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The Current Landscape and Clinical Challenges in Treating Relapsed/Refractory Multiple Myeloma

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Speaker Disclosure

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Recent and Possible Future FDA Approvals of Novel Agents for Patients with RRMM

Novel Agent or Regimen	FDA Approval Date	Patient Population
Panobinostat + bortezomib/dexamethasone	February 23, 2015	Patients with ≥2 prior standard therapies, including bortezomib and an immunomodulatory agent
Carfilzomib + lenalidomide/dexamethasone	July 27, 2015	Patients with relapsed disease who had received 1-3 prior lines of therapy
Daratumumab	November 16, 2015	Patients with at least 3 prior treatments
Ixazomib + lenalidomide/dexamethasone	November 20, 2015	Patients who had received at least 1 prior therapy
Elotuzumab + lenalidomide/dexamethasone	November 30, 2015	Patients with 1-3 prior therapies
Carfilzomib + dexamethasone	January 21, 2016	Patients with relapsed disease and 1-3 prior therapies
Daratumumab + bortezomib/dexamethasone	FDA review pending	Patients who had received at least 1 prior therapy
Daratumumab + lenalidomide/dexamethasone	FDA review pending	Patients who had received at least 1 prior therapy

Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Based on Robust Trials

Table 3. Outcomes data from key trials supporting recent and possible future food and drug administration approvals

Trial	Agent or regimen	PFS, mo	HR for PFS	ORR	DOR	CR rate	Median OS
PANORAMA1	Panobinostat/Bortezomib/Dex	11.99[a]	0.63	255/387 (60.7%)[a]	13.14 mo[a]	42/387 (11%)	33.64 mo
	Placebo/Bortezomib/Dex	8.08		208/381 (54.6%)	10.87 mo	22/380 (6%)	30.39 mo
ASPIRE	Carfilzomib/Lenalidomide/Dex	26.3[a]	0.69	345/396 (87.1%)[a]	28.6 mo[a]	126/396 (31.8%)[a]	73.3% at 24 mo[a]
	Lenalidomide/Dex	17.6		264/396 (66.7%)	21.2 mo	37/396 (9.3%)	65% at 24 mo
SIRIUS	Daratumumab	3.7	N.A.	31/106 (29.2%)	7.4 mo	3/106 (2.8%)	64.8% at 12 mo
TOURMALINE 1	Ixazomib/Lenalidomide/Dex	20.6[a]	0.74	282/360 (78%)[a]	20.5 mo	42/360 (12%)[a]	81 deaths at 23 mo
	Placebo/Lenalidomide/Dex	14.7		259/362 (72%)	15.0 mo	24/362 (7%)	90 deaths at 23 mo
ELOQUENT 2	Elotuzumab/Lenalidomide/Dex	19.4[a]	0.70	252/321 (79%)[a]	20.73 mo	14/321 (4%)	14 deaths
	Lenalidomide/Dex	14.9		213/325 (66%)	16.62 mo	24/325 (7%)	22 deaths
ENDEAVOR	Carfilzomib/Dex	18.7[a]	0.53	365/464 (76.7%)[a]	21.3 mo[a]	58/464 (13%)[a]	75 deaths
	Bortezomib/Dex	9.4		290/465 (62.3%)	10.4 mo	29/465 (6%)	88 deaths
CASTOR	Daratumumab/Bortezomib/Dex	Not reached[a]	0.39	199/240 (82.9%)[a]	Not reached[a]	46/240 (19.2%)	29 deaths
	Bortezomib/Dex	7.2		148/234 (63.2%)	7.9 mo	21/234 (9.0%)	26 deaths
POLLUX	Daratumumab/Lenalidomide/Dex	Not reached[a]	0.37	261/281 (92.9%)[a]	Not reached[a]	125/281 (43.1%)[a]	86.1% at 18 mo
	Lenalidomide/Dex	18.4		211/276 (76.4%)	17.4 mo	53/276 (19.2%)	75.6% at 18 mo[a]

NOTE: ORR defined as partial response or better.
Abbreviations: Dex, dexamethasone; N.A.; not applicable.
[a]Indicates that the value in question is statistically significantly better than the relevant control, where significance is defined by $P < 0.05$.

Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Relapsed and/or Refractory Options

Category 1 Preferred Regimens

- Bortezomib/dexamethasone
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone
- Daratumumab/bortezomib/dexamethasone
- Daratumumab/lenalidomide/dexamethasone
- Elotuzumab/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Lenalidomide/dexamethasone
- Pomalidomide/dexamethasone

Other Regimens

- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Daratumumab
- Pomalidomide/bortezomib/dexamethasone
- Pomalidomide/carfilzomib/dexamethasone

If relapse at >6 mo

- Repeat primary induction therapy

http://www.nccn.org. Version 3.2017.

Robust Alternatives

Other Regimens

- Bendamustine
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)
- Elotuzumab/bortezomib/dexamethasone
- High-dose cyclophosphamide
- Ixazomib/dexamethasone
- Panobinostat/bortezomib/dexamethasone (category 1)
- Panobinostat/carfilzomib
- Pomalidomide/cyclophosphamide/dexamethasone

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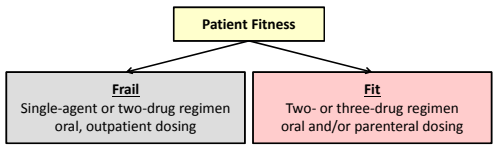
Therapeutic Guidelines



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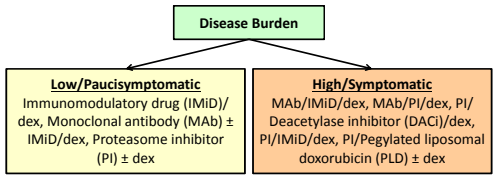
Therapeutic Guidelines



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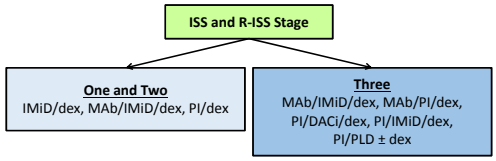

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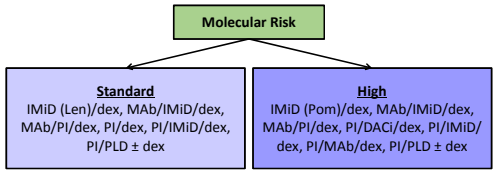
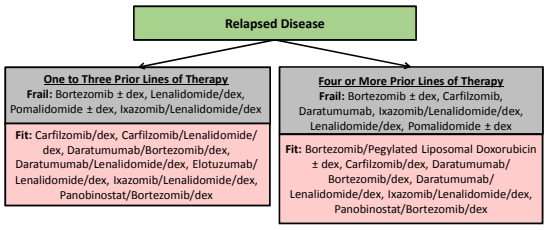
Therapeutic Guidelines



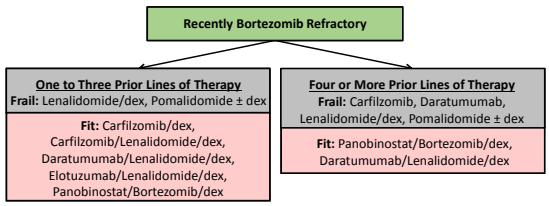
Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Options for Relapsed/Refractory Disease



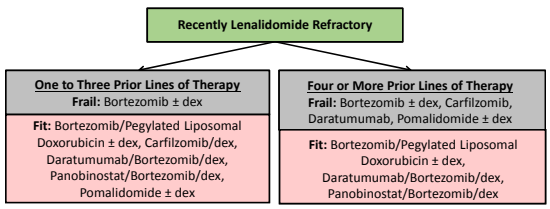
Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Therapeutic Guidelines



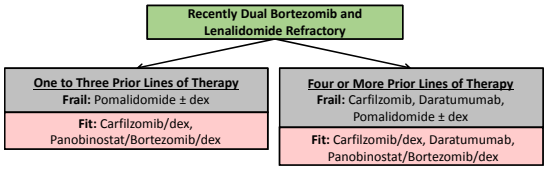
Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Therapeutic Guidelines



Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Therapeutic Guidelines



Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

Conclusions: Relapsed Disease

- PIs and IMiDs, and now MAbs, have made a dramatic impact on myeloma in multiple settings
- Their good tolerability, and both efficacy and flexibility in combination regimens with almost all other chemotherapeutics, have made them a mainstay and backbone of our standards of care
- However, their early use is increasing, making relapsed – especially refractory – disease more challenging to manage

Challenges Remain

- Optimal combinations and/or sequences of drugs remain to be defined
- Role of MRD in drug approvals and as a clinically relevant endpoint to inform therapeutic choices
- Selection of patients based on molecular and clinical grounds for their best regimens to maximize efficacy and minimize clinical and financial toxicity

Do Any of These Regimens Matter?

Individualizing Treatment for Your Patients with Relapsed/Refractory Multiple Myeloma: Selecting Among the Available Options

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Speaker Disclosure

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Outline

- Available therapeutic regimens
- General principles to guide therapy decisions
- Treatment of early relapse/progression (1 – 3 prior lines of therapy)
- Treatment of later relapse/progression (≥2 prior lines of therapy and/or lenalidomide/bortezomib refractory)
- Conclusions

Available Regimens in Early Relapse: NCCN Guidelines

Preferred Regimens	Other Regimens
Level 1 Regimens **Doublets** • Bortezomib/dexamethasone • Carfilzomib/dexamethasone • Lenalidomide/dexamethasone **Triplets** • Elotuzumab/lenalidomide/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/dexamethasone **Other Regimens** • Repeat primary induction therapy (if relapse at >6 months) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone	**Level 1 Regimens** • Bortezomib/liposomal doxorubicin • Panobinostat/bortezomib/dexamethasone ***Other*** **PI-Based** • Ixazomib/dexamethasone • Elotuzumab/bortezomib/dexamethasone **Alkylator-Based** • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • DCEP (dex/cyclophosphamide/etoposide/cisplatin) • DT-PACE (dex/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide

Note: NCCN Guidelines do not break out regimens into separate categories of early and late relapse

NCCN Guidelines, Version 3.2017, accessed August, 2017.

Available Regimens in Late Relapse: NCCN Guidelines

Preferred Regimens	Other Regimens
Late Relapse (≥2 prior lines or len/bort refractory) **Level 1 Regimens** **Doublets** • Pomalidomide/dexamethasone **Other Regimens** • Pomalidomide/bortezomib/dexamethasone • Pomalidomide/carfilzomib/dexamethasone • Pomalidomide/daratumumab/dexamethasone • Daratumumab	**Late Relapse (≥2 prior lines or len/bort refractory)** • Panobinostat/bortezomib/dexamethasone • Panobinostat/carfilzomib • Pomalidomide/cyclophosphamide/dexamethasone • DCEP (dex/cyclophosphamide/etoposide/cisplatin) • DT-PACE (dex/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide

Note: NCCN Guidelines do not break out regimens into separate categories of early and late relapse

NCCN Guidelines, Version 3.2017, accessed August, 2017.

Novel Lenalidomide/Dexamethasone-Based Therapy for Early Relapse

TOURMALINE-MM1: RD ± ixazomib for relapsed and relapsed/refractory multiple myeloma patients having received 1-3 prior lines of therapy.
ELOQUENT-2: RD ± elotuzumab for relapsed and relapsed/refractory multiple myeloma patients having received 1-3 prior lines of therapy.
ASPIRE: RD ± carfilzomib for relapsed and relapsed/refractory multiple myeloma patients having received 1-3 prior lines of therapy.
POLLUX: RD ± daratumumab for relapsed and relapsed/refractory multiple myeloma patients having received ≥1 prior line of therapy.

	TOURMALINE-MM1		ELOQUENT-2		ASPIRE		POLLUX	
Treatment Arm	**RD**	**IRD**	**RD**	**ERD**	**RD**	**KRD**	**RD**	**DRD**
ORR	71.5%	78.3%*	66%	79%	66.7%	87.1%*	76.4%	92.9%*
≥ VGPR	39%	48%*	28%	33%	40.4%	69.9%*	44.2%	75.8%*
Median PFS, mos	14.7	20.6*	14.9	19.4*	17.6	26.3*	1-yr 60.1%	1-yr 83.2%*
PFS HR	0.74		0.70		0.69		0.37	
Median OS	NR	NR	NR	NR	2-yr 65%	2-yr 73.3%	1-yr 86.6%	1-yr 92.1%

*Statistically significant
E=elotuzumab; I=ixazomib; K=carfilzomib; RD=lenalidomide-dexamethasone; mos=months; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; VGPR=very good partial response; yr=year

Lonial S, et al. *N Engl J Med.* 2015;373:621-631.; Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.; Stewart A, et al. *N Engl J Med.* 2014;372:142-152.; Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

Novel Lenalidomide-Free, Proteasome Inhibitor-Based Therapy for Early Relapse

PANORAMA-1: A phase III study of bortezomib-dexamethasone ± panobinostat for relapsed and relapsed/refractory multiple myeloma patients having received 1-3 prior therapies.
ENDEAVOR: A phase III study of bortezomib-dexamethasone vs carfilzomib-dexamethasone for relapsed and relapsed/refractory multiple myeloma patients having received 1-3 prior lines of therapy.
CASTOR: A phase III study of bortezomib-dexamethasone ± daratumumab for relapsed and relapsed/refractory multiple myeloma patients having received ≥1 prior line of therapy.

	PANORAMA-1		ENDEAVOR		CASTOR	
Treatment Arm	**VD**	**Pano-VD**	**VD**	**KD**	**VD**	**DVD**
Overall Response Rate	54.6%	60.7%	63%	77%*	63.2%	82.9%*
≥ VGPR	15.7%	27.6%*	29%	54%	29%	59.1%*
Median Progression-Free Survival, mos	All patients: 8.08	11.99*	9.4	18.7	7.2	Not yet reached*
	≥2 prior regimens + IMiD and bortezomib: 4.7	12.5				
PFS HR	0.63		0.53		0.39	
Median OS, mos	30.39	33.64	40.0	47.6	NR	NR

*Statistically significant
DVD=daratumumab-bortezomib-dexamethasone; KD=carfilzomib-dexamethasone; NR=not reported; Pano=panobinostat; VD=bortezomib-dexamethasone

San Miguel J, et al. *Lancet Oncol.* 2014;15:1195-1206.; Palumbo A, et al. *N Engl J Med.* 2016;375:754-766.; Dimopoulos M, et al. *Lancet Oncol.* 2016;17:27-38.; Dimopoulos M, et al. *Lancet Oncol.* 2017;17:30578-8.

Lenalidomide- vs Bortezomib-Based Platform for Early Relapse

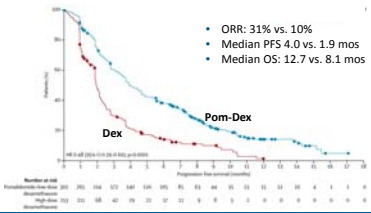
	MM1	ELO-2	ASPIRE	POLLUX	ENDEAVOR	CASTOR
Treatment Arm	**RD**	**RD**	**RD**	**RD**	**VD**	**VD**
ORR	71.5%	66%	66.7%	76.4%	63%	63.2%
≥ VGPR	39%	28%	40.4%	44.2%	29%	29%
Median PFS, mos	14.7	14.9	17.6	1-yr 60.1%	9.4	7.2
Median OS, mos	NR	NR	2-yr 65%	1-yr 86.6%		NR

- If the patient is a candidate for either a lenalidomide- or bortezomib-based strategy in first relapse/progression, consider a lenalidomide-based strategy as a first choice
- No head-to-head comparisons of the two doublets exist

Lonial S, et al. *N Engl J Med.* 2015;373:621-631.; Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331.; Stewart A, et al. *N Engl J Med.* 2014;372:142-152.; Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.; San Miguel J, et al. *Lancet Oncol.* 2014;15:1195-1206.; Palumbo A, et al. *N Engl J Med.* 2016;375:754-766.; Dimopoulos M, et al. *Lancet Oncol.* 2016;17:27-38; Dimopoulos M, et al. *Lancet Oncol.* 2017;17:30578-8.

Pomalidomide-Dex vs Dex for Relapsed/Refractory Multiple Myeloma

- Randomized, phase III study of Pom-Dex vs Dex in relapsed/refractory myeloma
- Baseline characteristics: 1) Median number of prior therapies = 5; 2) Len and bort refractory 75%



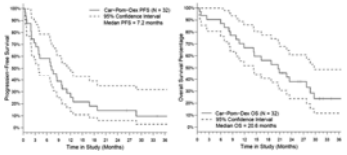
- ORR: 31% vs. 10%
- Median PFS 4.0 vs. 1.9 mos
- Median OS: 12.7 vs. 8.1 mos

Miguel JS, et al. *Lancet Oncol*. 2013;14:1055-1066.

Carfilzomib, Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma

- MTD in phase I: 4-week cycle.
  CFZ 27 mg/m^2 D1, 2, 8, 9, 15, 16;
  Pom 4 mg D1-21;
  Dex 40 mg D1, 8, 15, 22
- Median lines of therapy: 6 (2–12)
- Len-refractory: 100%
- Bortezomib-refractory: 93.5%

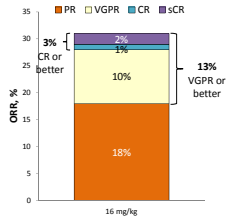
Best Overall Response	N=32
VGPR	16%
PR	34%
MR	16%
SD	25%
PD	9%



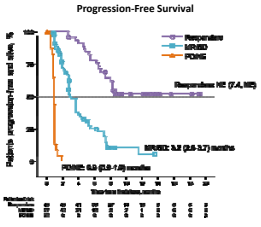
Median PFS 7.2 months,
Median OS 20.6 months

Shah JJ, et al. *Blood*. 2015;261:2284-2290.

Daratumumab as Monotherapy for Relapsed/Refractory Multiple Myeloma



N = 148

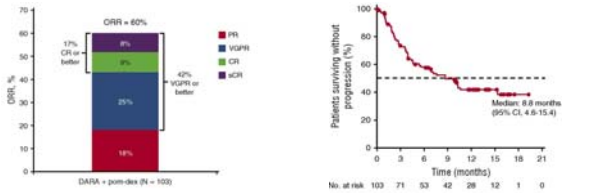


- Median OS: 19.9 months

Usmani S, et al. *Blood*. 2016;128:37-44.

Pomalidomide, Dexamethasone and Daratumumab for Relapsed/Refractory MM

Median number of prior lines of therapy: 4 (range 1 – 13), 71% PI and IMiD refractory, 25% with high-risk CGs



Of 17 patients in ≥ CR, 35%, 29%, and 6% were MRD- at thresholds of 10-4, 10-5, and 10-6, respectively

Median OS = 17.5 months (85% CI 13.3 – NE)

Median PFS in high-risk CG disease (N=22): 3.9 months (95% CI 2.3 – NE)

Chari A, et al. *Blood*. 2017;130:974-981.

General Treatment Principles

- Overlap between early and late relapse treatment choices
  - An early or late relapse regimen may be appropriate as 2nd – 4th line therapy (1 – 3 prior lines) depending on the circumstances
- Stick with the preferred regimens
  - Consider consulting with a myeloma specialist when having to make decisions outside of the preferred regimens category
- The role of doublets and monotherapy is limited
  - Several novel triplets now available with good toxicity profiles
  - Consider in the more frail, heavily pretreated patients

PABST: The Blue Ribbon Approach to Therapy Decisions for Previously Treated Multiple Myeloma

- **P**ast medical history
  - What comorbidities will impact tolerability of therapy?
- **A**dverse events
  - What toxicities were experienced with prior therapy?
- **B**iochemical vs clinical relapse/progression
- **S**tandard vs high-risk disease biology
- **T**reatment history
  - Is the disease resistant to specific drug classes?

Past Medical History and Adverse Events with Prior Therapy

ELOQUENT-2: Safety

Increased rate of high-grade lymphopenia and low-grade constitutional (fatigue, fever), GI (constipation, diarrhea) and respiratory (cough, nasopharyngitis) side effects with the addition of elotuzumab

	Elo-RD		RD	
AEs (%)	**All AEs**	**≥ Gr 3 or 4**	**All AEs**	**≥ Gr 3 or 4**
Neutropenia	82	34	89	44
Anemia	96	19	95	21
Thrombocytopenia	84	19	78	20
Lymphopenia	**99**	**77**	**98**	**49**
Diarrhea	**47**	**5**	**36**	**4**
Constipation	**36**	**1**	**27**	**<1**
Cough	**31**	**<1**	**18**	**0**
Nasopharyngitis	**25**	**0**	**19**	**0**
Fatigue	**47**	**8**	**39**	**8**
Fever	**37**	**3**	**25**	**3**

Lonial S, et al. *N Engl J Med.* 2015;373:621-631.

TOURMALINE-MM1: Safety

Increased rate of high-grade lymphopenia and low-grade hematologic (thrombocytopenia), gastrointestinal (nausea, constipation, diarrhea), constitutional (fatigue, fevers), neurologic (neuropathy) and respiratory (cough, nasopharyngitis) side effects with the addition of ixazomib

	IRD		RD	
AEs (%)	**All AEs**	**≥ Gr 3 or 4**	**All AEs**	**≥ Gr 3 or 4**
Neutropenia	82	34	89	44
Anemia	96	19	95	21
Thrombocytopenia	84	19	78	20
Lymphopenia	**99**	**77**	**98**	**49**
Diarrhea	**47**	**5**	**36**	**4**
Constipation	**36**	**1**	**27**	**<1**
Nausea	**29**	**2**	**22**	**2**
Cough	**31**	**<1**	**18**	**0**
Nasopharyngitis	**25**	**0**	**19**	**0**
Fatigue	**47**	**8**	**39**	**8**
Fever	**37**	**3**	**25**	**3**
Peripheral neuropathy*	**27**	**2**	**22**	**2**

*Gr 1 neuropathy with pain or ≥ Gr 2 neuropathy ineligible

Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634.

POLLUX: Safety

Increased rate of high-grade neutropenia and low-grade constitutional (fatigue, fever), GI (nausea, vomiting, diarrhea) and respiratory (URIs, dyspnea, cough, nasopharyngitis) side effects with the addition of daratumumab

	Dara-RD		RD	
AEs (%)	**All AEs**	**≥ Gr 3 or 4**	**All AEs**	**≥ Gr 3 or 4**
Neutropenia	**59.4**	**51.9**	**43.1**	**37.0**
Anemia	31.1	12.4	34.9	19.6
Thrombocytopenia	26.9	12.7	27.4	13.5
Febrile Neutropenia	**5.7**	**5.7**	**2.5**	**2.5**
Diarrhea	**42.8**	**5.3**	**24.6**	**3.2**
Nausea	**24.0**	**1.4**	**14.2**	**0**
Vomiting	**16.6**	**1.1**	**5.3**	**0.7**
Constipation	29.3	1.1	25.3	0.7
URI	**31.8**	**1.1**	**20.6**	**1.1**
Dyspnea	**18.4**	**3.2**	**11.4**	**0.7**
Cough	**29.0**	**0.0**	**12.5**	**0.0**
Nasopharyngitis	**24.0**	**0.0**	**15.3**	**0.0**
Fatigue	**35.3**	**6.4**	**27.8**	**2.5**
Fever	**20.1**	**1.8**	**11.0**	**1.4**
Muscle spasms	**25.8**	**0.7**	**18.5**	**1.8**

Dimopoulos MA, et al. *N Engl J Med*. 2016;375:1319-1331.

ASPIRE: Safety

Increased rate of hematologic (neutropenia, thrombocytopenia), gastrointestinal (diarrhea), constitutional (fevers), respiratory (URI, cough, dyspnea) and cardiovascular (HTN, CHF, VTE) side effects with the addition of carfilzomib

	KRD		RD	
AEs (%)	**All AEs**	**≥ Gr 3 or 4**	**All AEs**	**≥ Gr 3 or 4**
Neutropenia	**37.8**	**29.6**	**33.7**	**26.5**
Anemia	42.6	17.9	39.8	17.2
Thrombocytopenia	**29.1**	**16.6**	**22.6**	**12.3**
Diarrhea	**42.3**	**3.8**	**33.7**	**4.1**
URI	**28.6**	**1.8**	**19.3**	**1.0**
Cough	**28.8**	**0.3**	**17.2**	**0.0**
Dyspnea	**19.4**	**2.8**	**14.9**	**1.8**
Fatigue	32.9	7.7	30.6	6.4
Fever	**28.6**	**1.8**	**20.8**	**0.5**
Hypokalemia	**27.6**	**9.4**	**13.4**	**4.9**
Hypertension	**14.3**	**4.3**	**6.9**	**1.8**
Acute renal failure	8.4	3.3	7.2	3.1
Congestive heart failure	**6.4**	**3.8**	**4.1**	**1.8**
Ischemic heart disease	**5.9**	**3.3**	**4.6**	**2.1**
Deep vein thrombosis	**6.6**	**1.8**	**3.9**	**1.0**
Pulmonary embolism	**3.6**	**3.1**	**2.3**	**2.3**
Peripheral neuropathy	17.1	2.6	17.0	3.1

Stewart AK, et al. *N Engl J Med*. 2015;372:142-152.

ENDEAVOR: Safety

Less neuropathy and diarrhea with carfilzomib, more hematologic (anemia), constitutional (fevers), respiratory (dyspnea, cough) and cardiovascular/renovascular (HTN, ARF, CHF) side effects

	KD			VD		
AEs (%)	**Gr 1/2**	**Gr 3**	**Gr 4**	**Gr 1/2**	**Gr 3**	**Gr 4**
Anemia	**25**	**14**	**<1**	**17**	**10**	**<1**
Thrombocytopenia	12	5	4	8	4	5
Diarrhea	27	3	0	31	7	<1
Fatigue	24	5	0	21	7	0
Fever	**26**	**2**	**<1**	**13**	**<1**	**0**
Muscle spasms	**18**	**<1**	**0**	**5**	**<1**	**0**
URI	18	2	0	14	<1	0
Dyspnea	**23**	**5**	**0**	**11**	**2**	**0**
Cough	**25**	**0**	**0**	**14**	**<1**	**0**
Hypertension	**16**	**9**	**0**	**6**	**3**	**0**
Pulmonary hypertension	<1	<1	0	0	<1	0
Ischemic heart disease	<1	1	<1	0	<1	0
Congestive heart failure	**3**	**4**	**<1**	**1**	**1**	**<1**
Acute renal failure	**4**	**3**	**<1**	**2**	**2**	**<1**
Peripheral neuropathy	**17**	**2**	**0**	**43**	**8**	**<1**

Dimopoulos, et al. *Lancet Oncol*. 2016;17:27-38.

CASTOR: Safety

Increased rate of hematologic (neutropenia, lymphopenia, thrombocytopenia) and low-grade GI (diarrhea) and respiratory (URIs, dyspnea, cough) side effects with the addition of daratumumab

	Dara-VD		VD	
AEs (%)	**All AEs**	**≥ Gr 3 or 4**	**All AEs**	**≥ Gr 3 or 4**
Neutropenia	**17.7**	**12.8**	**9.3**	**4.2**
Anemia	26.3	14.4	31.2	16.0
Thrombocytopenia	**58.8**	**45.3**	**43.9**	**32.9**
Lymphopenia	**13.2**	**9.5**	**3.8**	**2.5**
Diarrhea	**31.7**	**3.7**	**22.4**	**1.3**
URI	**24.7**	**1.6**	**18.1**	**0.8**
Dyspnea	**18.5**	**3.7**	**8.9**	**0.8**
Cough	**23.9**	**0.0**	**12.7**	**0.0**
Fever	15.6	1.2	11.4	1.3

Palumbo A, et al. *N Engl J Med*. 2016;375:754-766.

PANORAMA-1: Safety

Increased rate of high-grade hematologic (neutropenia, lymphopenia, thrombocytopenia), GI (diarrhea, nausea, vomiting) and constitutional (loss of appetite, fatigue) side effects with the addition of panobinostat

	PVD			VD		
AEs (%)	**All AEs**	**Gr 3**	**Gr 4**	**All AEs**	**Gr 3**	**Gr 4**
Neutropenia	**75**	**28**	**7**	**36**	**9**	**2**
Anemia	**62**	**15**	**3**	**52**	**17**	**2**
Thrombocytopenia	**98**	**33**	**35**	**84**	**19**	**12**
Lymphopenia	**83**	**42**	**12**	**74**	**33**	**7**
Diarrhea	**68**	**24**	**1**	**42**	**7**	**<1**
Nausea	**36**	**5**	**<1**	**21**	**<1**	**0**
Vomiting	**26**	**7**	**<1**	**13**	**1**	**0**
Decreased appetite	**28**	**3**	**0**	**12**	**<1**	**<1**
Weight loss	**12**	**2**	**0**	**5**	**<1**	**0**
Asthenia/Fatigue	**57**	**23**	**1**	**41**	**12**	**<1**

Patients were required to have an ANC of ≥1.5 and platelets ≥100 to be eligible

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

Biochemical vs Clinical Progression

- **Biochemical progression:**
  - Progression of disease based on M-protein parameter increase only
  - Timing of therapy institution/escalation dependent on numerous factors
    - Pace of progression
    - Original clinical presentation
    - Standard- vs high-risk disease biology
    - Patient/physician comfort level
- **Clinical relapse:**
  - "Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma cell proliferative disorder"
  - Mandates immediate institution/escalation of therapy

IMWG Consensus Criteria for Response in MM

Biochemical Progression	Clinical Relapse
↑ of ≥25% from nadir response value in one or more of the following: 1) Serum M-protein (absolute increase ≥0.5 g/dL, ≥1 g/dL if nadir ≥5 g/dL) 2) Urine M-protein (absolute increase ≥200 mg/ 24 hours) 3) Measurable by serum FLC testing only: difference between involved and uninvolved FLCs (absolute increase ≥10 mg/dL) 4) Non-secretory: bone marrow PC % (absolute increase ≥10%)	1) Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) 2) Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion 3) Hypercalcemia (>11 mg/dL); 4) Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions 5) Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma 6) Hyperviscosity related to serum paraprotein
≥50% increase in circulating plasma cells (minimum 200 cells/mcL) if this is the only disease measure available	

Kumar S, et al. *Lancet Oncol*. 2016;17:328-346.

Standard- vs High-Risk Disease Biology: IMWG Consensus on Risk Stratification

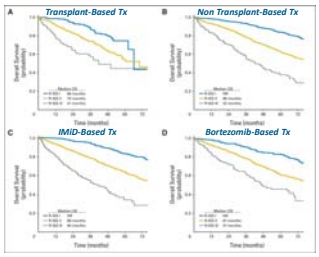
	High-Risk	Standard-Risk	Low-Risk
Parameters	ISS II/III and t(4;14) or del(17p13)	Others	ISS I/II and absence of t(4;14), del(17p13) and +1q21 and age <55
% of Patients	20%	60%	20%
Median OS	2 years	7 years	>10 years

- Other factors: Gene expression profile, LDH. circulating plasma cells, response to prior therapy

Chng WJ, et al. *Leukemia*. 2014;28:269-277.

Revised International Staging System

- R-ISS stage 1: normal LDH, no high-risk cytogenetic abnormality (CA),* ISS stage 1 disease
- R-ISS stage 2: not stage 1 or 3
- R-ISS stage 3: ISS stage 3 disease PLUS high LDH OR high-risk CA



*High risk CA = del(17p) and/or t(4;14) and/or t(14;16)

Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869.

Can We Choose Based on High-Risk Disease Biology?

	ASPIRE				POLLUX				ENDEAVOR			
Cytogenetic Risk	SR		HR		SR		HR		SR		HR	
Treatment Arm	RD	KRD	RD	KRD	RD	DRD	RD	DRD	VD	KD	VD	KD
ORR (%)	73.5	91.2	59.6	79.2								
≥ VGPR (%)	45.3	75.5	27	60.4					29.5	58.8	30.1	46.4
Median PFS, mos	19.5	29.6*	13.9	23.1	17.1	NR*	10.2	NR*	10.2	NR*	6.0	8.8*
	HR 0.66		HR 0.70		HR 0.30		HR 0.44		HR 0.439		HR 0.646	

High risk: del(17p) (in ≥60% of PCs for ASPIRE), t(4;14), t(14;16)
*Statistically significant

ELOQUENT-2: ERD vs RD. HR for PFS in del(17p): 0.65. HR for PFS in t(4;14): 0.44.
TOURMALINE: IRD vs RD. Median PFS in high-risk disease: 21.4 months (HR 0.54).

Novel combinations improve but do not overcome high-risk cytogenetics
Novel triplets should be used in high-risk disease

Avet-Loiseau H, et al. *Blood*. 2016;128:1174-1180.; Usmani S, et al. ASH 2016.; Chng W-J, et al. *Leukemia*. 2017 [Epub ahead of print].

Treatment History

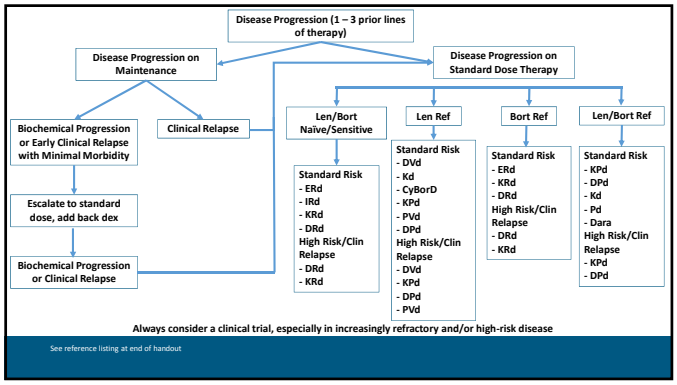
- What regimen(s) has the patient had in earlier lines of therapy?
- Is the disease refractory to a specific treatment?
  - Refractory per the IMWG guidelines: disease progression on or within 60 days of the last dose of therapy
    - Lack of response (stable disease) with prior therapy has been included in the definition of refractory in some studies
  - Carfilzomib has activity in bortezomib-refractory disease but the reverse has not been well studied
  - Pomalidomide has activity in lenalidomide-refractory disease but the reverse has not been well studied
- If refractory, did the patient have disease progression on standard dosing, reduced dosing due to prior toxicity, or maintenance dosing?
  - If dose-reduced for toxicity, what were the toxicities, and how could they be better managed?
  - For patients on maintenance, it is common practice to optimize therapy prior to changing to a non-cross-resistant regimen
    - Increase the dose of lenalidomide and reincorporate dexamethasone for a patient with progression on lenalidomide maintenance
    - A 3rd agent is often included in such a scenario (eg, elotuzumab) but patients with lenalidomide-refractory disease were not allowed to participate in the ELOQUENT-1 study and the additional impact of this maneuver has not been well studied

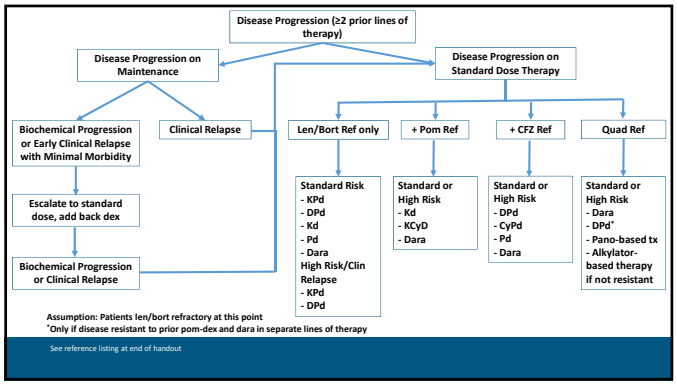
Other Factors to Consider

- What is the patient's preference? Are there logistical and/or socio-economic considerations to choice of regimen?
  - Len-dex-ixazomib for a patient who has difficulty traveling to an infusion center
- What options are available for later lines of therapy?
  - When len-dex-elo or len-dex-ixazomib are reasonable options, do we save dara for later lines of therapy?
    - Pomalidomide-dexamethasone-daratumumab, daratumumab monotherapy

Treatment Choice Algorithm

- First step
  - Review resistance pattern with prior therapy
  - Determine biochemical vs clinical relapse
  - Assess standard- vs high-risk disease
- Second step
  - Refine choice based on comorbidities and tolerability of previously used drug classes





Conclusions

- There are many right ways to treat patients with multiple myeloma in relapse
  - There are also wrong ways to do it
- As long as you have a PABST (review PMHx, adverse events, biochemical vs clinical relapse, standard- vs high-risk disease, treatment history), you will come to a good answer for your patient
- Use your local/regional myeloma specialists as a resource when questions arise about risk status, when to change treatment in biochemical relapse, optimal therapy when the preferred regimens may not be good options
- Always consider a clinical trial, especially in increasingly refractory and/or high-risk disease
  - We have gotten better at treating this disease but have a long way to go!

References for Algorithms

Bor=bortezomib (see also V below; VELCADE®)

Cy=cyclophosphamide

D/Dara=daratumumab (DARZALEX®)

d=dexamethasone

E=elotuzumab (EMPLICITI™)

K=carfilzomib (KYPROLIS®)

I=ixazomib (NINLARO®)

P=pomalidomide (POMALYST®)

R=lenalidomide (REVLIMID®)

V=bortezomib (see also Bor above; VELCADE®)

- CyBorD=cyclophosphamide-bortezomib-daratumumab
- CyPd=cyclophosphamide-pomalidomide-dexamethasone
- Dara=daratumumab
- DPd=daratumumab-pomalidomide-dexamethasone
- DRd=daratumumab-lenalidomide-dexamethasone
- DVd=daratumumab-bortezomib-dexamethasone
- ERd=elotuzumab-lenalidomide-dexamethasone
- Ird=ixazomib-lenalidomide-dexamethasone
- KCyD=carfilzomib-cyclophosphamide-daratumumab
- Kd=carfilzomib-dexamethasone
- KPd=carfilzomib-pomalidomide-dexamethasone
- KRd=carfilzomib-lenalidomide-dexamethasone
- Pd=pomalidomide-dexamethasone
- PVd=pomalidomide-bortezomib-dexamethasone

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- Chng WJ, et al. *Leukemia.* 2017 [Epub ahead of print - High risk disease boiology)
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- Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331. (Novel Lenalidomide/Dexamethasone-Based Therapy for Early Relapse; Lenalidomide- vs Bortezomib-Based Platform for Early Relapse; POLLUX: Safety)
- Dimopoulos M, et al. *Lancet Oncol.* 2017;17:30578-8. (Novel Lenalidomide-Free, Proteasome Inhibitor-Based Therapy for Early Relapse; Lenalidomide- vs Bortezomib-Based Platform for Early Relapse)
- Kumar S, et al. *Loncet Oncol.* 2016;17:328-346. (Biochemical vs Clinical Progression)
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- Usmani S, et al. *Blood.* 2016;128:37-44. (Daratumumab as Monotherapy for Relapsed/Refractory Multiple Myeloma)

Optimal Strategies for the Identification and Management of Treatment-Related Adverse Events

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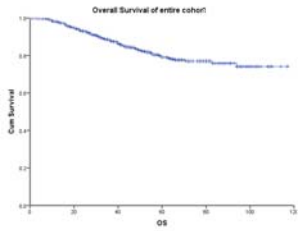
Speaker Disclosure

- Dr. Ajay Nooka has received honoraria as a consultant from Adaptive Biotechnologies, Novartis AG, Onyx, and Spectrum Pharmaceuticals, Inc.

Scope of the Problem



- Prevalence = incidence[1] (increasing) x duration[2] (life span increasing)
- Pool of myeloma patients will increase substantially
- Our responsibility as clinicians to spare patients from long-term treatment related toxicities
- Timely identification of treatment-related AEs helps tailor treatment regimens to facilitate uninterrupted delivery of therapy for better long-term outcomes and improved QOL

[1]Rajkumar SV, et al. *Lancet Oncol*. 2014;15(12):e538-548.;
[2]Nooka A, et al. unpublished data.

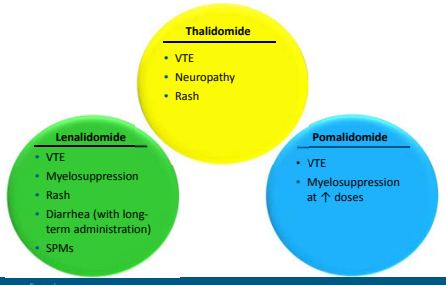
FDA-Approved Agents in RRMM

IMiDs	Proteasome Inhibitors	HDAC Inhibitors	Monoclonal Antibodies	Cytotoxic Agents
Thalidomide (50-200 mg PO q daily)	Bortezomib (1.3 mg/m^2 days 1, 4, 8 and 11 every 21 days IV/SC)	Panobinostat 20 mg days 1, 3, 5, 8, 10, 12 every 28 days	Elotuzumab 10 mg/kg days 1, 8, 15, 22 every 28 days	Cyclophosphamide 300 mg/m^2 days 1, 8, 15 every 28 days
Lenalidomide (25 mg PO q days 1-21/28 days)	Carfilzomib (20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16 every 28 days)		Daratumumab 16 mg/kg days 1, 8, 15, 22 every 28 days	Doxil
Pomalidomide (4 mg PO q days 1-21/28 days)	Ixazomib (4 mg PO days 1, 8, 15 every 28 days)			Melphalan

One size does not fit all...

RRMM patients may present with renal/hepatic insufficiency either due to the disease progression or due to other predisposing conditions (diabetes, hypertension, vascular disease, and use of nephro/hepato toxic drugs)

Treatment-Emergent AEs: IMiDs



SPMs=secondary primary malignancies

Risk Assessment for VTEs Among Patients Receiving IMiD-Based Therapy

- VTE prophylaxis for individual risk factors (eg, age or obesity) or myeloma-related risk factors (eg, immobilization or hyperviscosity)
  - If ≤1 risk factor present, aspirin 81-325 mg/day
  - If ≥2 risk factors present, LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin (target INR: 2-3)
  - NO DATA FOR DOACs
- VTE prophylaxis for myeloma therapy-related risk factors (eg, high-dose dexamethasone, doxorubicin, multi-agent chemotherapy)
  - LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin
- VTE secondary prophylaxis
  - Hold IMiD until acuity of the episode subsides
  - Continue LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin as long as patient remains on IMiD (no dose reduction necessary)

Palumbo A, et al. *J Clin Oncol.* 2014;32:587-600.;
Palumbo A, et al. *Leukemia.* 2008;22:414-423.

Myelosuppression and Infection Risk

- Myelosuppression is associated with the underlying disease as well as the drugs used to treat
  - Increased risk of infection due to hypogammaglobulinemia
  - Appropriate dose-modification guidelines are available in package inserts
  - Starting dose at dose level -1 when using combination therapies (eg, DPD)
  - Use prophylactic G-CSF if risk-benefit ratio favors administering treatment, and among patients with increased risk of neutropenic fevers
- Infection prophylaxis
  - Patients should remain up to date on appropriate vaccinations per CDC guidelines
  - VZV prophylaxis (when receiving PI combinations)
  - Use of prophylactic antibiotics is controversial and should only be used when warranted
  - Use of IVIG, if ≥3 infections in 6 months
  - Patient education emphasizing importance of alerting treating clinicians of potential infection can reduce unnecessary antibiotics

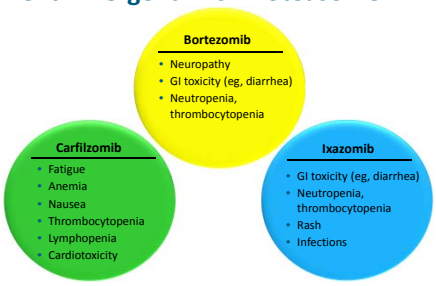
Mateos MV. *Cancer Treat Rev.* 2010;36 Suppl 2:S24-32.

Rash, Diarrhea, SPMs

- Rash (morbilliform, acneform, scaly, can be limited to scalp) occur during the first few months of therapy
  - Hold IMiDs for the rest of the cycle and re-challenge with steroid support for the next cycle (topical corticosteroids, alternate days of prednisone, etc.)
  - NOT AN ABSOLUTE CONTRAINDICATION
- Diarrhea
  - Essential to rule out other etiologies
  - Loperamide (2 mg PO with every BM, daily maximum of 16 mg) reduced bowel movement frequency
  - Colesevelam* (1875 mg PO twice daily) resulted in complete symptom resolution in 30% patients and symptom improvement in 85% patients
- SPMs
  - Continue or discontinue lenalidomide based on the risk-benefit assessment
  - Age appropriate screening

*Colesevelam is not FDA approved for this use in the U.S.
Nardone B, et al. *Clin Lymphoma Myeloma Leuk.* 2013;13(4):424-429.;
Watson M, et al. ASH 2014.

Treatment-Emergent AEs: Proteasome Inhibitors



Peripheral Neuropathy: Risk Factors and General Considerations

General Considerations

- Endocrine disorders
  - Hypothyroidism
  - Diabetes
- Nutritional disease
- Connective tissue disease
- Vascular disease
- Medications
- Herpes zoster
- Most common symptoms
  - Sensory deficits
  - Neuropathic pain

Disease- and Treatment-Related Factors

- Hyperviscosity syndrome
- Hypergammaglobulinemia
- Incidence of peripheral neuropathy in untreated patients: 39%
- Incidence of grade 3/4 CIPN with novel agents
  - Bortezomib: 26% to 44%
    - ↓ with weekly vs twice-weekly dosing
    - ↓ with SC administration
  - Thalidomide: 28% to 41%
    - ↑ with higher doses and prolonged therapy
  - Carfilzomib: overall 14%

Gleason C, et al. *J Natl Compr Cancer Netw.* 2009;7:971-979.;
Palumbo A, et al. *J Clin Oncol.* 2014;32:587-600.;
Kurtin S, et al. *J Adv Pract Oncol.* 2013;4:307-321.

Neuropathy: Bortezomib Modifications

Approaches	Comments
IFM approach[1]: vTD uses modified bortezomib dosing	• Bortezomib dose: 1 mg/m²/day, d 1, 4, 8, 11 • Associated with fewer grade 3/4 PN vs VD: 3% vs 11% (*P* = .03)
SC administration of bortezomib[2]	• Significantly lowers any grade or grade ≥3 PN with SC vs IV bortezomib (*P* = .044 and .03, respectively)
Weekly bortezomib[3]	• Weekly dose used for induction: 1.3 mg/m², d 1, 8, 15, and 22 (cycles 1-9) • Associated with lower all-grade and grade 3/4 sensory PN vs twice-weekly dosing

IFM=Intergroupe Francophone du Myélome; SC=subcutaneous; VD=bortezomib-dexamethasone; vTD=reduced-dose bortezomib-thalidomide-dexamethasone

[1]Moreau P, et al. *Blood*. 2011;118:5752-5758.
[2]Moreau P, et al. *Lancet Oncol*. 2011;12:431-440.
[3]Bringhen S, et al. *Blood*. 2010;116:4745-4753.

TOURMALINE-MM1: AEs after Median Follow-up of 23 Months

	IRd (N=361), %			Placebo-Rd (N=359), %		
Preferred terms	**All-grade**	**Grade 3**	**Grade 4**	**All-grade**	**Grade 3**	**Grade 4**
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathies	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism	8	2	<1	11	3	<1
Neutropenia	33	18	5	31	18	6

Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634.

TOURMALINE-MM1

Why is the risk of PN low in TOURMALINE-MM1 trial?

Key inclusion criteria:

- Confirmed diagnosis of MM
- Measurable disease by at least 1 of:
  - Serum protein electrophoresis
  - Urine protein electrophoresis
  - Free light chain (FLC) assay
- Received 1–3 prior treatments
- Relapsed and/or refractory disease
  - Including primary refractory patients (ie, patients refractory to all prior therapies)
  - Refractory = PD on treatment or within 60 days after last dose of therapy
- Creatinine clearance ≥30 mL/min
- Key exclusion criteria:
  - Refractory to previous proteasome inhibitor-based or lenalidomide-based treatment
  - Patients were not eligible if they had peripheral neuropathy of grade 1 with pain or grade 2 or higher

Dose modifications of ixazomib for PN

Peripheral Neuropathy	
Grade 1 Peripheral Neuropathy with Pain or Grade 2 Peripheral Neuropathy	• Withhold ixazomib until peripheral neuropathy recovers to Grade 1 or lower without pain or patient's baseline • Following recovery, resume ixazomib at its most recent dose
Grade 2 Peripheral Neuropathy with Pain or Grade 3 Peripheral Neuropathy	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming ixazomib • Following recovery, resume ixazomib at the next lower dose
Grade 4 Peripheral Neuropathy	• Discontinue treatment regimen

Recommended starting dose	First reduction to	Second reduction to	
4 mg	3 mg	2.3 mg	Discontinue

Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634.;
Ixazomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf*

Other Supportive Care: Neurotoxicity

- BiPN is cumulative, occurs subacutely
  - Patients with prior insults from underlying comorbidities may be at higher risk for PN
  - Frequent questioning, especially after the first 2 cycles, helps with early recognition of PN and prevents debilitating consequences
    - Formal neuro questionnaires are encouraged, at least a careful focused neuro H&P is mandatory
  - Gabapentin and/or SNRIs
  - Local care with lidocaine patches, capsaicin cream, acupuncture may help
- Autonomic neuropathy
  - Unless you think you will miss, needs prompt recognition
  - Midodrine and/or fludrocortisone therapy

Bortezomib-Induced Blepharitis

- Hold bortezomib based on the risk-benefit assessment
- Ophthalmology consult
- Doxycycline x 1 month until symptoms resolve

Nooka A, et al. Personal file.

Cardiotoxicity of Proteasome Inhibitors in the Treatment of Multiple Myeloma

- In a phase III trial of bortezomib, there was a 2% incidence of heart failure, including a number of cardiac deaths[1]
  - It is unclear if this rate of cardiotoxicity is above baseline
- Cardiotoxicity associated with carfilzomib needs to be better defined[2]

Table 5. Special analysis of grouped-term organ system adverse events.

Grouped adverse event, n, (%)	Any AE	≥Grade3	SAE
Any cardiac	116 (22.1)	50 (9.5)	41 (7.8)
Cardiac arrhythmia	70 (13.3)	12 (2.3)	11(2.1)
Cardiac failure	38 (7.2)	30 (5.7)	26 (4.9)
Ischemic heart disease	18 (3.4)	7 (1.3)	5 (1.0)
Cardiomyopathy	9 (1.7)	3 (0.6)	2 (0.4)
Any respiratory	363 (69.0)	54 (10.3)	34 (6.5)
Dyspnea	222 (42.2)	26 (4.9)	11 (2.1)
Cough	137 (26.0)	1 (0.2)	1 (0.2)
Pneumonia	67 (12.7)	55 (10.5)	52 (9.9)
Any grouped renal impairment	174 (33.1)	38 (7.2)	32 (6.1)
Increased serum Creatinine	127 (34.1)	14 (2.7)	7 (1.3)
Acute renal failure	28 (5.3)	23 (4.4)	22 (4.2)
Renal failure	20 (3.8)	6 (1.1)	7 (1.3)

[1]Richardson PG, et al. *N Engl J Med*. 2005;352:2487-2498.
[2]Siegel DS, et al. *Haematologica*. 2013;98(11):1753-1761.

Carfilzomib in RRMM: Managing Cardiopulmonary Risk

- Carfilzomib may cause cardiovascular toxicity such as hypertension (in around 15%) and cardiac failure (in 5%)
- Usually reversible upon drug discontinuation
- Risk factor evaluation: patients with pre-existing cardiac disease are at increased risk for cardiotoxicity
  - Systolic heart failure
  - Coronary artery disease/prior MI
  - Hypertension
  - Advanced valvular disease

Bringhen S, et al. ASH 2016:1145.

Carfilzomib in RRMM: Managing Cardiopulmonary Risk

- BP monitoring 24 hrs/day
  - Before and after carfilzomib administration
  - Patient at-home diary
- BP target: <140/90 mmHg
- If BP ≥140/90 mmHg or diastolic BP ↑ ≥20 mmHg, carfilzomib withheld
  - Use RAAS inhibitors, calcium channel blockers and/or diuretics, or β-blockers
- Infusion times should be over 30 minutes and consistent, regardless of dose
- Clinically relevant SE
  - Non-cardiac, non-pulmonary dyspnea may improve with dose reduction and prolonged infusion times
  - Hypertension
- Heart failure: low incidence and important
- Anecdotally, patients recovery EF over several months post discontinuation with minimal long-term sequelae
  - Carfilzomib treatment may be re-challenged based on risk-benefit assessment
- Importance of co-management with cardio-oncologist

Bringhen S, et al. ASH 2016:1145.

Treatment-Emergent AEs: HDAC Inhibitors

Panobinostat

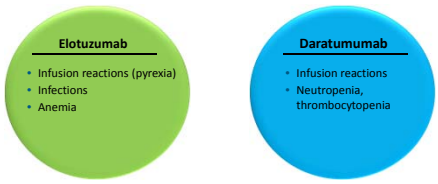
- Fatigue
- GI toxicity (eg, diarrhea)
- Neutropenia, thrombocytopenia

Management of AEs with HDAC Inhibitors

- Diarrhea
  - Higher grade 3 diarrhea seen in combination with bortezomib – choose carfilzomib as a partner (Berdeja, Kaufman car/pan) or decrease frequency of bortezomib, SC administration of bortezomib
  - Decrease dosing of panobinostat and start loperamide
- Fatigue
  - Alternate schedule: deliver panobinostat during week 1 and week 3 of the cycle instead of week 1 and 2 consecutively
  - Dose reduction of panobinostat and usage of stimulants as appropriate
- Thrombocytopenia
  - Alternate schedule: deliver panobinostat during week 1 and week 3 of the cycle, using an alternate partner carfilzomib
  - NO role for TPO mimetics

San Miguel J, et al. *Blood.* 2014;124(21):4742.;
Richardson PG, et al. *Blood.* 2014;124(21):2120.

Treatment-Emergent AEs: Monoclonal Antibodies



Infusion-Related Reactions

- Infusion-related reactions (IRR) constitute the most common adverse events of elotuzumab and daratumumab
  - Approximately 50% of MM patients receiving elotuzumab and daratumumab will have an IRR:
    - Majority are mild, occur during the first cycle
    - Steroids, acetaminophen, antihistamines as premeds
    - Infusion initiated in 1,000 mL at 50 mL/hr and escalated to escalated to 200 mL/hr
  - If > grade 2 IRR, temporarily hold infusion and restart at 50 mL/hr with goal to escalate to 200 mL/hr
  - For prevention of delayed IRR, oral corticosteroids (20 mg methylprednisolone or equivalent) should be administered for two days after the infusion

Voorhees P. ASH 2015:1827;
Usmani S. ASH 2016.

Infusion-Related Reactions (continued)

- NO DOSE REDUCTIONS NEEDED for both monoclonal antibodies while re-challenging for next cycle
- PERMANANTLY DISCONTINUE for recurrent IRRs (<1% of patients discontinued in the original studies)
- May split the dosing of daratumumab to 8 mg/kg x 2 consecutive days
- SC daratumumab (15 cc) may reduce the time of administration and IRRS

Voorhees P. ASH 2015:1827;
Usmani S. ASH 2016.

Use of Montelukast to Reduce IRR

Table 4. Infusion Related Reactions

	Infusion Related Reactions (N=348)
Grade <3 IRRs	8%
Percentage of Patients with IRRs	
First infusion	56%
Second infusion	2%
All subsequent infusions	2%
Respiratory or thoracic symptoms	31%
Cough	14%
Dyspnea	9%
Throat irritation	6%
Nasal congestion	5%
Bronchospasm	2%

Table 5. Observed IRRs in Patients With and Without Montelukast Therapy

	Montelukast 10 mg as Pre-Infusion (n=50)	No Montelukast Given as Pre-Infusion (n=298)
IRR rate at first infusion	38.0%	38.3%
Respiratory symptoms	20%	32%
Gastrointestinal symptoms	4%	11%
Chills	14%	14%
Median time for first infusion (hours)	6.7	7.6

*Montelukast is not FDA approved for this use in the U.S.
Chari A, et al. ASH 2016:2142.

Myelosuppression

- Myelosuppression is associated with the underlying disease due to the refractory nature of the disease by the time patient is receiving the drug
  - NO DOSE REDUCTION FOR MONOCLONAL ANTIBODIES
  - When used in combinations, dose of the myelosuppressive combination agent can be at started at dose level-1 (eg, DPD)
  - Use prophylactic G-CSF if risk-benefit ratio favors administering treatment, and among patients with increased risk of neutropenic fevers
  - Routine use of prophylactic antibiotics should be discouraged
  - Supportive PRBC transfusions per institutional parameters

Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.;
Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.

Daratumumab Interference

Problem

- Daratumumab is a human IgG1 kappa monoclonal antibody that targets cells expressing CD38
- CD38 is not only expressed on the myeloma cells but also on the red blood cells
- DARA binding to RBCs results in pan-reactivity on RBC panel testing using an indirect antiglobulin test

Solution

- Treating reagent RBCs with dithiothreitol (DTT), which removes DARA, is a robust method to negate the DARA interference
  - Allows for accurate antibody testing and enabling the safe provision of blood to DARA-treated patients
- Another approach to prevent DARA binding is neutralization of free DARA in plasma by adding soluble CD38 or an anti-DARA idiotype
- Obtaining a red cell phenotype prior to initiating DARA treatment and providing phenotypically matched blood thereafter to avoid resultant difficulties in new alloantibody identification and delays in providing compatible PRBCs

Chari A. *Blood*. 2015;126:3571.;
Chapuy CI, et al. *Transfusion*. 2015;55(6pt2):1545-1554.

Suggested Empiric Age-Adjusted Dose Reduction in Patients with Myeloma

Agent	Younger Than 65 Years	65-75 Years	Older Than 75 Years
Dexamethasone	40 mg/day on Days 1-4, 15-18 Q4W or Days 1, 8, 15, 22 Q4W	40 mg/day on Days 1, 8, 15, 22 Q4W	20 mg/day on Days 1, 8, 15, 22 Q4W
Melphalan	0.25 mg/kg on Days 1-4 Q6W	0.25 mg/kg on Days 1-4 Q6W or 0.18 mg/kg on Days 1-4 Q4W	0.18 mg/kg on Days 1-4 Q6W or 0.13 mg/kg on Days 1-4 Q4W
Cyclophosphamide	300 mg/m^2 on Days 1, 8, 15, 22 Q4W	300 mg/m^2 on Days 1, 8, 15 Q4W or 50 mg/day on Days 1-21 Q4W	50 mg/day on Days 1-21 Q4W or 50 mg/day QOD on Days 1-21 Q4W
Thalidomide	200 mg/day	100 mg/day or 200 mg/day	50 mg/day to 100 mg/day
Lenalidomide	25 mg/day on Days 1-21 Q4W	15-25 mg/day on Days 1-21 Q4W	10-25 mg/day on Days 1-21 Q4W
Bortezomib	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 Q3W	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 Q3W or on Days 1, 8, 15, 22 Q5W	1.0-1.3 mg/m^2 bolus on Days 1, 8, 15, 22 Q5W

Palumbo A, et al. *N Engl J Med*. 2011;364:1046-1060.

Renal Dose Modifications: IMiDs

Drug	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Thalidomide[1] 50-200 mg PO q daily	100%	100%	100%	100%
Lenalidomide*[2] 25 mg PO q days 1-21/28 days	25 mg once daily	10 mg once daily	15 mg every alternate day	5 mg once daily
Pomalidomide[3] 4 mg PO q days 1-21/28 days	4 mg once daily	4 mg once daily	4 mg once daily	3 mg once daily

*Lenalidomide is primarily excreted unchanged by the kidney
IMiDs=immunomodulatory drugs; ESRD=end-stage renal disease; HD=hemodialysis; PO=by mouth

[1]Thalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020785s055lbl.pdf*.
[2]Lenalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf*.
[3]Pomalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf*.

Hepatic Dose Modifications: IMiDs

Drug	Normal	Mild	Moderate	Severe
Thalidomide[1] 50-200 mg PO q daily	No dedicated study done			
Lenalidomide*[2] 25 mg PO q days 1-21/28 days	No dedicated study done			
Pomalidomide[3] 4 mg PO q days 1-21/28 days	4 mg once daily	3 mg once daily	3 mg once daily	2 mg once daily

*Lenalidomide is primarily excreted unchanged by the kidney

[1]Thalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020785s055lbl.pdf.*
[2]Lenalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf.*
[3]Pomalidomide Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf.*

Renal Dose Modifications: PIs

Drug	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Bortezomib[1] 1.3 mg/m^2 days 1, 4, 8 and 11 every 21 days IV/SC	100%	100%	100%	100%
Carfilzomib[2] 20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16 every 28 days	100%	100%	Hold until renal functions stabilize and start at 1 dose level reduction	Hold until renal functions stabilize and start at 1 dose level reduction
Ixazomib[3] 4 mg PO days 1, 8, 15 every 28 days	4 mg	4 mg	3 mg	3 mg

PIs=proteasome inhibitors; IV=intravenous; SC=subcutaneous

[1]Bortezomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf.*
[2]Carfilzomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf.*
[3]Ixazomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.*

Hepatic Dose Modifications: PIs

Drug	Normal	Mild	Moderate	Severe
Bortezomib*[1] 1.3 mg/m^2 days 1, 4, 8 and 11 every 21 days IV/SC	100%	100%	Reduce to 0.7 mg/m^2 in 1st cycle; escalation to 1 mg/m^2 in subsequent cycles based on tolerability	Reduce to 0.7 mg/m^2 in 1st cycle; escalation to 1 mg/m^2 in subsequent cycles
Carfilzomib[2] 20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16 every 28 days	100%	75%	75%	Has not been studied in this population
Ixazomib[3] 4 mg PO days 1, 8, 15 every 28 days	100%	100%	75%	75%

*Bortezomib is metabolized by liver and clearance may decrease in patients with hepatic impairment

[1]Bortezomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf.*
[2]Carfilzomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf.*
[3]Ixazomib Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.*

Renal and Hepatic Dose Modifications: Monoclonal Antibodies

Renal	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Elotuzumab[1] 10 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	100%
Daratumumab[2] 16 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	100%

Hepatic	Normal	Mild	Moderate	Severe
Elotuzumab[1] 10 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	Has not been studied in this population
Daratumumab[2] 16 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	Has not been studied in this population

[1]Elotuzumab Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf.*
[2]Daratumumab Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761036s000lbl.pdf.*

Renal and Hepatic Dose Modifications: Other (HDAC Inhibitor and Cyclophosphamide)

Renal	Mild CrCl ≥50 to <80 mL/min	Severe CrCl <30 mL/min	ESRD or HD
Panobinostat[1] 20 mg days 1, 3, 5, 8, 10, 12 every 28 days	100%	100%	Has not been studied in this population

Hepatic	Normal	Mild	Moderate	Severe
Panobinostat 20 mg days 1, 3, 5, 8, 10, 12 every 28 days	100%	75%	50%	Not recommended

Renal	CrCl >10 mL/min	CrCl <10 mL/min	ESRD or HD
Cyclophosphamide*[2] 300 mg/m^2 days 1, 8, 15 every 28 days	100%	75%	50%

Hepatic	Serum bilirubin 3.1-5 mg/dL or transaminases >3 x ULN	Serum bilirubin >5 mg/dL
Cyclophosphamide*[3] 300 mg/m^2 days 1, 8, 15 every 28 days	75%	Avoid use

HDAC=histone deacetylase
*No dosing adjustments provided in the package insert.

[1]Panobinostat Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf.*
[2]Arnolf I, et al. *Euro J Cancer*. 2007;43:14-34.
[3]Floyd J, et al. *Semin Oncol*. 2006;33(1):50-67.

Conclusions

- Identifying treatment-emergent adverse events is crucial
  - Awareness of AEs associated with individual agents
- Appropriate dose modifications are needed to prevent long-term toxicity
  - At the same time, not compromising on the efficacy is the key for better long-term outcomes
- **One size does not fit all…**
- Identifying the need for dose modifications for elderly with poor reserve
- Identifying the right agent for patients' renal or hepatic comorbidities, and the need for dose modifications, will limit toxicities and enable delivery of treatments without interruptions