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CCO LIVE

Strategies to Assist Patients With Treatment Decision Making and Managing Adverse Events of Multiple Myeloma

Saturday, September 7, 2019

GLONS Day of Education Meeting

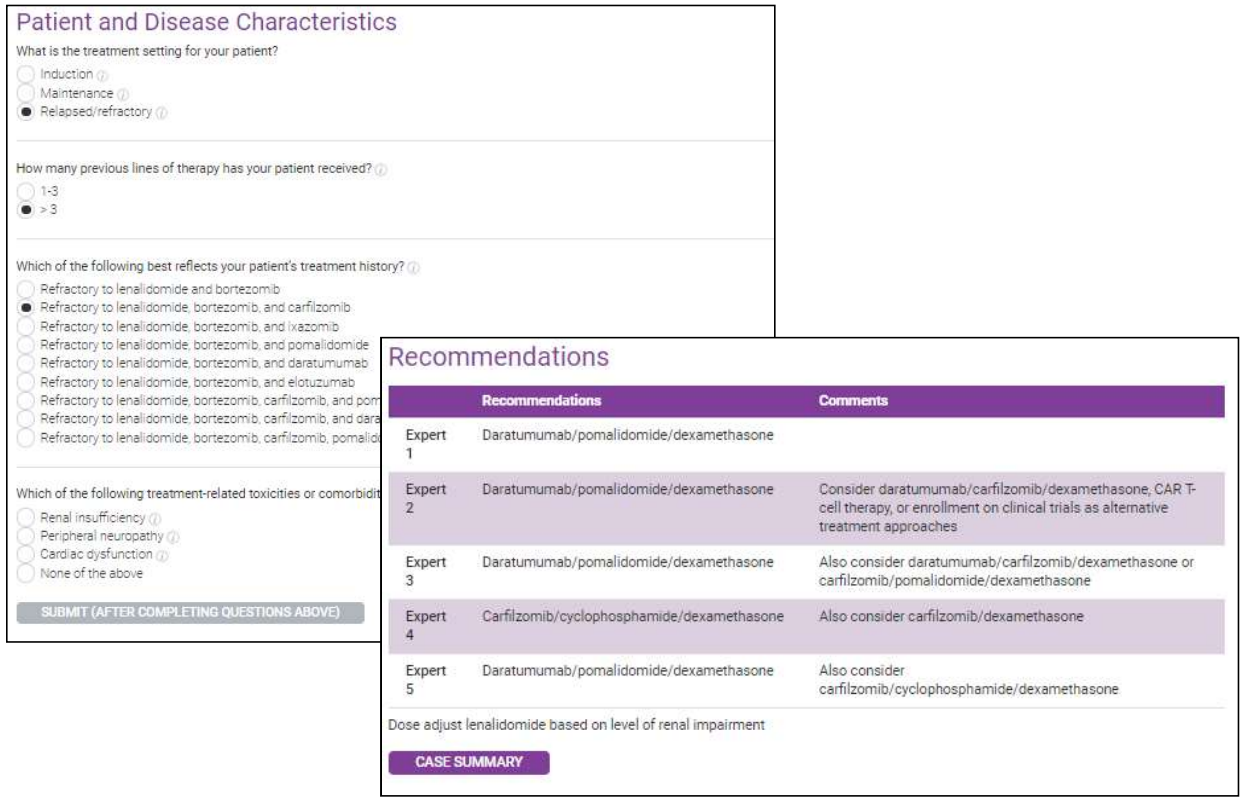
This program is supported by educational grants from Amgen and Celgene Corporation.

Agenda

- Diagnosis and staging
- Recent advances in MM treatment
- Identifying and managing AEs associated with new treatment approaches and complex combination regimens
- Patient adherence issues, comorbidities, frailties, psychosocial support
- Strategies and resources for educating patients and their families about their treatment options at each stage of disease

Online Treatment Decision Aid for MM

- Enter specific patient and disease characteristics by answering a series of multiple choice questions and get recommendations for your specific patient case from 5 hematologic cancer experts
  - Drs. Irene M. Ghobrial, Sagar Lonial, Carol Ann Huff, Noopar Raje, and Shaji Kumar



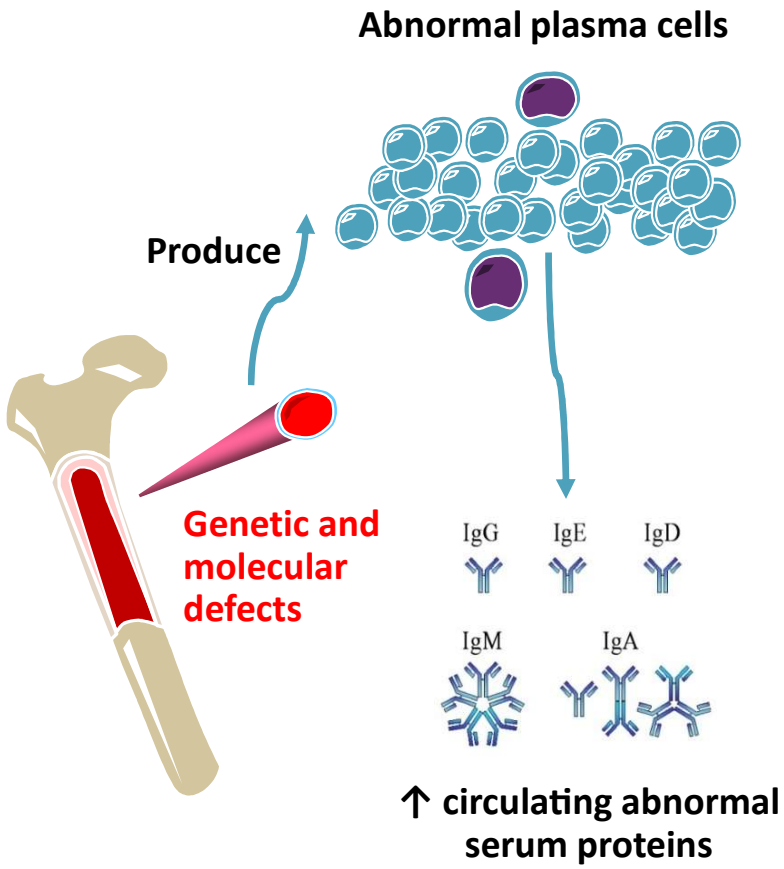
Available at: clinicaloptions.com/MyelomaTool

Slide credit: clinicaloptions.com

Multiple Myeloma: Overview and Diagnosis

What Is Multiple Myeloma?

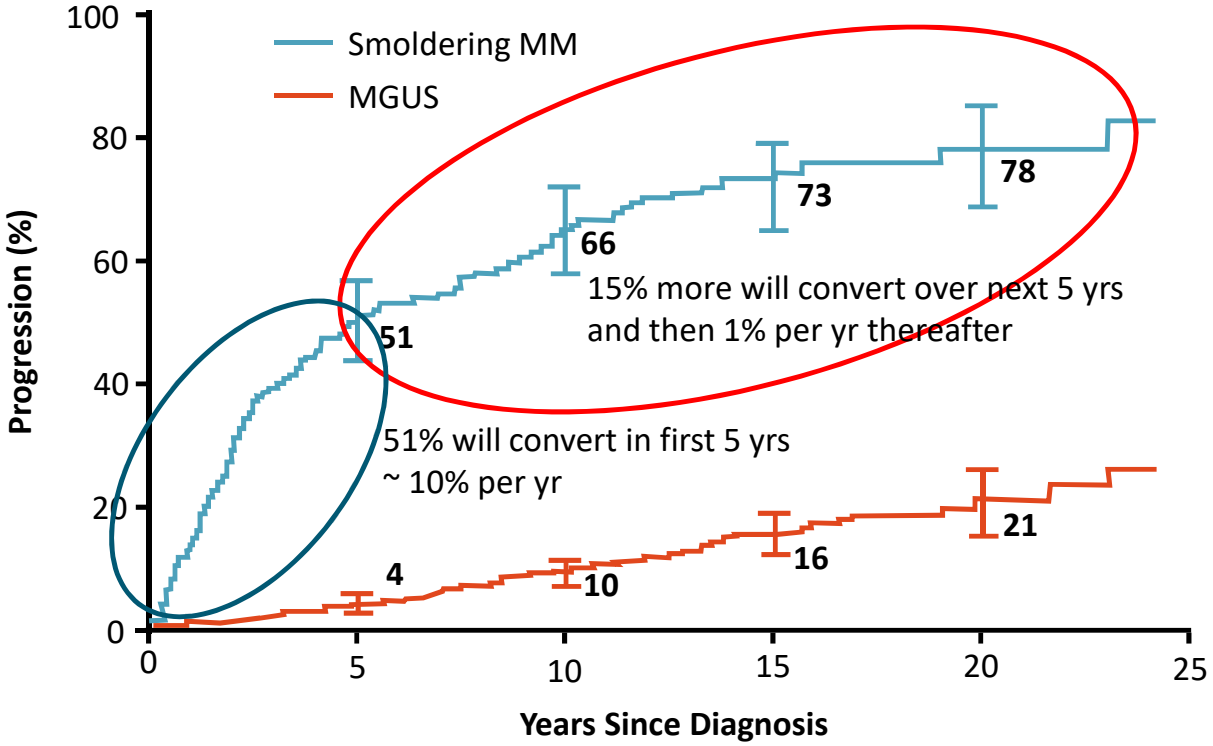
- Cancer of the plasma cells
- 2019: 32,110 new cases
- Median age: 69 yrs
- Risk factors include advanced age, AA, race, environmental and genetic factors
- 17% may never need another treatment



Faiman B, et al. Multiple myeloma. In: Hematologic malignancies in adults. ONS Publishing. 2014. SEER stat fact sheets: myeloma. Siegel RL, et al. CA Cancer J Clin. 2018;68:7-30; Grieb B, et al. ASH 2018. Abstract #1912.

Slide credit: clinicaloptions.com

Progression to Symptomatic Myeloma



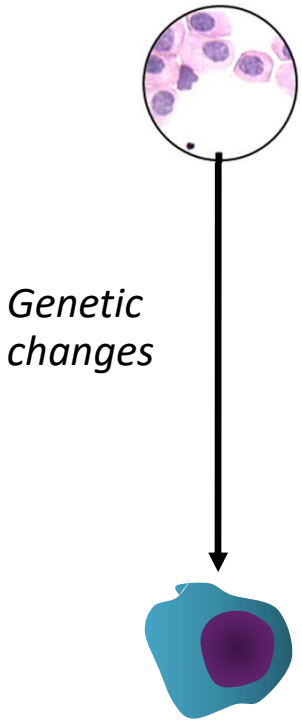
Strategy: Identify patients with high risk of progression; suggest early treatment before organ damage occurs

Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Slide credit: clinicaloptions.com

Diagnostic Workup

- Lab tests
  - Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), complete metabolic panel (CMP), CBC + differential, plasma ratio of free kappa/lambda light chains, serum and urine immunofixation electrophoresis
- Bone marrow biopsy
  - FISH, cytogenetics, and gene expression profiling (GEP)
- Imaging:
  - Skeletal survey, MRI/CT, PET scan ± MRI, CT



Ghobrial IM, et al. Blood. 2014;124:3380-3388. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-3548. Faiman B. Clin Lymphoma Myeloma Leuk. 2014;14:436-440.

Slide credit: clinicaloptions.com

IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥ 1 SLiM-CRAB* feature

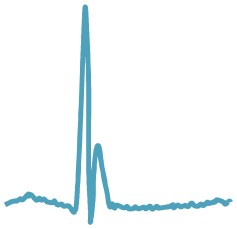
*S: **S**ixty percent clonal bone marrow plasma cells
Li: Serum free **Li**ght chain ratio ≥ 100 (involved kappa) or ≤ .01 (involved lambda)
M: **M**RI studies with > 1 focal lesion (> 5 mm in size)

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

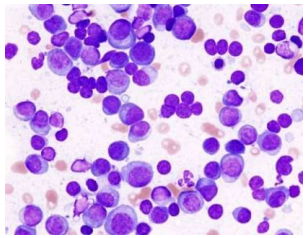
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Multiple Myeloma: Clinical Manifestations

- Series of genetic mutations, translocations, normal cell turns malignant
- Hallmarks of myeloma: CRAB (also known as myeloma-defining events)
- "SLiM CRAB" is the new criteria when treatment is recommended

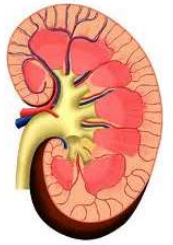


C = Calcium elevation

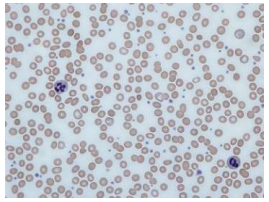


Recurrent infections*

*Not an MDE, yet relatively common



R = Renal insufficiency



A = Anemia

B = Bone disease

SLiM:

- > 60% bone marrow plasma cells
- Serum FLC ratio K:L >100
- MRI >1 focal lesion > 5mm

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

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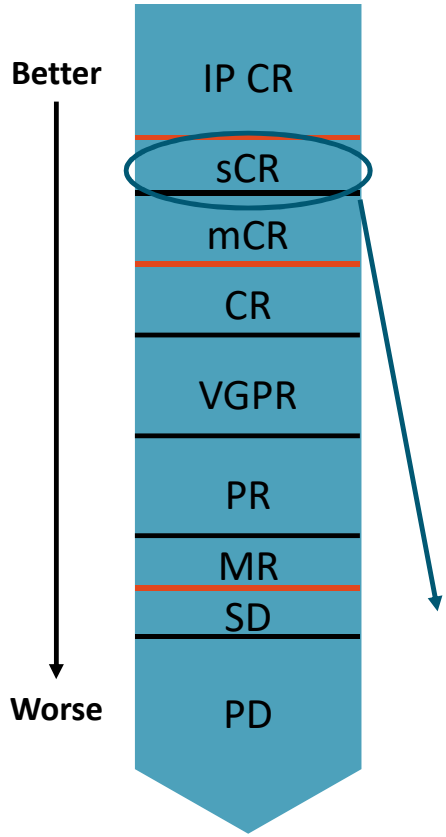
Diagnosis AND Monitoring Disease Are Essential: IMWG Myeloma Response Criteria



Category	Response Criteria
sCR	Normal FLC ratio; no clonal BM plasma cells
CR	Negative IFX and < 5% BM plasma cells
VGPR	Positive IFX and negative SPEP; ≥ 90% urine protein decrease; urine M-protein level < 100 mg/24 hrs
PR	≥ 50% decrease serum M-protein and ≥ 90% decrease in 24-hr urinary M-protein
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease

- IP CR: sCR AND BM negative by next gen flow (10^{-6})
- sCR: CR AND normal FLC ratio, BM negative by flow, 2 measures
- mCR: CR AND negative PCR (10^{-5})
- CR: negative IFX; < 5% PC in BM; 2 measures

Palumbo A, et al. J Clin Oncol. 2014;32:587-600. Durie BM, et al. Leukemia. 2006;20:1467-1473.

Slide credit: clinicaloptions.com

When and Why Should a Clinical Trial Be Considered?

- Before organ damage occurs (preferred)
- Clinical trials (preferred)
  - A Cancer Moonshot Initiative priority area of the BRP recommendations
  - Emphasize benefits of clinical trials
    - Access to new drugs
    - Collect information in logical manner
    - Can benefit patient and others
  - Risks also exist and should be discussed with patients and caregivers
    - Stringent monitoring, placebo, etc.

Ghobrial IM, et al. Blood. 2014;124:3380-3388.

Slide credit: clinicaloptions.com

Current Treatment Options in Newly Diagnosed Myeloma

Therapeutic Options in Myeloma: The Current Landscape

Immuno-modulatory Drugs	Proteasome Inhibitors	XPO-1 inhibitor	Chemotherapy Alkylators	Steroids	Histone Deacetylase Inhibitor	Monoclonal Antibodies
Thalidomide (PO)	Bortezomib (IV/SC)	Selinexor (PO)	Cyclophosphamide (IV, PO)	Dexamethasone (IV, PO)	Panobinostat (PO)	Elotuzumab (IV)
Lenalidomide (PO)	Carfilzomib (IV)		Bendamustine (IV)	Prednisone (PO)		Daratumumab (IV)
Pomalidomide (PO)	Ixazomib (PO)		Melphalan (IV, PO)			TQ25

Supportive care drugs should be integrated at diagnosis and throughout:

- Bone modifying agents (denosumab, pamidronate, and zoledronic acid)
- Antibiotics (acyclovir/valacyclovir, sulfamethoxazole, and trimethoprim)
- Palliative care should be integrated at diagnosis and throughout (aggressive control of symptoms)

National Cancer Institute. Drugs approved for multiple myeloma and other plasma cell neoplasms.

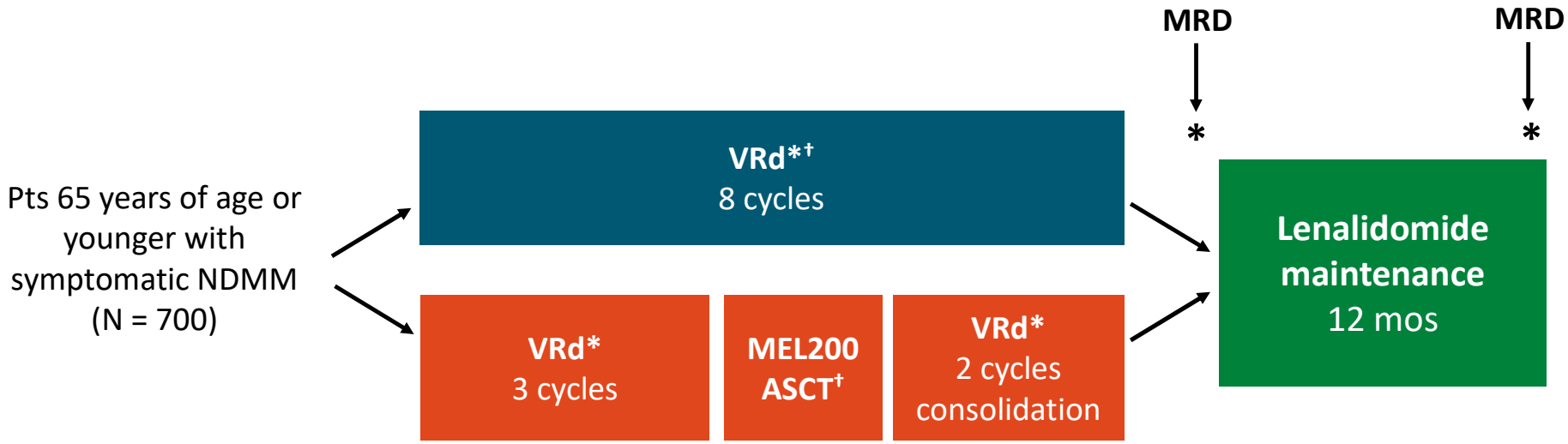
Slide credit: clinicaloptions.com

Induction and Maintenance Therapy for Patients With Transplant-Eligible Myeloma

Treatment Phase	Preferred Regimens	Other Regimens
Initial therapy (induction) for transplantation-eligible patients (response assessment after cycle 2)	▪ VRd ▪ CyBorD	▪ Bort/dox/dex ▪ KRd ▪ Ird
Maintenance therapy	▪ Lenalidomide ▪ Ixazomib	▪ Bortezomib

Dimopoulous MA, et al. *Lancet*. 2019;393:253-264.
Dimopoulos MA, ASH 2018. Abstract 301.

Phase III IFM/DFCI 2009: VRd ± ASCT in Newly Diagnosed Myeloma



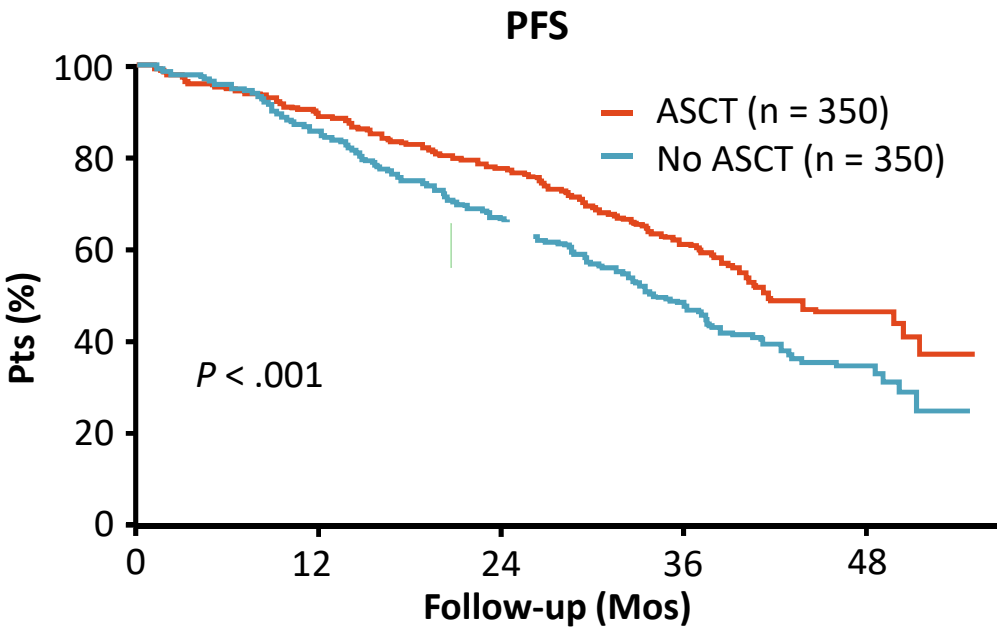
*VRd: bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, 11 + lenalidomide 25 mg on Days 1-14 + dexamethasone 40 mg on Days 1, 8, 15.
†Included PBSC collection with cyclophosphamide 3 g/m^2 + G-CSF after cycle 3.

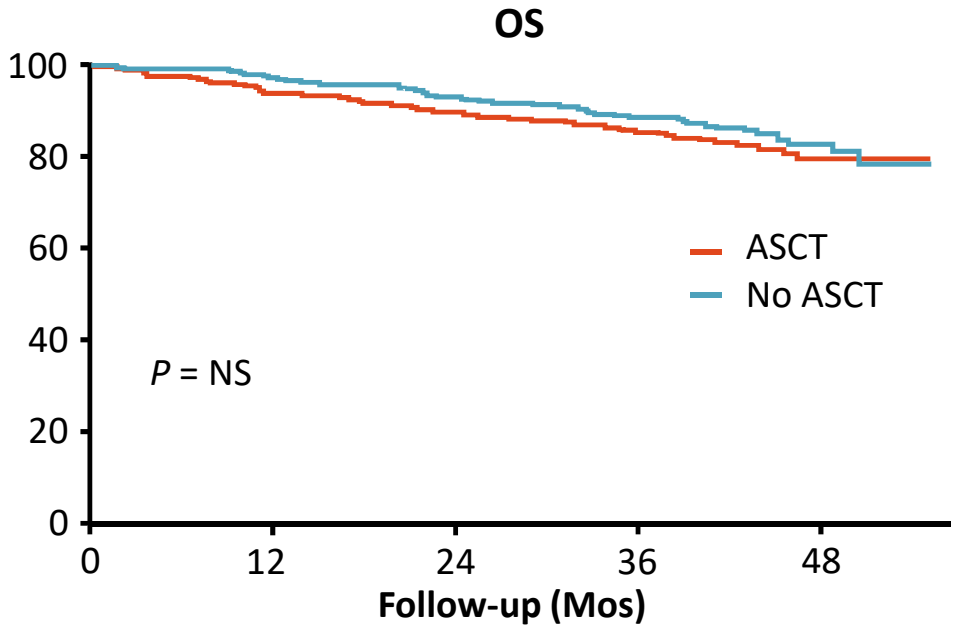
- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, safety

Attal M, et al. N Engl J Med. 2017;376:1311-1320.

Slide credit: clinicaloptions.com

Phase III IFM/DFCI 2009: VRd ± ASCT in Newly Diagnosed Myeloma



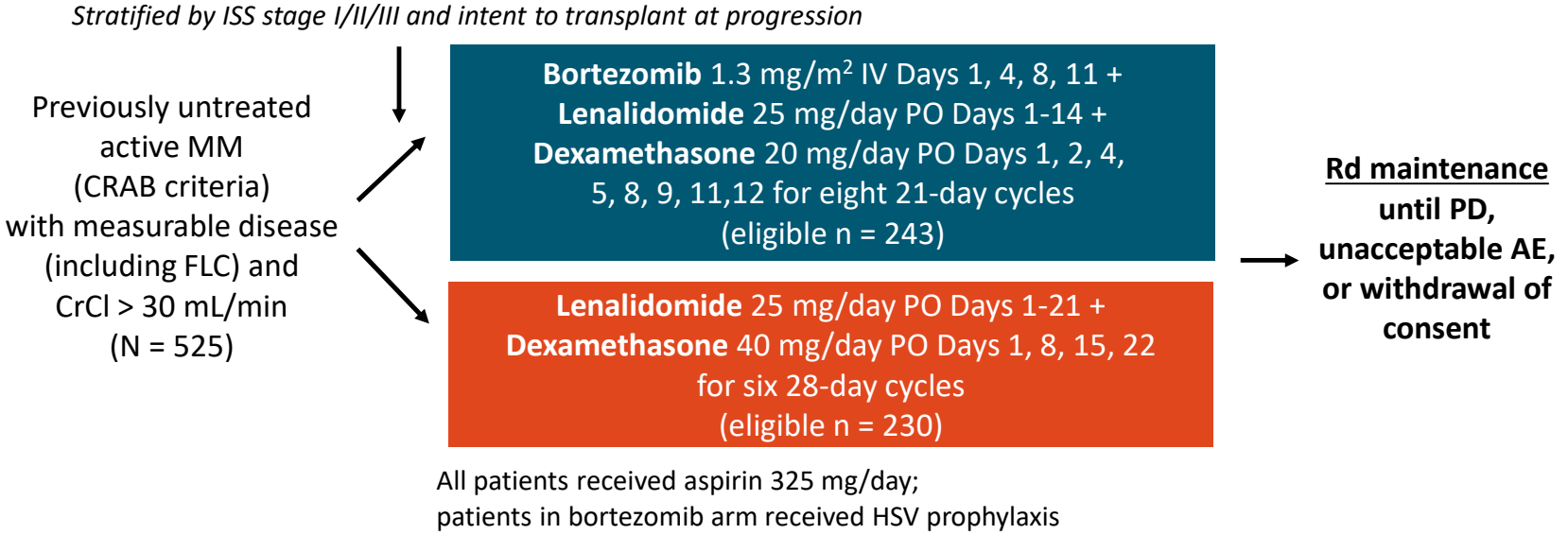


Attal M, et al. N Engl J Med. 2017;376:1311-1320.

Slide credit: clinicaloptions.com

Phase III SWOG 0777: Len/Dex ± Bortezomib in Newly Diagnosed MM With Delayed ASCT

- Randomized phase III trial of VRd vs Rd

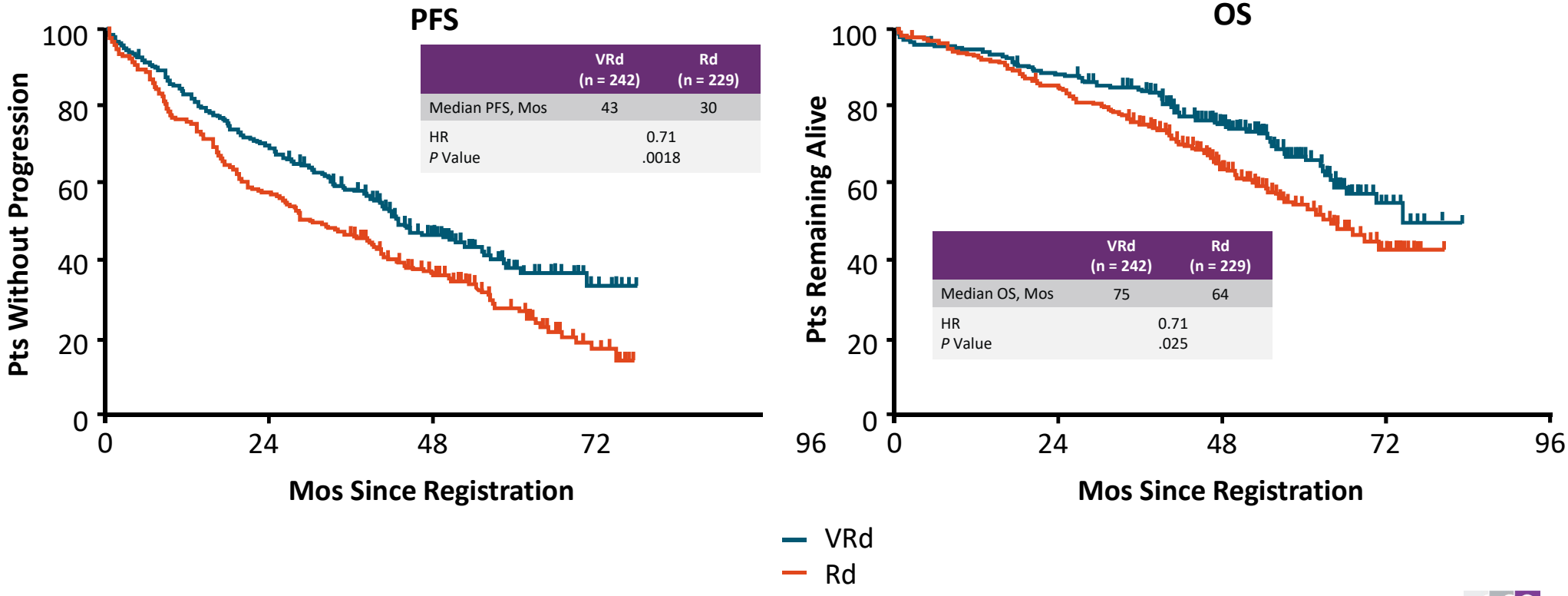


- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety

Durie B, et al. Lancet. 2017;389:519-527.

Slide credit: clinicaloptions.com

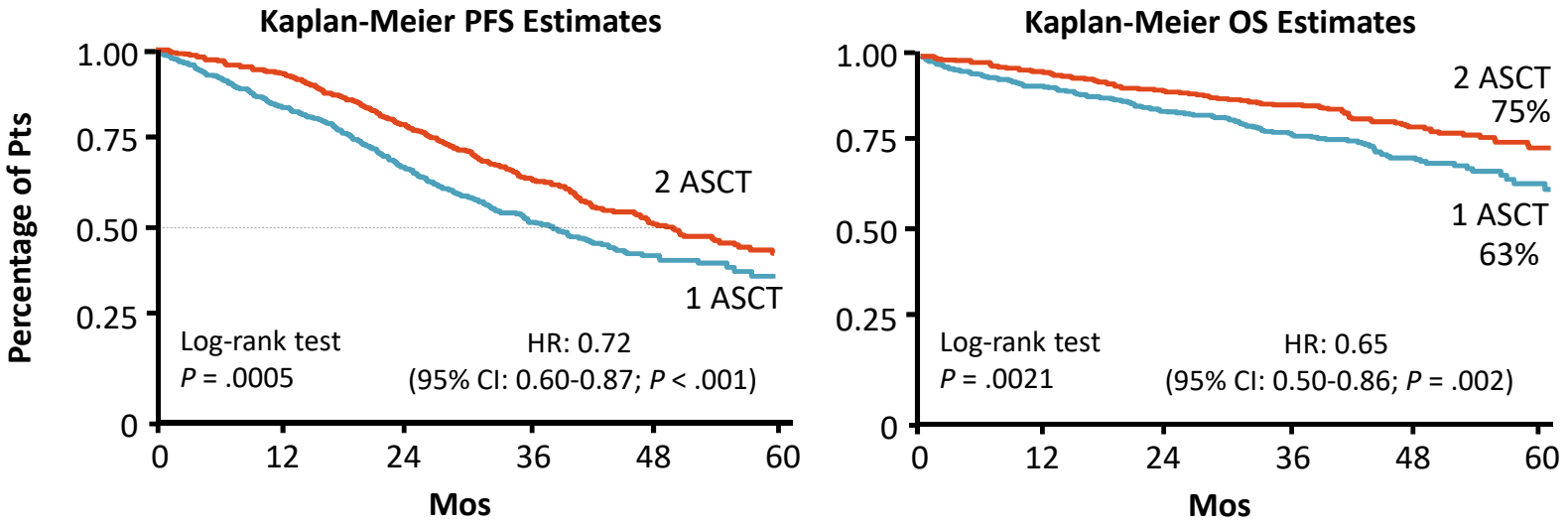
Phase III SWOG 0777: Len/Dex ± Bortezomib in Newly Diagnosed MM



Durie B, et al. Lancet. 2017;389:519-527.

Slide credit: clinicaloptions.com

Single vs Double ASCT: Analysis of 3 Studies



- Compilation of European phase III studies
- Median PFS: 2 ASCT, 50 mos; 1 ASCT, 38 mos
- Maximum benefit in pts with high-risk disease, especially del(17p) and t(4;14)

Cavo M, et al. Blood. 2013;122:767.

Slide credit: clinicaloptions.com

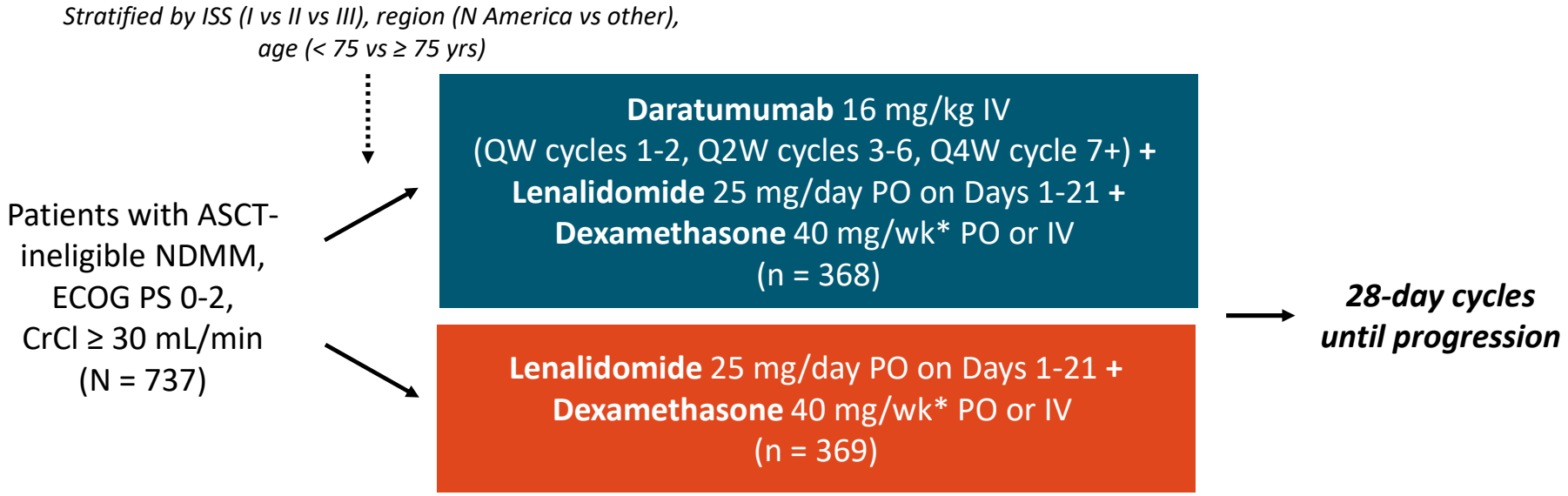
Induction and Maintenance Therapy for Transplantation-Ineligible Patients With Myeloma

Treatment Phase	Preferred Regimens	Other Regimens
Initial therapy (induction) *Response assessment after cycle 2*	▪ VRd ▪ Rd ▪ CyBorD ▪ Dara + VMP ▪ Dara/Rd	▪ KRd ▪ KCd ▪ IRd
Continuous (maintenance) therapy	▪ Lenalidomide	▪ Bortezomib

Slide credit: clinicaloptions.com

MAIA: Study Design

- Randomized phase III trial



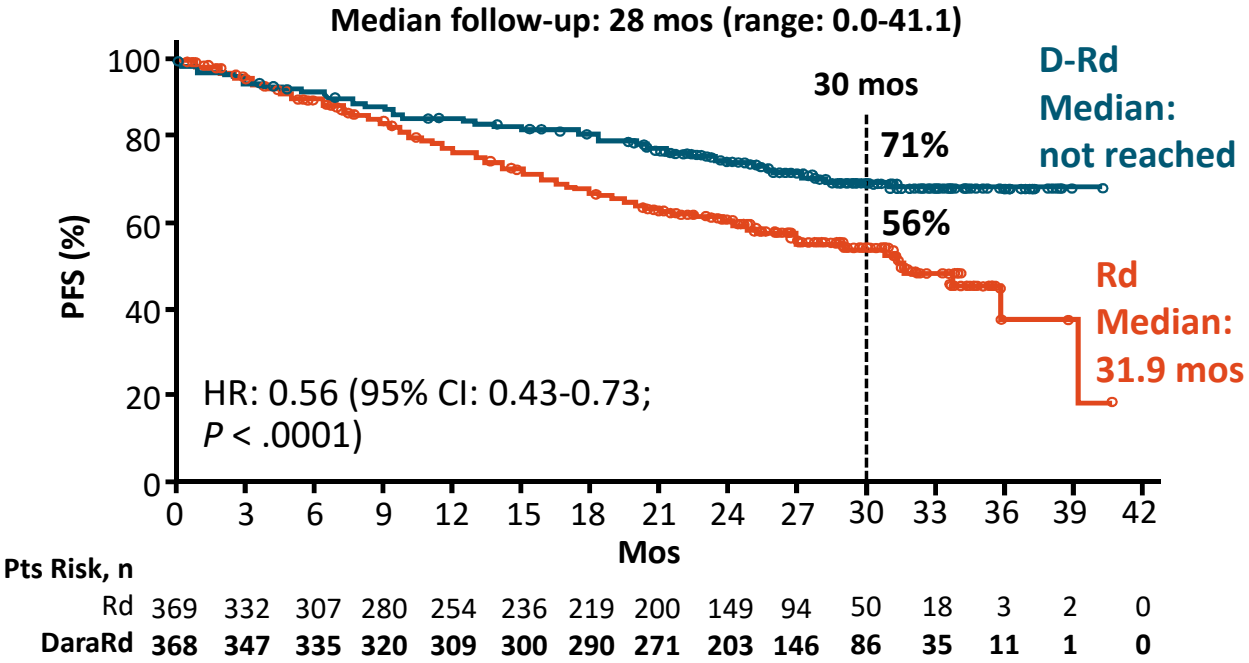
*Reduced to 20 mg/wk if > 75 yrs of age or BMI < 18.5.

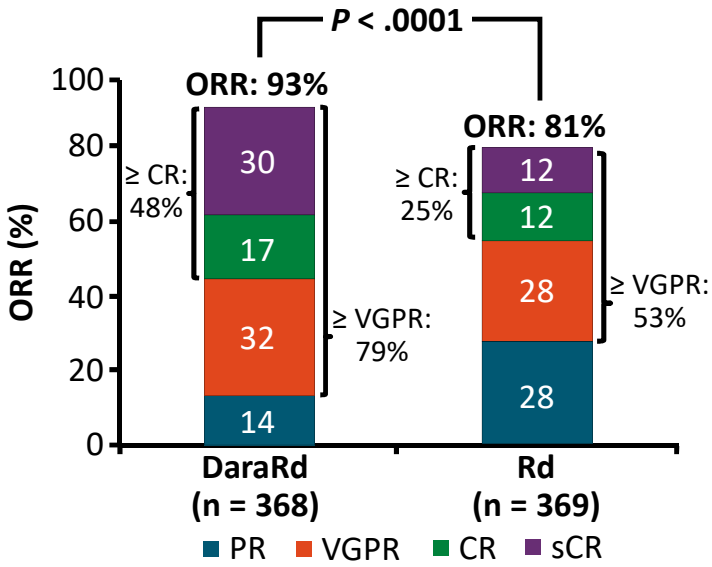
- Primary endpoint: PFS
- Secondary endpoints : ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, safety

Facon. ASH 2018. Abstr LBA-2.

Slide credit: clinicaloptions.com

Phase III MAIA Trial: Survival With DaraRd vs Rd in Older or ASCT-Ineligible Patients



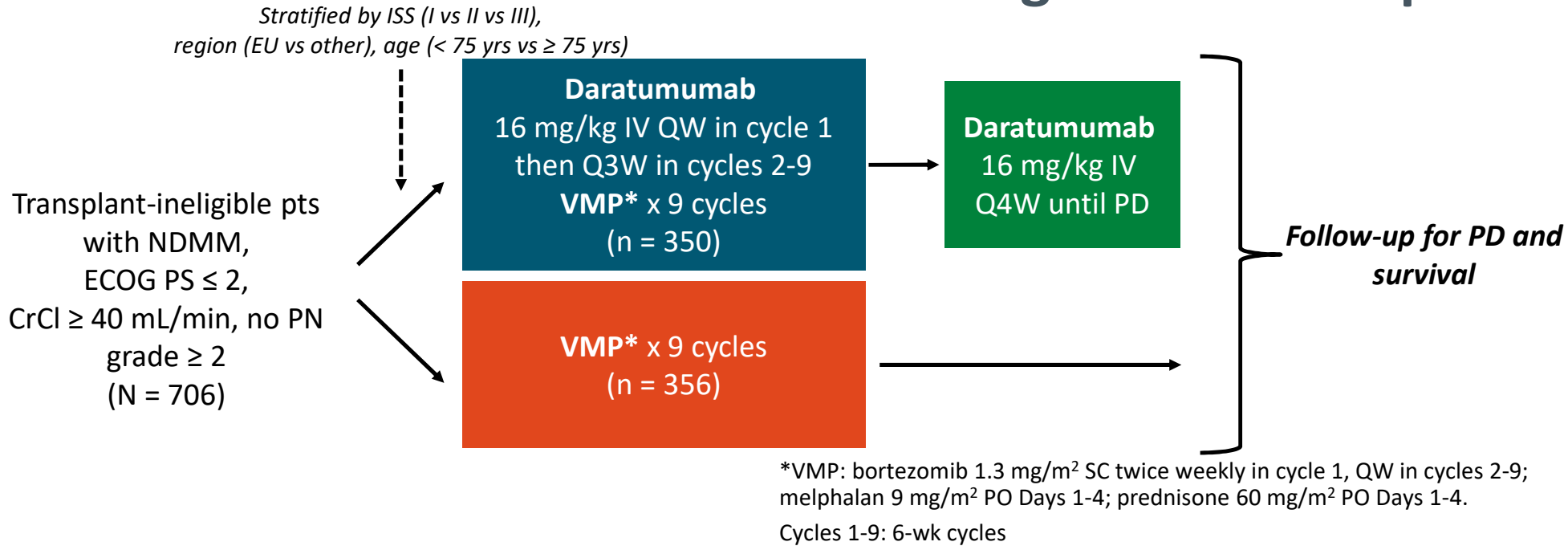


- Daratumumab treatment favored in most subgroups analyzed, including age, race, ISS stages, ECOG PS scores
- Reduced risk of progression or death with MRD negativity in both arms
- MRD negativity increased with addition of daratumumab
  - **DaraRD: 24% MRD negative**
  - Rd: 7% MRD negative

Facon. ASH 2018. Abstr LBA-2.

Slide credit: clinicaloptions.com

ALCYONE: Open-Label, Phase III Study Design
Daratumumab + VMP in Patients Ineligible for Transplant



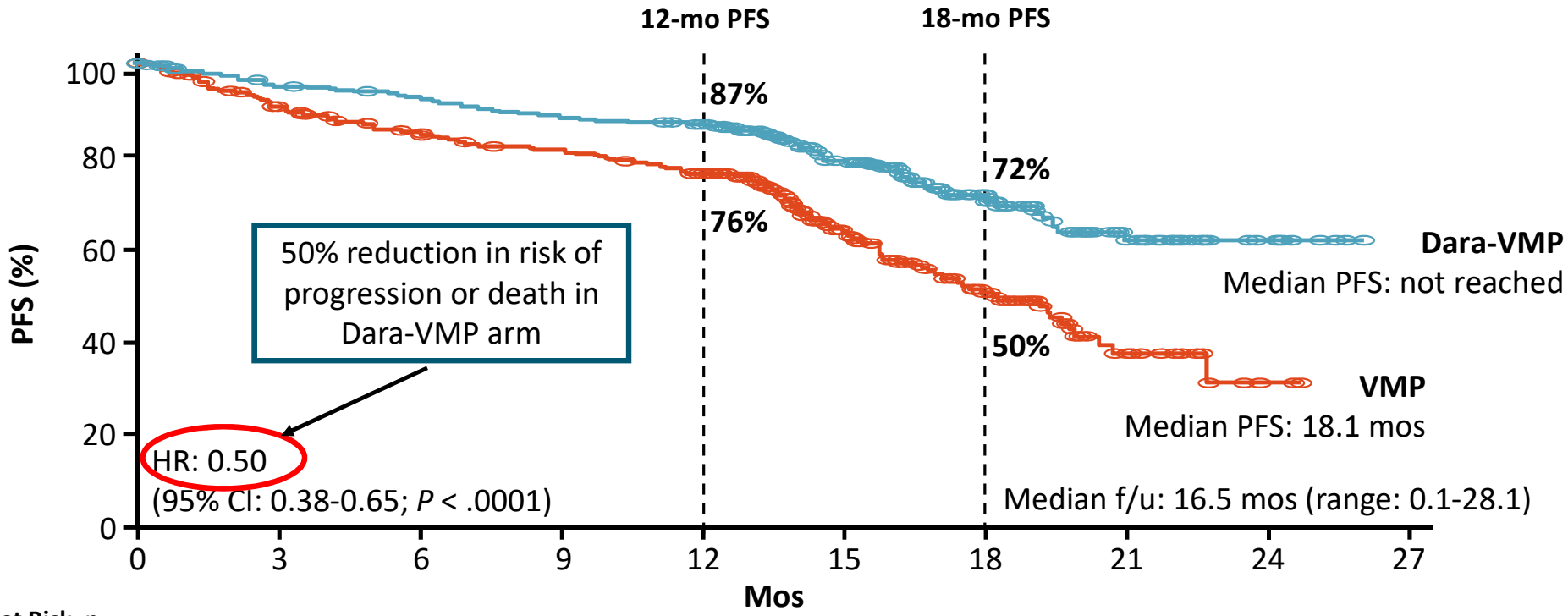
*VMP: bortezomib 1.3 mg/m^2 SC twice weekly in cycle 1, QW in cycles 2-9; melphalan 9 mg/m^2 PO Days 1-4; prednisone 60 mg/m^2 PO Days 1-4.

Cycles 1-9: 6-wk cycles

- Primary endpoint: PFS
- Secondary endpoints: ORR, ≥ VGPR, ≥ CR, MRD, OS, safety
- Statistical analysis: 360 PFS events with 85% power for 8-mo improvement
- Interim analysis at ~ 216 PFS events

Mateos MV, et al. N Engl J Med. 2018;378:518-528.

ALCYONE: PFS



Pts at Risk, n										
VMP	356	303	276	261	231	127	61	18	2	0
Dara-VMP	350	322	312	298	285	179	93	35	10	0

- Consistent PFS benefit across subgroups

Mateos MV, et al. N Engl J Med. 2018;378:518-528.

Slide credit: clinicaloptions.com

Nursing Implications

- Patients receiving 3-4 drug regimens can experience better responses but more/greater severity AEs than 2 drugs (especially neuropathy)
  - Manage AEs proactively to keep patients on therapy
- Key points with DARA + VMP or DARA + Rd in transplant eligible patients w/ newly diagnosed MM:
  - DARA can lead to infusion reactions
  - Shingles prevention with proteasome inhibitors (valacyclovir, acyclovir)
  - Adherence with oral melphalan, prednisone (calendars, electronic reminders) in light of other indications
  - Aggressive management of symptoms

Slide credit: clinicaloptions.com

Maintenance in Myeloma

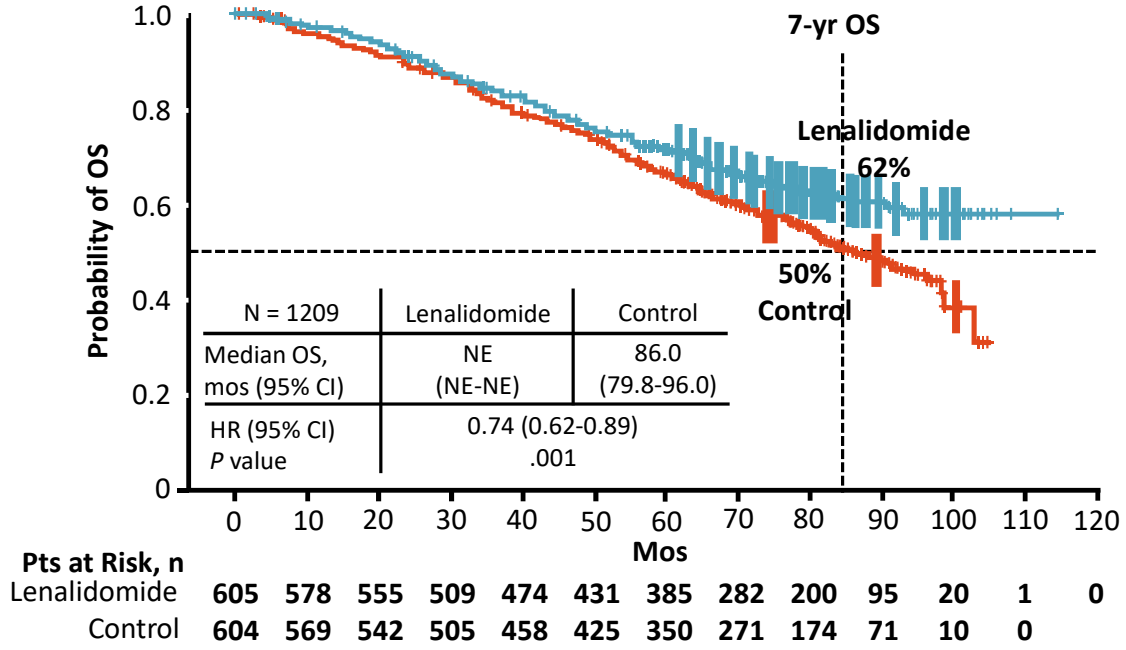
Summary of Lenalidomide and Bortezomib Maintenance Trials in Myeloma

Trial	Comparison Arms	Duration	Median Follow-up, Mos	PFS, Mos	OS
Lenalidomide					
IFM 2005-02[1]	LEN vs PBO	Stopped after median 32 mos	45	Median: 41 vs 23 (*P* < .001)	3 yrs 80% vs 84% (*P* = .7)
CALGB-100104[2]	LEN vs PBO	Until progression	48	Median: 50 vs 27 (*P* < .001)	NR vs 73% (*P* = .008)
RV-MM-PI-209[3]	LEN vs No maintenance	Until progression	51	Median: 42 vs 22 (*P* < .001)	3 yrs 88% vs 79% (*P* = .14)
Bortezomib					
HOVON 65 MM/GMMG-HD4[4]	BTZ vs THAL	2 yrs	91	96 mos 17% vs 10% (*P* = .001)	96 mos 48% vs 45% (*P* = .22)
PETHEMA/GEM[5]	VT vs THAL vs Interferon-α	3 yrs	35	2 yrs 78% vs 63% vs 49% (*P* = .01)	NS

1. Attal M, et al. N Engl J Med. 2012;366:1782-1791. 2. McCarthy PL, et al. IMW 2013. Abstract S15-5.
3. Palumbo A, et al. N Engl J Med. 2014;371:895-905. 4. Sonneveld P, et al. Blood. 2015;126:27.
5. Rosiñol L, et al. Blood. 2012;120:1589-1596.

Lenalidomide Maintenance After ASCT in Myeloma Improves OS (Meta-analysis)

- Trials: IFM 2005-02, CALGB 100104, GIMEMA RV-209 (N = 1209)
- Treatment: lenalidomide maintenance (n = 605) vs placebo or no maintenance (n = 604)
- At median follow-up of 80 mos, 26% ↓ in risk of death and 2.5-yr ↑ in median OS



OS, %	Lenalidomide	Control	*P* Value
OS at 5 yrs	71	66	.001
OS at 6 yrs	65	58	.001
OS at 7 yrs	62	50	.001

Risk of secondary primary malignancy post-ASCT higher in lenalidomide group (HR: 2.03; 95% CI: 1.14-3.61)

McCarthy PL, et al. J Clin Onc. 2017;35:3279-3289.

Slide credit: clinicaloptions.com

High-Risk MM: RVD Maintenance-Consolidation Improved Survival vs Bortezomib, Lenalidomide

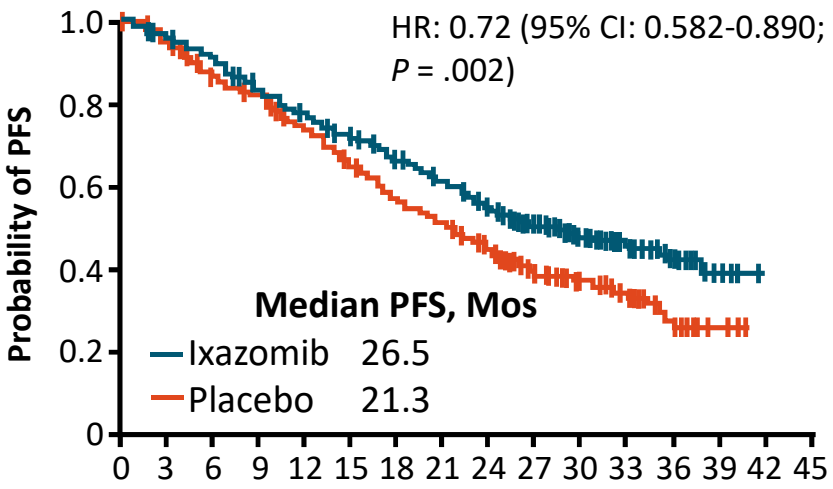
Outcome	RVD Maintenance-Consolidation in High-Risk MM[1]	Bortezomib Maintenance in del(17p) MM[2]	Lenalidomide in High-Risk Cytogenetics MM[3]
3-yr OS, %	93	69	--
Median PFS, mos	32	26.2	27

- Overall population and del(17p) subgroup had similar OS, PFS benefits with RVD

1. Nooka AK, et al. Leukemia. 2014;28:690-693. 2. Neben K, et al. Blood. 2012;119:940-948. 3. Chakraborty R, et al. Leukemia. 2018;32:712-718.

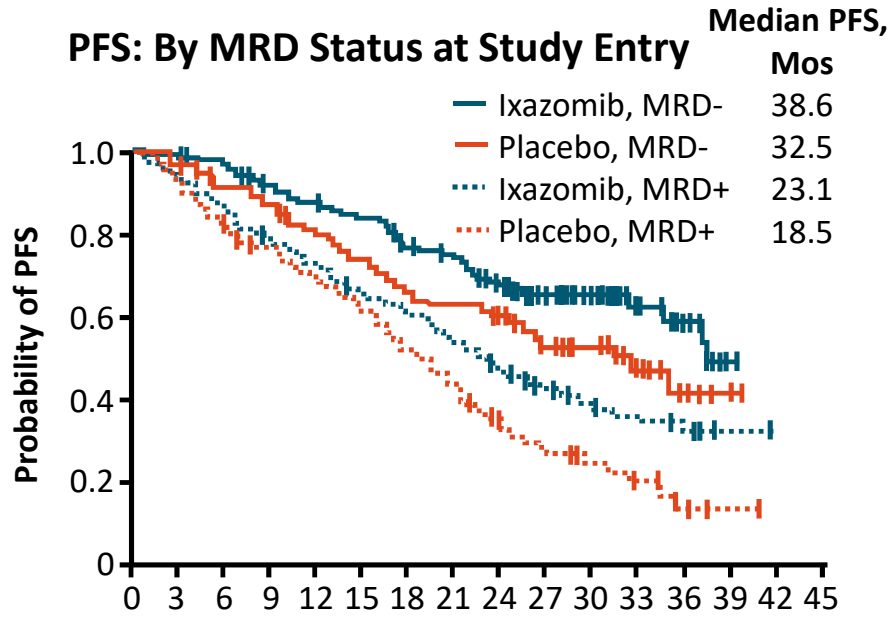
TOURMALINE-MM3: PFS

PFS: Overall (Primary Endpoint)



Patients at Risk, n															
Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0

PFS: By MRD Status at Study Entry



Patients at Risk, n															
Ixazomib, MRD-	117	111	107	99	92	88	84	77	69	54	41	26	17	3	0	0
Ixazomib, MRD+	75	72	66	64	56	51	46	42	41	30	21	17	7	2	0	0
Placebo, MRD-	225	204	188	170	152	134	124	109	93	64	43	25	15	4	2	0
Placebo, MRD+	139	123	106	94	85	75	62	53	38	22	15	9	4	1	0	0

- At median follow-up of 31 mos, median OS not reached in either treatment arm

Dimopoulos. ASH 2018. Abstr 301. Reproduced with permission.

Slide credit: clinicaloptions.com

How Do (Should) We Use MRD in the Clinic Today?

Flow Cytometry	Next-Gen Sequencing	Imaging
▪ Defined: absence of clonal plasma cells in bone marrow aspirate using next-gen flow cytometry	▪ Defined: absence of clonal plasma cells in BM aspirate with < 2 identical DNA sequence reads	▪ Defined: disappearance of areas of tracer uptake at baseline PET/CT or decrease to < normal surrounding tissue
▪ Sensitivity: 10^{-4} to 10^{-6}	▪ Sensitivity: 10^{-4} to 10^{-6}	▪ Sensitivity: high (?)
▪ Need for specialized, validated equipment	▪ Sent to lab for evaluation (clonoSEQ)	▪ Can be used as monitoring along with other assays

- ClonoSEQ FDA approved for MRD testing in acute lymphoblastic leukemia or myeloma
- **BUT there are currently no data on altering length of induction therapy, need for ASCT and/or consolidation, or maintenance based on MRD results**

Slide credit: clinicaloptions.com

Recently Approved Agents and Combination Regimens for R/R MM

Factors in Selecting Treatment for Relapsed/ Refractory Myeloma

- Disease-related factors
  - Duration of response to initial therapy
  - High-risk vs low-risk status
  - Molecular disease progression vs symptomatic progression
  - Other comorbid conditions, patient frailty
- Treatment-related factors
  - Previous therapy exposure (relapsed or refractory)
  - Toxicity/tolerability of previous regimen (combination vs single agent)
  - Mode of administration (ie, PO or IV)
  - Cost and convenience (out-of-pocket copays for IV vs PO)
- PATIENT PREFERENCE: Control may be more desirable than cure at relapse

Chim CS, et al. Leukemia. 2018;32:252-262.

Recommended Regimens for Pts With Relapsed/Refractory Myeloma

Preferred Regimens	Other Regimens	
▪ Bortezomib/lenalidomide/dex ▪ Carfilzomib (twice weekly)/dex ▪ Carfilzomib/lenalidomide/dex ▪ Daratumumab/bortezomib/dex ▪ Daratumumab/lenalidomide/dex ▪ Elotuzumab/lenalidomide/dex ▪ Ixazomib/lenalidomide/dex	▪ Bendamustine/bortezomib/dex ▪ Bendamustine/lenalidomide/dex ▪ Bortezomib/liposomal doxorubicin/dex ▪ Bortezomib/cyclophosphamide/dex ▪ Carfilzomib (weekly)/dex ▪ Cyclophosphamide/lenalidomide/dex ▪ Bortezomib/dex ▪ Daratumumab ▪ Daratumumab/pomalidomide/dex	▪ Elotuzumab/bortezomib/dex ▪ Elotuzumab/pomalidomide/dex ▪ Ixazomib/dex ▪ Ixazomib/pomalidomide/dex ▪ Lenalidomide/dex ▪ Panobinostat/bortezomib/dex ▪ Panobinostat/carfilzomib ▪ Panobinostat/lenalidomide/dex ▪ Pomalidomide/cyclophosphamide/dex ▪ Pomalidomide/dex ▪ Pomalidomide/bortezomib/dex ▪ Pomalidomide/carfilzomib/dex ▪ Selinexor/dex

Chim CS, et al. Leukemia. 2018;32:252-262.

Slide credit: clinicaloptions.com

How to Make the Best Choice for Therapy in R/R MM

PD While Not on Lenalidomide Maintenance	*PD On Lenalidomide Maintenance (Len-Refractory)*
Triplets (with Rd as backbone)	**Triplets (with other backbones)**
Daratumumab + Rd	Daratumumab + Vd
Carfilzomib + Rd	Daratumumab + PomD
Ixazomib + Rd	Daratumumab + KD
Elotuzumab + Rd	Carfilzomib + PomD
	Ixazomib + PomD
	Elotuzumab + PomD

Other options: Kd, PomD, selinexor/dex, clinical trial

Continue with triplet combinations with ≥ 1 new agent at each relapse

Slide credit: clinicaloptions.com

Recently Approved Agents and Regimens for Relapsed/Refractory Myeloma

Treatment	Number of Previous Lines of Therapy
Carfilzomib (IV proteasome inhibitor) + lenalidomide + dexamethasone	1-3
Ixazomib (PO proteasome inhibitor) + lenalidomide + dexamethasone	≥ 1
Panobinostat (PO HDAC inhibitor) + bortezomib + dexamethasone	≥ 2
Elotuzumab (IV anti-SLAMF7 antibody) + lenalidomide + dexamethasone	1-3
Elotuzumab (IV anti-SLAMF2 antibody) + pomalidomide + dexamethasone	≥ 2
Daratumumab (IV CD38-targeted antibody) monotherapy	≥ 3
Daratumumab (IV CD38-targeted antibody) + dexamethasone + either lenalidomide, bortezomib, or pomalidomide	≥ 1
Selinexor + dexamethasone	≥ 3

Chim CS, et al. Leukemia. 2018;32:252-262.
FDA.gov.

New Agents in Relapsed MM: Lenalidomide-Based Studies

Outcomes	POLLUX DRd vs Rd[1]	ASPIRE KRd vs Rd[2]	ELOQUENT-2 ERd vs Rd[3,4]	TOURMALINE-MM1 IRd vs Rd[5]
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	34	48
≥ CR, %	43	32	5	14
DoR, mos	NE	28.6	20.7	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. EHA 2016. Abstract LB238. 2. Stewart AK, et al. N Engl J Med. 2015;372:142-152.
3. Lonial S, et al. N Engl J Med. 2015;373:621-631. 4. Dimopoulos MA, et al. Blood. 2015;126. Abstract 28. 5. Moreau P, et al. N Engl J Med. 2016;374:1621-1634.

New Agents in Relapsed MM: PI-Based Studies

Outcomes	CASTOR DVd vs Vd[1]	ENDEAVOR Kd vs Vd[2]	Panobinostat PVd vs Vd[3,4]	Elotuzumab EVd vs Vd[5]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
ORR, %	83	77	61	66
Median PFS, mos	NR	18.7	12.0	9.7
≥ VGPR, %	59	54	28	36
≥ CR, %	19	13	11	4
DoR, mos	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47-1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Palumbo A, et al. N Engl J Med. 2016;375:754-766. 2. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38. 3. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206. 4. San-Miguel JF, et al. Blood. 2015;126. Abstract 3026. 4. Jakubowiak A, et al. Blood. 2016;127:2844-2840.

Selinexor

- A nuclear export inhibitor indicated in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody
- Ongoing studies in combination with bortezomib and other agents

Chen C, et al. EHA 2014.

Selinexor in Heavily Pretreated Patients With MM and 5 Prior Therapies

MM patients with a **median of 7 prior treatment regimens**; 5 prior therapies

- **ORR of 26.2%**, including 2 stringent CRs
  - 2 pts with stringent CR (sCRs were MRD negative at 10^{-6} and 10^{-4})
  - 2 pts with previous PD after CAR T-cell therapy achieved PR
- Median time to response was 1 month (range 1 to 14 weeks)
- Median OS: 8.6 mos
  - 15.6 mos in patients with ≥ MR vs 1.7 mos in patients with PD/NE

Nursing implications:

- Most commonly occurring grade ≥ 3 AEs were hematologic, GI-related, constitutional symptoms, and hyponatremia; typically responsive to dose modification and standard supportive care agents
- Oral adherence, dosing
- Consideration in heavily pre-treated patients

TQ30
TQ37

hari A, et al. ASH Abstract 598.

Identifying and Managing Adverse Events Associated with MM Treatment

Major Considerations When Choosing Treatment for Individual Patients

- Financial, physical (patient frailty, comorbid illness)
- Can the patient take PO or IV? Transportation and frequency?
- *Consider effectiveness and patient preference*
  - Add proteasome inhibitor (PO, SC, or IV)
  - Add an antibody to Rd (eg, ERd, DRd) or to Vd (eg, DVd)
  - Switch to another IMiD (eg, pomalidomide), alone or in combination with a PI or antibody
  - Consider selinexor if progression after 4 or more therapies
- Discuss all options with patients and employ shared decision making (quality vs quantity of life, goals of care)

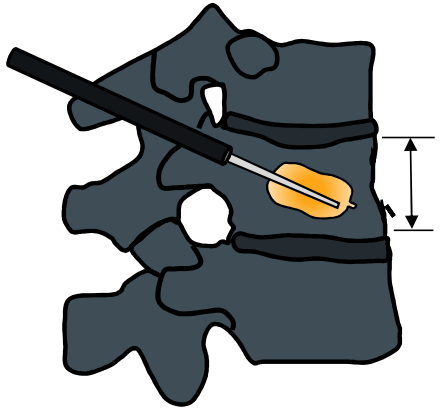
Slide credit: clinicaloptions.com

Management of Bone Disease: Supportive Care

- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
  - Both require monitoring for renal function and osteonecrosis of jaw
- Denosumab
  - Noninferior to zoledronic acid
  - Administered SQ
  - Requires monitoring for calcium levels, osteonecrosis of jaw

- Kyphoplasty/vertebroplasty

Kyphoplasty uses a "balloon" to create a cavity for bone cement to reduce vertebral fracture and pain



- Use of spinal support (braces) may be indicated
- Ongoing evaluation of bone health

Niesvizky. J Natl Compr Canc Netw. 2010;8(suppl 1):S13. Coleman. Ann Oncol. 2014;25(suppl 3):iii124. Terpos. J Clin Oncol. 2013;31:2347. Raje N. Lancet Oncol. 2018;3:370.

Slide credit: clinicaloptions.com

Myelosuppression and Infection

- Myeloma and some treatment regimens associated with myelosuppression[1]
  - Increased risk of infection, potential for decreased QoL and treatment interruption
  - Dose modification guidelines available in package inserts
- Infection prophylaxis[2]
  - Patients should remain up to date on appropriate vaccinations
  - VZV prophylaxis when receiving PIs or daratumumab
  - IVIG/prophylactic antibiotics controversial; use only when warranted
  - Patient education emphasizing importance of alerting treating clinicians of potential infection can reduce unnecessary antibiotics

1. Miceli. Clin J Oncol Nurs. 2008;12(3 suppl):13. 2. Delforge. Blood. 2017;129:2359.

Use of Vaccinations for Patients With Myeloma

- Inactivated vaccines are safe for patients with myeloma
- All patients with myeloma should receive annual flu vaccine
- Consider pneumococcal vaccine every 5 yrs
  - Pneumococcal conjugate vaccine 13 (PCV13)
  - Then pneumococcal polysaccharide vaccine 23 (PPV23) 2-3 mos later

- Vaccines post ASCT

4-6 Mos After
Flu
6-12 Mos After
Polio
Diphtheria-tetanus-pertussis
Pneumococcal (PCV13, then PPV23 2-3 mos later)
H influenzae type B (Hib)
Meningococcal group C (often Hib/MenC combined, then MenACWY 1 mo later)
Meningococcal group B

Slide credit: clinicaloptions.com

MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
Proteasome inhibitors	Bortezomib	PN, T, M, F	IV, SC; monitor platelets; safe in renal failure
	Carfilzomib	PN, C, M, F, DVT	Hydration, cardio/pulmonary
	Ixazomib	PN, T, GI, R	Reduce dose for hepatic/renal disease
Immunomodulatory agents	Lenalidomide	DVT, M, BD, R, D	ASA or LMWH if high risk for clots; weekly CBC x 8 wks
	Thalidomide	DVT, M, BD	As above
	Pomalidomide	DVT, M, BD, F	As above
Monoclonal antibodies	Daratumumab	IR, M, RD	Infusion reaction risk; pre/post med as directed; interrupt infusion if reaction
	Elotuzumab	IR, M, RD	As above
XPO-1 inhibitor	Selinexor	N, GI, T	Hyponatremia, GI, weight loss, oral adherence

BD, birth defects; C, cardiac; D, diarrhea; DVT, deep vein thrombosis; F, fatigue; GI, gastrointestinal toxicities; IR, infusion reaction; M, myelosuppression; N, nausea; PN, peripheral neuropathy; R, renal dose adjustment necessary; RD, response disruption; T, thrombocytopenia.

US Food and Drug Administration. FDA approved drug products.

Slide credit: clinicaloptions.com

MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
Alkylating agents	Melphalan	M, N	CBC diff monthly; renal dose adjustment
	Cyclophosphamide	M, N	As above
Corticosteroids	Prednisone	H, MS	Monitor blood sugar, insomnia, weight gain
	Dexamethasone	H, MS	As above
HDAC inhibitors	Panobinostat	C, D	Baseline EKG and mag/K+ monitoring; loperamide for diarrhea

C, cardiac; D, diarrhea; H, hyperglycemia; M, myelosuppression; MS, metabolic syndrome; N, nausea.

US Food and Drug Administration. FDA approved drug products.

Slide credit: clinicaloptions.com

Nursing Implications: IMiDs (lenalidomide, pomalidomide and thalidomide) TQ38

- Taken PO same time daily
  - Capsules swallowed whole with water
  - Special consideration on timing (with or without food, bedtime)
  - Capsules stored in original packaging
- Adverse Events
  - Embryonic/fetal toxicity
  - Venous thromboembolism
  - Fatigue
  - Rash
  - Thrombocytopenia
  - Neutropenia

Nursing Implications: IMiDs

- **Teratogenicity**
  - Drug available only through REMS Program
  - Ensure compliance with REMS program requirements
    - Pregnancy testing
    - Contraception requirements
      - Females with childbearing potential: 2 methods of contraception
      - Males: use of condom during sexual intercourse; must not donate sperm
    - Participation in telephone surveys
    - Must not donate blood or blood products

- **Drug Interactions**
  - Drugs that affect kidney function (lenalidomide)
    - **Note: Pomalidomide can be used in patients with renal insufficiency at full dose 4 mg PO QD (25% dose reduction if on hemodialysis)[1]**
  - Drugs that may increase the risk of thrombosis
    - Erythropoietic agents
    - Estrogen-containing therapies

Dimopoulos M, et al. J Clin Oncol. 2018;36:2035-2043.

Nursing Implications—IMiDs: Prevention of Serious Adverse Events

- **Prevention of SAEs**
  - Ensure appropriate prophylactic anticoagulation (eg, ASA, warfarin, LMWH)
  - Compliance to REMS program requirements
  - Pt/caregiver education
  - Monitor blood counts, neuropathy, response

- **Provide instructions to report signs and symptoms of SAEs to the healthcare team immediately**
  - DVT: unilateral leg swelling
  - PE: sudden shortness of breath
  - Thrombocytopenia: easy bruising or uncontrolled bleeding
  - Neutropenia: fever or signs of infection

Venous Thromboembolism Prophylaxis and Treatment (ASCO clinical practice guideline update 2014)

Prophylaxis with either LMWH or low-dose aspirin to prevent VTE

Lyman GH, et al. J Clin Oncol. 2015;33:654-656.

Slide credit: clinicaloptions.com

Nursing Implications—IMiDs: Patient Education

- Emphasize importance of adherence
  - Use of reminders: calendars, apps
  - Pill count during clinic visit
  - Online monitoring of monthly refills
- Infection prevention: MM patients have 7-fold increased risk of infection vs general population[1]
- Refrain from smoking (reduces pomalidomide exposure)
- Protect renal health
  - Avoid NSAIDS, IV contrast, other drugs with renal interactions
- Hydration
- Strategies to manage fatigue

1. Blimark C, et al. Haematologica. 2015;100:107-113.

Nursing Implications: Bortezomib

Intravenous

- FDA approved in 2003

Subcutaneous

- FDA approved in 2012
- Equivalent efficacy as IV
- Reduced neuropathy, GI AEs

Recommended injection sites: thigh and abdomen

Use "air sandwich" technique

- Higher risk for peripheral neuropathy
- Associated with higher incidence of herpes zoster infection—**administer prophylaxis for herpes virus**
- Advise pts against driving or operating machinery if they experience asthenic conditions
- Higher risk for gastrointestinal disturbance
- Pt monitoring and supportive care
- **Monitor for potential drug interactions**
  - Ketoconazole (increases plasma concentration)
  - Rifampin (decreases plasma concentration)
  - St John's wort

Barbee MS, et al. J Clin Pathways. 2016;2:35-41. Mateos MV, et al. Ther Adv Hematol. 2012;3:117-124. Bortezomib [package insert]. Kurtin S, et al. J Adv Pract Oncol. 2012;3:406-410.

Slide credit: clinicaloptions.com

Nursing Implications: Carfilzomib

- ***Administration*:** IV over 10 or 30 mins based on dose
  - Approved for 2 consecutive days/wk for 3 wks but multiple studies give weekly dosing *(ensure adherence to treatment schedule)*

TQ41

- ***Premedication*:** 4-mg dexamethasone before each dose
- ***Hydration*:** 250-500 mL IV saline before carfilzomib for all doses in cycle 1 and in subsequent cycles *(monitor for fluid overload)*
- ***Prophylaxis*:** decrease risk of herpes zoster reactivation with acyclovir
- ***Monitor*:** signs of infection, blood counts (renal, liver function), TLS *(consider uric acid–lowering* drugs); cardiac eval: to prevent new onset or worsening of preexisting cardiac failure (eg, CHF, pulmonary edema, decreased ejection fraction)

Carfilzomib 28-Day Cycle						
1	**2**	3	4	5	6	7
8	**9**	10	11	12	13	14
15	**16**	17	18	19	20	21
22	23	24	25	26	27	28

Cycle 1: 20 mg/m^2

Cycle 2+: 27 mg/m^2, 56 or 70mg/m^2

Patient Education

- Instruct pts to monitor and report symptoms (eg, dyspnea, fatigue, anemia, thrombocytopenia, TLS)
- Teach pt measures to prevent infection.

Carfilzomib [package insert].

Slide credit: clinicaloptions.com

Nursing Implications: Ixazomib

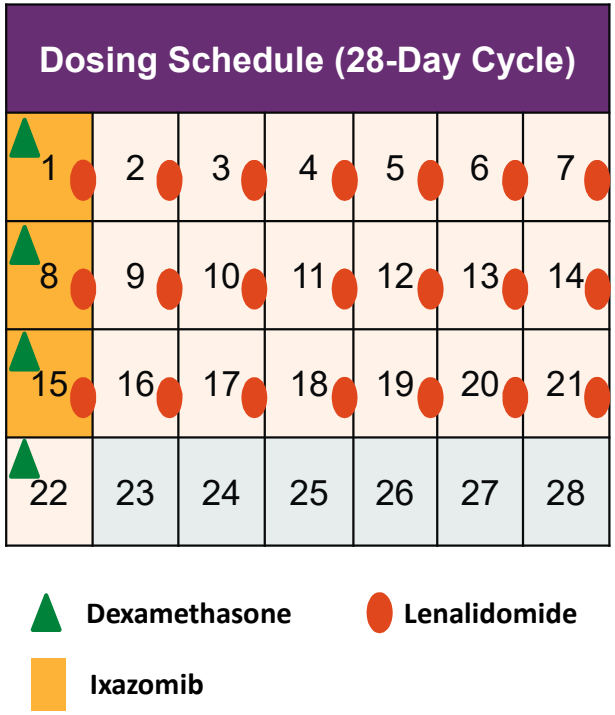
Indication: MM and ≥ 1 prior therapy
Route: PO

- In combination with len/dex
- Once weekly at similar time
- Dose should be taken ≥ 1 hr before or ≥ 2 hrs after food

Adverse events: thrombocytopenia, GI toxicity, peripheral neuropathy

Drug interaction: rifampin, phenytoin, carbamazepine, St. John's Wort

Monitor: blood counts (renal, liver function at least monthly but consider more frequently during early cycles); dose reduction for hepatic/renal disease



Ixazomib [package insert].

Slide credit: clinicaloptions.com

Nursing Implications: Daratumumab

- Daratumumab: human CD38-directed antibody, approved for myeloma as monotherapy and in combination with dexamethasone plus either lenalidomide or bortezomib
- Dosing
  - Monotherapy or with lenalidomide and low-dose dexamethasone: weekly in Wks 1-8, Q2W in Wks 9-24, then monthly until progression
  - Combination with bortezomib/dexamethasone: weekly in Wks 1-9, Q3W in Wks 10-24, then monthly until PD
- Premedication: corticosteroids (methylprednisolone for monotherapy, dexamethasone for combination treatment), antipyretics, antihistamine

Daratumumab [package insert]. Gleason C, et al. J Adv Pract Oncol. 2016;7(suppl 1):53-57.
Usmani S, et al. Blood. 2016;128:37-44.

Slide credit: clinicaloptions.com

Nursing Implications: Daratumumab (cont'd)

- Approximately 50% patients experience infusion reactions
- Postinfusion medication (monotherapy): oral corticosteroid for 2 days after infusion
  - Combination regimen: low-dose methylprednisolone day after infusion; may not be needed due to dexamethasone in regimen
  - Loratadine 10 mg/monteleukast 10 mg day before and for 3 days after first infusions
- Educate patients about infusion reactions (nasal stuffiness, hypertension)
- Administer herpes prophylaxis
- Interference with complete response, type can crossmatch issues
- Long infusion time (often 10 hrs first day); 90 mins after 2 doses

Daratumumab [package insert]. Gleason C, et al. J Adv Pract Oncol. 2016;7(suppl 1):53-57.
Usmani S, et al. Blood. 2016;128:37-44.

Nursing Implications: Elotuzumab

Dosing: Cycles 1 and 2 (28-Day Cycles)				
Day of cycle	1	8	15	22
Elotuzumab, mg/kg (IV)	10	10	10	10
Lenalidomide, 25 mg (PO)	QD (x 21 days)			
Dexamethasone, mg (PO/IV)	28/8	28/8	28/8	28/8
Dosing: Cycles 3 and Beyond (28-Day Cycles)* monthly 20mg/kg with Pomalidomide +Dex				
Day of cycle	1	8	15	22
Elotuzumab, mg/kg (IV)	10 (20)		10	
Lenalidomide, 25 mg (PO) (or POM 4mg)	QD (x 21 days)			
Dexamethasone, mg (PO/IV)	28/8	40/0	28/8	40/0

- Infusion reaction prevention: dexamethasone 28 mg 3-24 hrs prior; dexamethasone 8 mg IV 1 hr prior; H1, H2, and acetaminophen premed 45-90 mins prior
- HSV prophylaxis; DVT prophylaxis (lenalidomide)

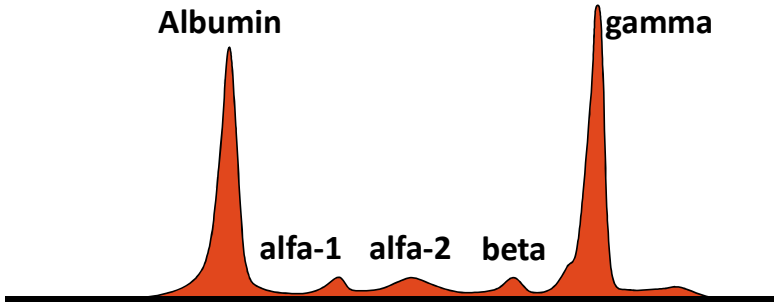
Elotuzumab [package insert].

Slide credit: clinicaloptions.com

Understanding Interference in Laboratory Assays by Monoclonal Antibodies

Potential interference with laboratory tests

- Antibodies can be detected in the gamma region
- 50% of IgG kappa M bands co-migrate with daratumumab and elotuzumab, resulting in overestimation of M protein and underestimation of CR
- Interference reduces after completion of therapy



SPEP and immunofixation solutions

- Development of daratumumab interference reflex assay (DIRA assay)
- Shifts migration of daratumumab
- Performed in IgG kappa < 2 and deep response achieved
- New assays in development for elotuzumab, isatuximab

Lonial S, et al. Lancet. 2016;387:1551-1560. Van de Donk N, et al. Blood. 2016;127:681-695.
Catamero D, et al. ONS 2016. Abstract 54.

Slide credit: clinicaloptions.com

Proposed Drug Dosing by Frailty/Risk Score

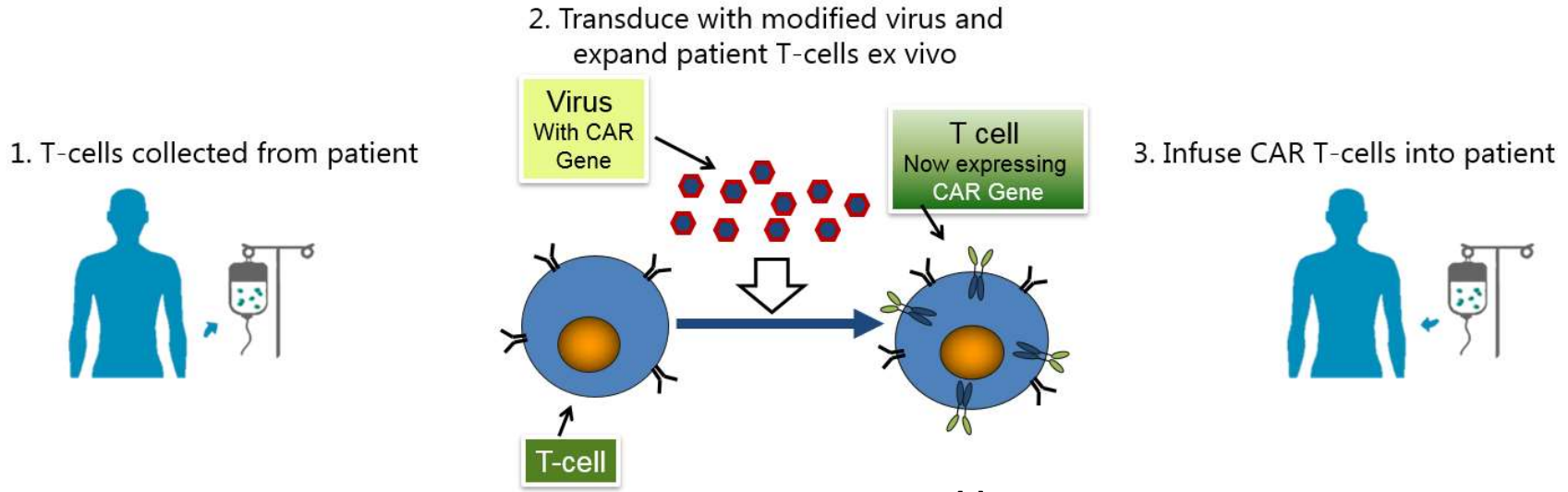
Agent	Dose Level 0 (No Risk Factors)	Dose Level -1 (≥ 1 Risk Factor)	Dose Level -2 (≥ 1 Risk Factor + Grade 3/4 Nonheme AE)
Dexamethasone	40 mg/day Days 1,8,15, 22/4 wks	20 mg/day Days 1, 8, 15, 22/4 wks	10 mg/day Days 1, 8, 15, 22/4 wks
Melphalan	0.25 mg/kg or 9 mg/m^2 Days 1-4/4-6 wks	0.18 mg/kg or 7.5 mg/m^2 Day 1-4/4-6 wks	0.13 mg/kg or 5 mg/m^2 Day 1-4/4-6 wks
Thalidomide	100 mg/day	50 mg/day	50 mg QOD
Lenalidomide	25 mg/day Days 1-21/4 wks	15 mg/day on Days 1-21/4 wks	10 mg/day Days 1-21/4 wks
Pomalidomide	4 mg/day Days 1-21/4 wks	Reduce dose to 3 mg/day or further due to hematologic toxicity, reduce dose by 50% with strong CYP1A2 inhibitor	
Bortezomib	1.3 mg/m^2 2x/wk Days 1, 4, 8, 11/3 wks	1.3 mg/m^2 1x/wk Days 1, 8, 15, 22/5 wks	1.0 mg/m^2 1x/wk Days 1, 8, 15, 22/5 wks
Ixazomib	4 mg/day Days 1, 8, 15/4 wks	First reduction: 3 mg Hold Tx if low blood counts or PN (resume at lower dose)	Second reduction: 2.3 mg/day; discontinue if grade 4 PN
Prednisone	60 mg/m^2 Days 1-4 or 50 mg QD	30 mg/m^2 Days 1-4 or 25 mg QD	15 mg/m^2 Days 1-4 or 12.5 mg QD
Cyclophosphamide	100 mg/day Days 1-21/4 wks or 300 mg/m^2/day Days 1, 8, 15/4 wks	50 mg/day Days 1-21/ 4 wks or 150 mg/m^2/day Days 1, 8, 15/4 wks	50 mg/day Days 1-21/4 wks or 75 mg/m^2/day Days 1, 8, 15/4 wks

Palumbo A, et al. Blood. 2011;118:4519-4529. Palumbo A, et al. Blood. 2015;125:2068-2074.
Ixazomib [package insert]. Pomalidomide [package insert].

Slide credit: clinicaloptions.com

The CAR T-cell Preparation Process

- Anti-BCMA-CART bb2121: optimized autologous T-cell product expressing chimeric antigen receptors specific to BCMA, which is expressed by nearly all MM cells[1,2]



- 95.5% ORR in phase I trial with dose of > 150 x 106 (n = 22)[3]
  - All 16 patients with response to bb2121 evaluated for MRD were MRD negative at ≥ 1 time point
- 63% of pts experienced CRS; mostly low grade and manageable with tocilizumab and corticosteroids[3]

1. Friedman KM, et al. Hum Gene Ther. 2018;29:585-601. 2. Ali SA, et al. Blood. 2016;128:1688-1700. 3. Raje NS, et al. ASCO 2018. Abstract 8007.

Slide credit: clinicaloptions.com

Questions?