Treatment of Multiple Myeloma in First Relapse

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TOPA

Disclosures

- Nothing to disclose

Objectives

- Review initial treatment recommendations and considerations for multiple myeloma (MM)
- Compare recent literature on multi-agent treatment regimens for myeloma in first relapse
- Assess toxicity profile and important supportive considerations for novel agents
- Apply novel treatment strategies to patient cases based on literature supported outcomes as well as patient-specific comorbidities

Multiple Myeloma

- Accounts for ~15% of US hematologic malignancies
  - 1.8% of overall cancers
- ~30,330 new cases in US in 2016
  - ~12,650 associated deaths
  - Median age at diagnosis is 69 years old
- Rates of new diagnosis rising each year over past decade at the same rate as annual deaths over the same period
  - Remains an incurable disease

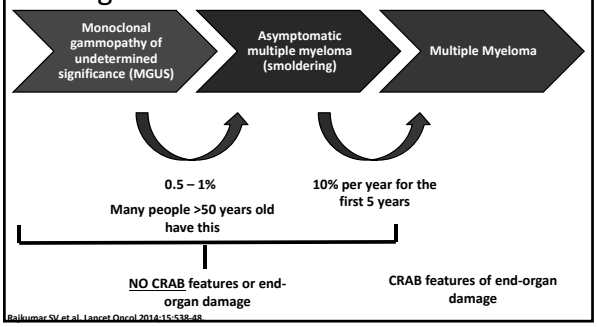
National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.

Multiple Myeloma

- Immortalized malignant plasma cells
  - Adhere and accumulate in bone marrow
  - Lead to bone destruction and marrow failure
  - Production of M protein
- Exact etiology not completely defined
  - Overexpression of apoptotic genes (ex. p53)
  - Molecules stimulate clonal growth (ex. IL-6)

National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.
Rajkumar SV et al. Lancet Oncol 2014;15:538-48.

Malignant Plasma Cells



Rajkumar SV et al. Lancet Oncol 2014;15:538-48.

International Myeloma Working Group Diagnostic Criteria for Plasma Cell Dyscrasia

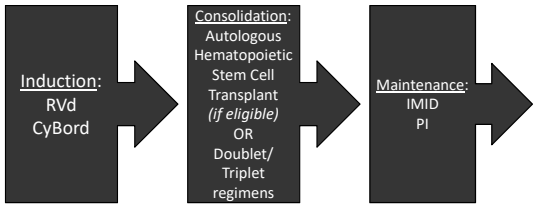
Diagnosis	M-protein	Bone Marrow Plasma Cells	Myeloma-defining events	Biomarkers of malignancy
MGUS	<3g/dL	<10%	No	None
Solitary Plasmacytoma of Bone	Not required	No clonal PCs	No	Not defined
Solitary Plasmacytoma of Bone with Minimal Marrow Involvement	Not required	<10%	No	Note defined
Smoldering myeloma	≥3g/dL in serum or >500mg/24h in urine OR >10-60% PCs		No	None
Multiple Myeloma	Not required	≥10% (or <10% if plasmacytoma + CRAB or biomarker of malignancy or ≥1 plasmacytoma	Present	One of the following: • Clonal bone marrow PCs>60% • Involved:uninvolved SFLC ratio >100 • >1 focal lesion on MRI studies

*CRAB criteria for myeloma-defining events
1. HyperCalcemia. Serum calcium >1mg/dL higher than the ULN or >11mg/dL
2. Renal insufficiency. CrCl <40ml/min or SCr >2mg/dL
3. Anemia. Hgb <10g/dL or >2g/dL below the LLN
4. Bone lesions. ≥1 osteolytic lesion on skeletal radiography, CT, or PET-CT

National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.
Rajkumar SV et al. Lancet Oncol 2014;15:538-48.

Frontline Treatment Paradigm

- Goal to achieve a deep response, complete remission, and optimize progression-free survival



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Rajkumar SV et al. Lancet Oncol 2014;15:538-48.

Prognosis

- Survival improved notably in recent years
  - Introduction of immunomodulatory drugs (IMIDs) and proteasome-inhibitors (PIs) initially in relapsed disease
  - With transplant PFS >5 years and OS >10 years is a reality
- 5 year survival rate in 2003 estimated as 34%
  - More recent statistics (2016) estimate 49%
  - Considered a chronic condition

National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.
Rajkumar SV et al. Lancet Oncol 2014;15:538-48.
Kumar S et al. Lancet Oncol. 2016; 17: e328-e346.

MM as a Chronic Disease

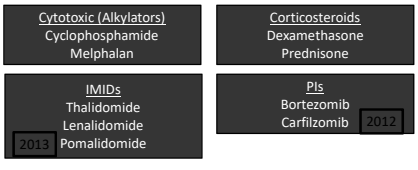
- Despite improving prognosis remains incurable
  - Majority of patients relapse at which point disease is difficult to manage
- Finding effective treatment at each consecutive relapse is CRITICAL for prolonging overall survival
  - Difficult with increasing drug resistance and decreasing remission duration with each successive regimen

National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.
Blade J, et al. Blood. 2015; 125(10): 1532-1540.
Laubach J, et al. Leuk. 2016; 30(5): 1005-1017.

An Evolving Paradigm

National Comprehensive Cancer Network. Multiple Myeloma V3.2017. Accessed 8/18/2017.

An Evolving Paradigm



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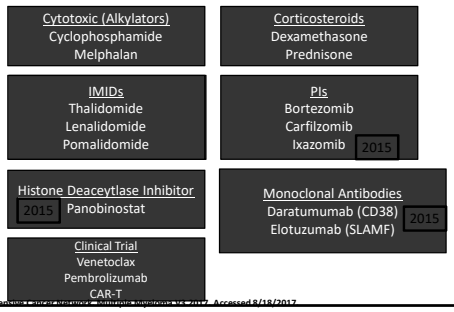
An Evolving Paradigm



National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. NCCN.org. Accessed 8/18/2017.

The New Novel Agents for MM

Options in relapse disease

TOPA

Ixazomib

- 20S reversible proteasome inhibitor, oral
- Approved after at least 1 prior line of therapy
- Pearls
  - Adherence – oral regimens increasingly complicated
    - Taken on empty stomach, 1 hour before or 2 hours after meals
  - Peripheral neuropathy – generally not expected to worsen
  - Diarrhea
  - Thrombocytopenia
  - Back pain

Ninlaro® [package insert]. Cambridge, MA. Milineaum Pharmaceuticals. 11/2015.

TOURMALINE-MM1

- Lenalidomide-dexamethasone triplet
  - Phase 3 RD ± **ixazomib** for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - IRD, 28-day cycle: ixazomib 4mg PO days 1, 8, and 15; lenalidomide 25mg days 1-21, dexamethasone 40mg days 1, 8, 15, 22
- PFS significantly longer with ixazomib (IRD) arm – study reported at 1st pre-specified analysis
  - Serious adverse events similar in both groups
  - Patient reported quality of life similar in both groups

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

Elotuzumab

- Monoclonal antibody targets CS-1 (or SLAMF7)
- Approved for after at least 1 prior therapy
- Pearls:
  - Infusion reactions primary concern
    - Premedication regimen (30-90 minutes prior): diphenhydramine (25-50mg), ranitidine (50mg), acetaminophen (650-1000mg)
    - Split PO and IV dex dosing
  - Lymphopenia, leukopenia, thrombocytopenia
  - Electrolyte changes

Empliciti™ [package insert]. Princeton, PA: Bristol-Myers Squibb. 5/2017.

ELOQUENT-2

- Lenalidomide-dexamethasone triplet
  - RD ± **elotuzumab** for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - ERD, 28-day cycle: elo 10mg/kg weekly cycles 1 & 2 then days 1 & 15; len 25mg daily days 1-21; dex 40mg on weeks without elo and 8mg + 28mg on elo days
- PFS and ORR significantly improved in ERD group at the interim analysis
  - Fewer complete responses seen in ERD group
  - Similar safety profiles, ERD with increased risk of herpes zoster and risk of infusion reactions
  - Patient reported quality of life similar in both groups

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

Carfilzomib

- 20S irreversible proteasome inhibitor
- Approved after at least 1 prior line of therapy
- Pearls:
  - Dosing escalation, various dosing schemes (often multiday; 20mg/m2 followed by doses 27-70mg/m2)
  - IV, PO dex with each dose (myeloma dosing)
  - Pre- and post-hydration considerations
  - Cardiotoxicity

Kyprolis® [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals: 5/2017.

ENDEAVOR

- Bortezomib combination
  - Phase III study of bortezomib-dex vs **carfilzomib**-dex for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - KD, 28-day cycle: carfilzomib twice weekly for 3 weeks with 20-56 dosing scheme; dex 20mg twice weekly
  - VD, 21-day cycle: bortezomib 1.3mg/m2 days 1, 4, 8, 11; dex 20mg days 1, 2, 4, 5, 8, 9, 11, 12
- PFS significantly improved in KD group at interim analysis
  - PFS improvement in subgroups with previous bortezomib
  - Higher ORR with KD, no difference at this time in OS

Dimopoulos M et al. Lancet Oncology 2016;17:27-38.

ASPIRE

- Lenalidomide-dexamethasone triplet
  - RD ± **carfilzomib** for relapsed and relapsed/refractory MM patients having received 1-3 prior lines of therapy
  - KRD, 28-day cycle: carfilzomib twice weekly for 3 weeks (cycles 1-12) and every other week after (cycles 13-18) then stopped with 20-27 dosing scheme; len 25mg daily days 1-21; dex 40mg once weekly
- PFS significantly improved in KRD group at interim analysis
  - Higher ORR with KRD
  - Median OS not reached in either group at interim
  - Similar safety profiles between groups
  - Patient reported higher quality of life similar in KRD group

Stewart A et al. N Engl J Med 2014;372:142-152.

Daratumumab

- Monoclonal antibody targets CD38
- Indicated in combination with IMID or PI after at least 1 prior line of therapy
  - Monotherapy after at least 3 prior lines of therapy (original approval)
- Pearls:
  - Disrupts Coombs test, interferes with antibody screening and cross matching – important to screen prior to administration
  - High rate of infusion reactions (specifically 1st dose)
    - Infusion duration, volume, premedications (post-steroid?)
    - (Not on package insert) premdicate with montelukast
  - Neutropenia
  - Diarrhea

Darzalex® [package insert]. Horsham, PA. Janssen Biotech: 6/2017.

POLLUX

- Lenalidomide-dexamethasone triplet
  - RD ± **daratumumab** for relapsed and relapsed/refractory MM patients having received ≥1 prior line of therapy
  - DRD, 28-day cycles: dara 16mg/kg weekly for 2 cycles, every other week cycles 3-6, week 1 only thereafter; len 25mg daily days 1-21; dex 40mg weekly
- Median PFS was not reached in DRD group, significantly improved
  - ORR improved in DRD, OS comparison ongoing
  - Daratumumab with a notable side effect profile but manageable with less DRD discontinuation

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

CASTOR

- Bortezomib combination
  - Phase III study of bortezomib-dex ± **daratumumab** for relapsed and relapsed/refractory MM patients having received ≥1 prior line of therapy
  - DVD, 21-day cycles: dara 16mg/kg weekly for 3 weeks in cycles 1-3, once every 3 weeks cycles 4-8, monthly thereafter; bor 1.3mg/m2 days 1, 4, 8, 11 cycles 1-8; dex 20mg days 1, 2, 4, 5, 8, 9, 11, 12
- Median PFS was not reached in DVD group, significantly improved
  - ORR improved in DVD, OS comparison ongoing

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

EQUULEUS

- Pomalidomide triplet combination
  - Phase 1b study, open-label study of daratumumab combined with multiple therapies, results of **dara** + pomalidomide-dex reported in 103 cases of relapsed/refractory MM ≥1 line of therapy
  - DPd, 28-day cycle: dara 16mg/kg weekly for 3 weeks in cycles 1-2, once every 3 weeks cycles 3-6, monthly thereafter; pom 4mg days 1-21; dex 40mg weekly
- Median PFS 8.8 months, 12-month PFS 42%
  - ORR 60% (42% VGPR, CR, sCR)

Chari A et al. Blood 2017; 130(8): 974-981

Panobinostat

- Histone deacetylase (HDAC) inhibitor
  - Promotes immune function and decreases malignant proliferation
- Approved in combination with PI and dex after at least 2 prior regimen
- Pearls:
  - Diarrhea (BBW)
    - Managed with recommended dosing and aggressive antidiarrheals
  - Thrombocytopenia, neutropenia, lymphopenia
  - Fatigue
  - Peripheral neuropathy
  - ECG changes (QTc prolongation; BBW)

Farydak® [package insert]. East Hanover, NJ. Novartis Pharmaceuticals: 6/2016.

PANORAMA

- Bortezomib combination
  - Phase III study of bortezomib-dex ± **panobinostat** for relapsed and relapsed/refractory MM patients having received >1-3 prior line of therapy
  - PVD, 21-day cycles: pano 20mg 3 times weekly for first 2 weeks; bor 1.3mg/m2 day 1, 4, 8, 11; dex 20mg days of and days after bor; bor schedule adjusted to weekly after 8 cycles
- PFS significantly longer in the PVD group
  - Duration of treatment shorter in PVD group
  - Trend towards improved OS in PVD group
  - Notable differences in grade 3/4 adverse events with PVD

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

Comparing treatment options

Assessing studied combination therapies

Lenalidomide-Dex Triplets

	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, mos	NR	NR	NR	NR	2-yr 65%	2-yr 73.3%	1-yr 86.6%	1-yr 92.1%

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

*Statistically significant

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

Improving PI Combinations

	ENDEAVOR		CASTOR	
Treatment Arm	VD	KD	VD	DVD
Overall Response Rate	63%	77%	63.2%	82.9%
≥Very Good Partial Response Rate	29%	54%	29%	59.1%*
Median Progression-Free Survival, mos	9.4	18.7	7.2	Not yet reached*
PFS HR	0.53		0.39	
Median Overall Survival	NR	NR	NR	NR

DVD=daratumumab-bortezomib-dexamethasone, KD=carfilzomib-dexamethasone, NR=not reported, pt=patient, VD=bortezomib-dexamethasone

*Statistically significant

Dimopoulos M et al. Lancet Oncology 2016;17:27-38.
Palumbo A et al. N Engl J Med 2016;375:754-766

Len- vs Bor-based Combinations

	MM1	ELO-2	ASPIRE	POLLUX	ENDEAV	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%
Med PFS, mos	14.7	14.9	17.6	1-yr 60.1%	9.4	7.2
Med PFS, mos	NR	NR	2-yr 65%	1-yr 86.6%	XX	NR

- The lenalidomide-dexamethasone doublet has outperformed the bortezomib-dexamethasone doublet across phase III studies
- No head-to-head comparisons

Moreau P et al. N Engl J Med 2016;374:1621-1634.
Lonial S et al. N Engl J Med 2015;373:621-631
Dimopoulos M et al. Lancet Oncology 2016;17:27-38
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Prior Treatment Exposure

HR for PFS				
Treatment Regimen	PI naïve	PI exposed	IMID naïve	IMID exposed
IRD	0.75	0.74	0.70	0.74
KRD	0.73	0.70	0.69	0.80 (Len)
KD	0.48	0.56	0.38	0.60
DVD	0.25	0.46	0.50	0.38
ERD	0.72	0.68	0.78	0.64 (Thal)
DRD	0.35	0.37	0.36	0.42 (Len)

Moreau P et al. N Engl J Med 2016;374:1621-1634.
Lonial S et al. N Engl J Med 2015;373:621-631
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Resistance Profile

HR for PFS		
Treatment Regimen	Lenalidomide Refractory	Bortezomib Refractory
IRD	N/A	N/A
KRD	0.64 (IMID Refractory)	0.80
KD	0.80	0.37
DVD	0.50 (IMID Refractory)	N/A
ERD	NR	NR
DRD	N/A	0.50

Moreau P et al. N Engl J Med 2016;374:1621-1634.
Lonial S et al. N Engl J Med 2015;373:621-631
Dimopoulos M et al. Lancet Oncology 2016;17:27-38.
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High Risk Disease Considerations

	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).

Moreau P et al. N Engl J Med 2016;374:1621-1634.
Lonial S et al. N Engl J Med 2015;373:621-631
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Considering Safety Profiles

Toxicities to individualize therapy selection

TOPA

TOURMALINE-MM1 Safety

	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
Rash	**36**	**5**	**23**	**2**
Fatigue	47	8	39	8
Fever	37	3	25	3
Peripheral neuropathy*	**27**	**2**	**22**	**2**

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

ELOQUENT-2 Safety

	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

ENDEAVOR Safety

	KD			VD		
AEs (%)	**Gr1/2**	**Gr3**	**Gr4**	**Gr1/2**	**Gr3**	**Gr4**
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**
CHF	**3**	**4**	**<1**	**1**	**1**	**<1**
Acute renal failure	4	3	<1	2	2	<1
Peripheral neuropathy	**17**	**2**	**0**	**43**	**8**	**<1**

Dimopoulos M et al. Lancet Oncology 2016;17:27-38.

ASPIRE Safety

	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
Muscle spasms	26.5	1.0	21.1	0.8
Hyopkalemia	**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 A et al. N Engl J Med 2014;372:142-152.

POLLUX Safety

	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

CASTOR Safety

	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

Selecting therapy

Tailoring therapy based on literature and patient factors

How to Choose?

- Is the patient better suited for a lenalidomide- or non-lenalidomide-based therapy?
- Does the patient have symptomatic progression?
- Does the patient have high risk disease biology?
- Toxicity?

Miscellaneous Factors

- Patient's preference
- Logistical/socio-economic considerations to choice of regimen
  - i.e. all-oral regimen for patients limited by travel and distance
- Options for later lines of therapy

Candidates for Len-based Therapy

- Disease progression on proteasome inhibitor-based regimen
- Disease progression on bortezomib maintenance therapy
- Disease progression on no treatment after a prior course of therapy of defined duration
- Intolerant to bortezomib
- Lenalidomide-sensitive or naïve disase

Len-based therapy selection

- Clinical progression:
  - len-dex-carfilzomib or len-dex-daratumumab
- Bridge to salvage first or second autologous stem cell transplant:
  - len-dex-carfilzomib or len-dex-daratumumab
  - Limited data on feasibility of stem cell collection after dara-RD
- High-risk disease (clinical or biochemical progression):
  - len-dex-carfilzomib or len-dex-daratumumab
- Biochemical progression, standard risk disease:
  - may consider len-dex-elotuzumab
  - May consider saving carfilzomib and daratumumab for later lines

Len-based therapy selection

- Notable comorbidities:
  - Significant cardiopulmonary disease (CHF, pulmonary HTN): consider alternative to carfilzomib
  - Significant asthma/COPD: consider alternative to daratumumab or closer monitoring
- Refractoriness to prior treatment
  - Avoid ixazomib in a PI refractory patient, consider len-dex-dara over len-dex-car in PI refractory patient
- Cost and burden of care considerations
- None of these regimens tested rigorously in len-refractoriness
  - Adding car, ixaz, elo, or dara while adding back dex and increasing dose of len in patient with indolent biochemical progression on len maintenance is reasonable

Candidates for non-Len-based Therapy

- Disease progression on lenalidomide-based regimen
- Clinical disease progression on lenalidomide maintenance therapy
- Intolerance to lenalidomide

Non-Len-based therapy selection

- Bortezomib-dexamethasone no longer an appropriate standard of care
  - Select situations when not a good candidate for alternatives
- Car-dex or bor-dex-dara appropriate for clinical or biochemical progression
  - Consider off-label cyclophosphamide/PI-based triplet for clinical progression (CyBorD, Car-Cy-dex)
  - Consider off-label pom-based triplets for clinical progression especially in high risk disease (PVD, KPD, Pom-Dara-dex)
- Co-morbidities
  - Pre-existing neuropathy: consider alternative to bortezomib
  - Significant cardiopulmonary disease: consider alternative to carfilzomib
  - Severe COPD/asthma: consider alternative to dara or monitor

Non-Len-based therapy selection

- Role of bor-dex-panobinostat
  - Bor-dex or car-dex + pano used more commonly off-label in pan-resistant patients (≥2 prior therapies) with preserved PS
- Resistance pattern
  - Avoid bor-dex-dara in PI-resistant disease
  - Car-dex is reasonable in patients with len-, bor-, or ixazomib-resistant disease
- High risk cytogenetics
  - Bor-dara-dex or off-label pom-based triplet (Car-Pom-dex, Pom-Dara-dex)

Symptomatic Progression

- Myeloma Urgencies/Emergencies
  - Hypercalcemia
  - New or worsening lytic bone lesions
  - Progressive renal dysfunction
- Urgent/emergent, symptomatic relapse requires therapy that has a high likelihood of producing a deep response
  - First consideration: KRD and DRD (≥VGPR in 70-75%)
  - Second consideration: DVD and KD (≥VGPR in 55-60%)
  - Third consideration: IRD and ERD (≥VGPR in 35-50%)
    - Consider for biochemical or clinical relapse with isolated anemia

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Future of MM therapy

- Optimizing frontline therapy
- Cost and availability
- Treatment duration
  - Particularly in first relapse where long remission seen
- More novel therapies and approaches in the pipeline
- Pharmacists involvement

Conclusions

- First-generation novel agents dramatically improved OS in MM
- Finding effective treatment at each consecutive relapse critical for prolonging OS
- Triplet therapy preferred in a patient-specific, risk-adapted approach to therapy selection at relapse
- Treatment paradigms in MM continuing to evolve
- Pharmacy team can play a huge role in optimizing outcomes

Treatment of Multiple Myeloma in First Relapse

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