicated that the tumor had acquired a second chromosomal abnormality: t(11;14), del 17p

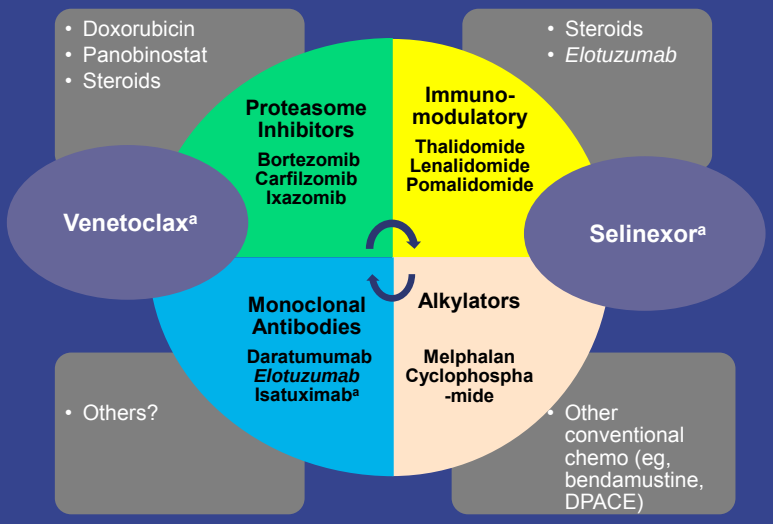
Risk-Adapted Management of MM—Second or Later Relapse

	Agent(s) to Which Tumor Is Refractory	Treatment[b]
Single-refractory MM[a]	• Either IMiD or PI	Refractory to IMiD: DVd Refractory to PI: DRd
Dual-refractory MM[a]	• Bortezomib and/or ixazomib • Lenalidomide	Pomalidomide-based regimen (Pd or PCd) + daratumumab (elotuzumab if refractory to daratumumab) or KPd/KRd
Triple-refractory MM[a]	• Bortezomib and/or ixazomib • Lenalidomide • Carfilzomib	Pomalidomide-based regimen (Pd or PCd) + daratumumab (elotuzumab if refractory to daratumumab)
	• Bortezomib and/or ixazomib • Lenalidomide • Pomalidomide	Daratumumab-based regimen (elotuzumab if refractory to daratumumab), or alkylator-based regimen if alkylator-naïve, or PI + panobinostat
Quadruple-refractory MM	• Bortezomib • Lenalidomide • Pomalidomide • Carfilzomib	VDT-PACE x 2 cycles (CVAD for older or frail patients); if ASCT not possible, use agent to which tumor is not refractory (eg, regimens containing daratumumab, panobinostat, bendamustine, alkylator, anthracycline)

[a]Not plasma cell leukemia or similar extramedullary disease.
[b]Consider for ASCT candidacy for all patients if feasible.

1. mSMART guidelines. www.msmart.org/about.html;
2. Rajkumar SV. *Am J Hematol*. 2016;91:719-34.

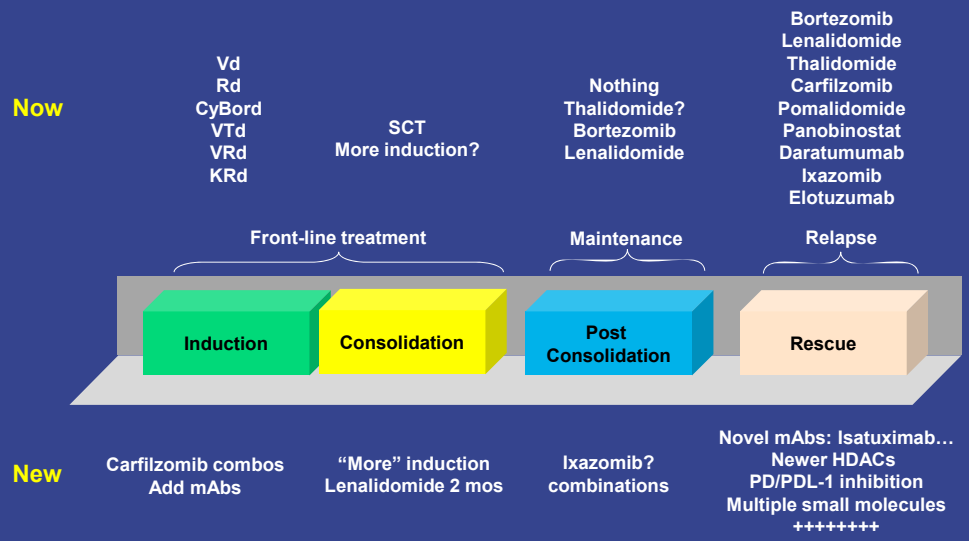
The Future of MM Treatment



[a]Investigational agents.

Expert opinion; Martin T, et al. *Blood.* 2015;126:509; Moreau P, et al. ASH 2016. Abstract 975; Vogl DT, et al. ASH 2016. Abstract 491.

Treatment Sequencing in MM



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Abbreviations/Acronyms

ASCT = autologous stem cell transplantation
BUN = blood urea nitrogen
CBC = complete blood count
CR = complete response
CyBord = cyclophosphamide/bortezomib/dexamethasone
DRd = daratumumab/lenalidomide/dexamethasone
DVd = daratumumab/bortezomib/dexamethasone
eGFR = estimated glomerular filtration rate
ERd = elotuzumab/lenalidomide/dexamethasone
FISH = fluorescence in situ hybridization
FLC – free light chain
GEP = gene expression profiling
GI = gastrointestinal
Hb = hemoglobin
ICd = ixazomib/cyclophosphamide/dexamethasone
IRd = ixazomib/lenalidomide/dexamethasone
Ig = immunoglobulin
IMiD = immunomodulatory agent
ITT = intent to treat
IMWG = International Myeloma Working Group
KPd = carfilzomib/pomalidomide/dexamethasone
KRd = carfilzomib/lenalidomide/dexamethasone
LDH = lactate dehydrogenase
mAbs = monoclonal antibodies
MRD = minimal residual disease
MM = multiple myeloma
mOS = median overall survival
mPFS = median progression-free survival
MPT = melphalan/prednisone/thalidomide
mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy
ORR = overall response rate
OS = overall survival
PC = plasma cell
PCd = Pomalidomide/cyclophosphamide/dexamethasone
Pd = Pomalidomide/dexamethasone
PI = proteasome inhibitor
PFS = progression-free survival
QOL = quality of life
Rd = lenalidomide/dexamethasone
SCH = stem cell harvest
SPEP = serum protein electrophoresis
SPM = second primary malignancy
TLS = tumor lysis syndrome
ULN = upper limit of normal

VCd = bortezomib/cyclophosphamide/dexamethasone
Vd = bortezomib/dexamethasone
VGPR = very good partial response
VRd = bortezomib/lenalidomide/dexamethasone
VTd = bortezomib/thalidomide/dexamethasone
WBC = white blood cell