Levine Cancer Institute

Updates on Options for Relapsed/Refractory Disease

Saad Usmani, MD, FACP
Director, Plasma Cell Disorders Program
Director, Clinical Research in Hematologic Malignancies
Department of Hematologic Oncology & Blood Disorders
Levine Cancer Institute
Charlotte, North Carolina

Outline

- Practical considerations in choosing therapy for relapsed and/or refractory MM
- New options for relapsed MM (1–3 prior therapies)
- Role of transplant in relapsed and/or refractory MM

When to Consider Retreatment in Relapsed/Refractory MM

- Nature of relapse/progression
  - Slow/biochemical vs rapid/high burden
  - Renal failure, sPCL, EMD, bone fractures, cytogenetic abnormalities
- Host factors
  - Age, comorbidities, performance status, organ failure
- Prior therapies/treatment-related factors
  - Tolerability, dose reductions, adverse events (AEs)/serious adverse events (SAEs)
  - Duration of therapy and durability of previous response
- Socioeconomic aspects
  - Insurance issues, access to care, adequate social support
- Availability of clinical trials

Treatment Approaches in Relapsed/Refractory MM

Slow relapse or first relapse

Participate in clinical trials with novel agents

Immunomodulatory drug (IMiD)–based regimen	Proteasome inhibitor (PI)–based regimen	Autologous transplant
• Underlying PN • Prior IMiD use with durable/deep response • Prior bortezomib use	• Prior IMiD use • Prior bortezomib use with durable/deep response • Translocation (4;14)	• Long remission post first transplant (>24–36 months) • Transplant not part of primary therapy

PN, peripheral neuropathy

Usmani SZ, Lonial S. *Clin Lymphoma Myeloma Leuk*. 2014;14 Suppl:S71.

ASPIRE Study Design

28-day cycles

Randomization
N=792

Stratification:
- **β2 microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

KRd

Carfilzomib 27 mg/m² IV (10 min)
Days 1, 2, 8, 9, 15, 16 (20 mg/m² Days 1, 2, cycle 1 only)
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on Days 1, 2, 15, 16
After cycle 18, carfilzomib discontinued

Rd

Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

LEN NAÏVE OR LEN SENSITIVE

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

ASPIRE Results

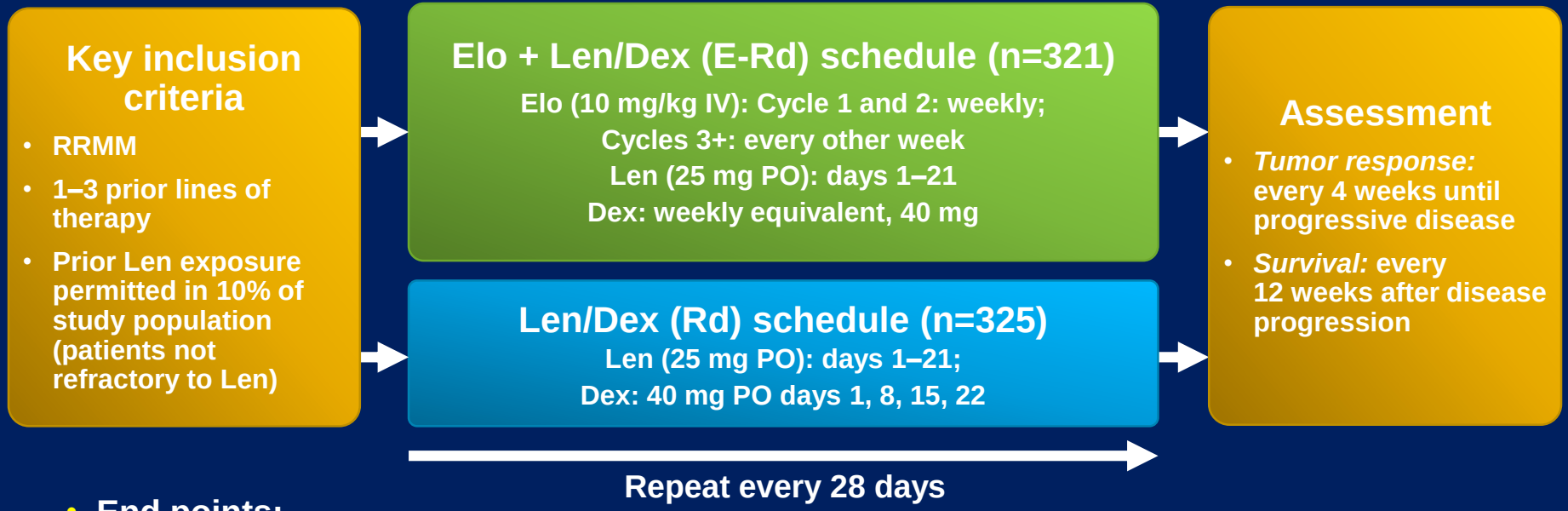
	KRd (n=396)	Rd (n=396)	HR	*P* Value
Median PFS, mos	26.3	17.6	0.69	0.0001
24-mo OS, %	73.3	65	0.79	0.04
≥CR, %	31.8	9.3	—	<0.001
Discontinuation	15.3	17.7	—	—
AEs, %				
≥G3 cardiac failure	3.8	1.8	—	—
≥G3 ischemic heart disease	3.3	2.1	—	—
≥G3 hypertension	4.3	1.8	—	—
≥G3 acute renal failure	3.3	3.1	—	—

No benefit observed in patients who were previously non-responsive to bortezomib and refractory to immunomodulatory agent.

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

ELOQUENT-2 Study Design

Open-label, international, randomized, multicenter phase 3 trial (168 global sites)



- End points:
  - Co-primary: PFS and overall response rate (ORR)
  - Other: OS (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

LEN NAÏVE OR LEN SENSITIVE

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

ELOQUENT-2 Results

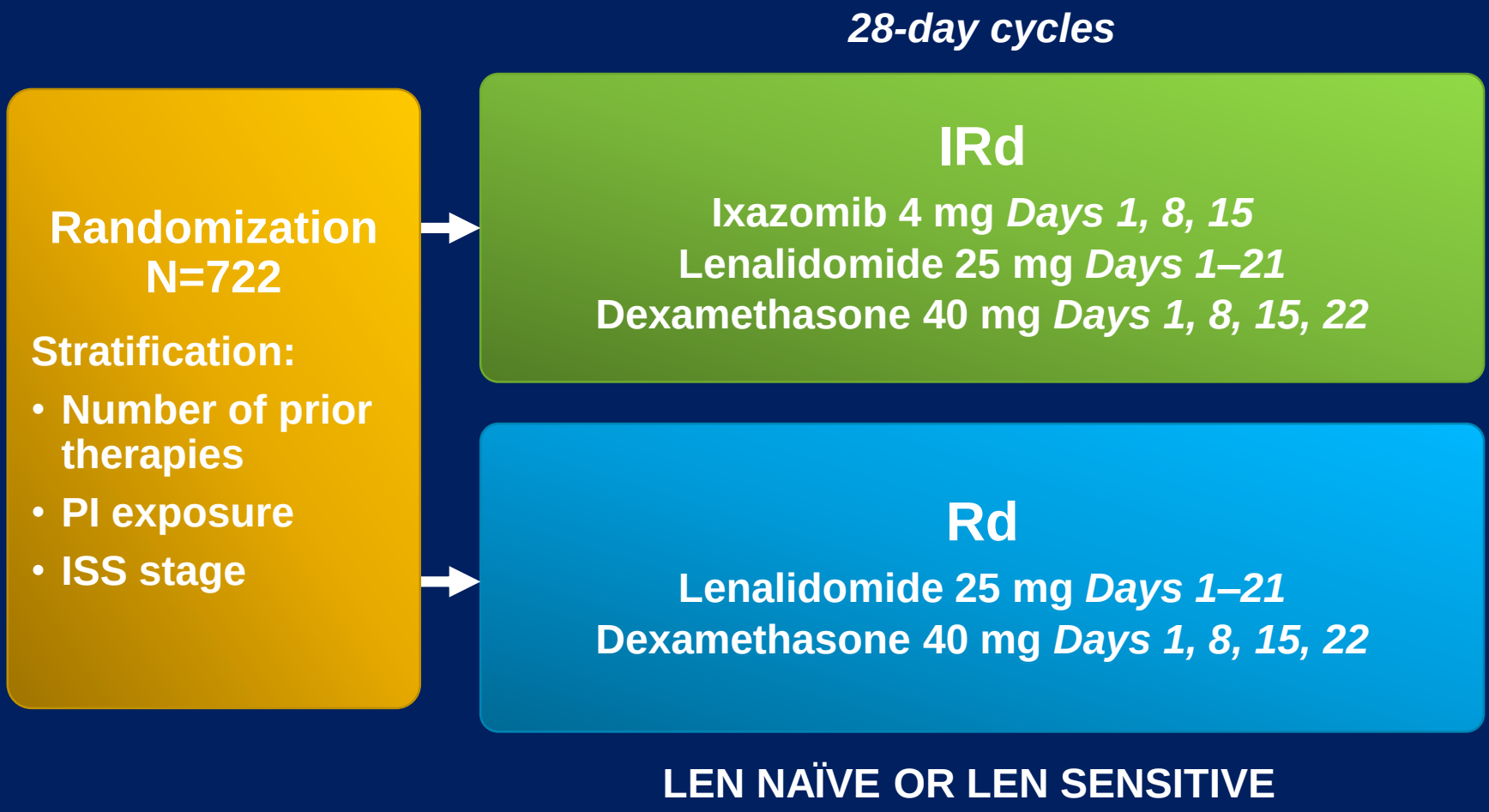
	E-Rd (n=321)	Rd (n=325)	HR	*P* Value
Median PFS, mos	19.4	14.9	0.70	<0.001
ORR, %	79	66	—	<0.001
≥VGPR, %	33	28	—	—
AEs, %				
≥G3 cardiac failure	4	6	—	—
≥G3 acute renal failure	4	4	—	—

No benefit observed in patients who were previously exposed to immunomodulatory agent.

Patients with del17p, 1q21 amplifications and t(4;14) faired as well as standard risk.

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

TOURMALINE-MM1 Study Design



Moreau P et al. Presented at: 57th ASH Annual Meeting & Exhibition. Orlando, FL; December 2015. Abstract 727.

TOURMALINE-MM1 Results

	I-Rd (n=360)	Rd (n=362)	HR	*P* Value
Median PFS, mos	20.6	14.7	0.742	0.012
ORR, %	78.3	71.5	—	0.035
≥VGPR, %	48.1	39.0	—	0.014
AEs, %				
≥G3 Diarrhea	6	2	—	—
≥G3 PN	2	2	—	—

Benefit with IRd was also noted in pts with high-risk cytogenetics.

Moreau P et al. Presented at: 57th ASH Annual Meeting & Exhibition. Orlando, FL; December 2015. Abstract 727.

ENDEAVOR Study Design

Randomization 1:1
N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of administration

Kd

Carfilzomib 56 mg/m^2 IV
Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 Days 1, 2, cycle 1 only)
Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg
Days 1, 2, 8, 9, 15, 16, 22, 23
28-day cycles until disease progression or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m^2 (3–5 second IV bolus or subcutaneous injection)
Days 1, 4, 8, 11

Dexamethasone 20 mg
Days 1, 2, 4, 5, 8, 9, 11, 12
21-day cycles until disease progression or unacceptable toxicity

BOR NAÏVE OR BOR SENSITIVE

ISS, International Staging System

Dimopoulos MA et al. *J Clin Oncol*. 2015;33. Abstract 8509.

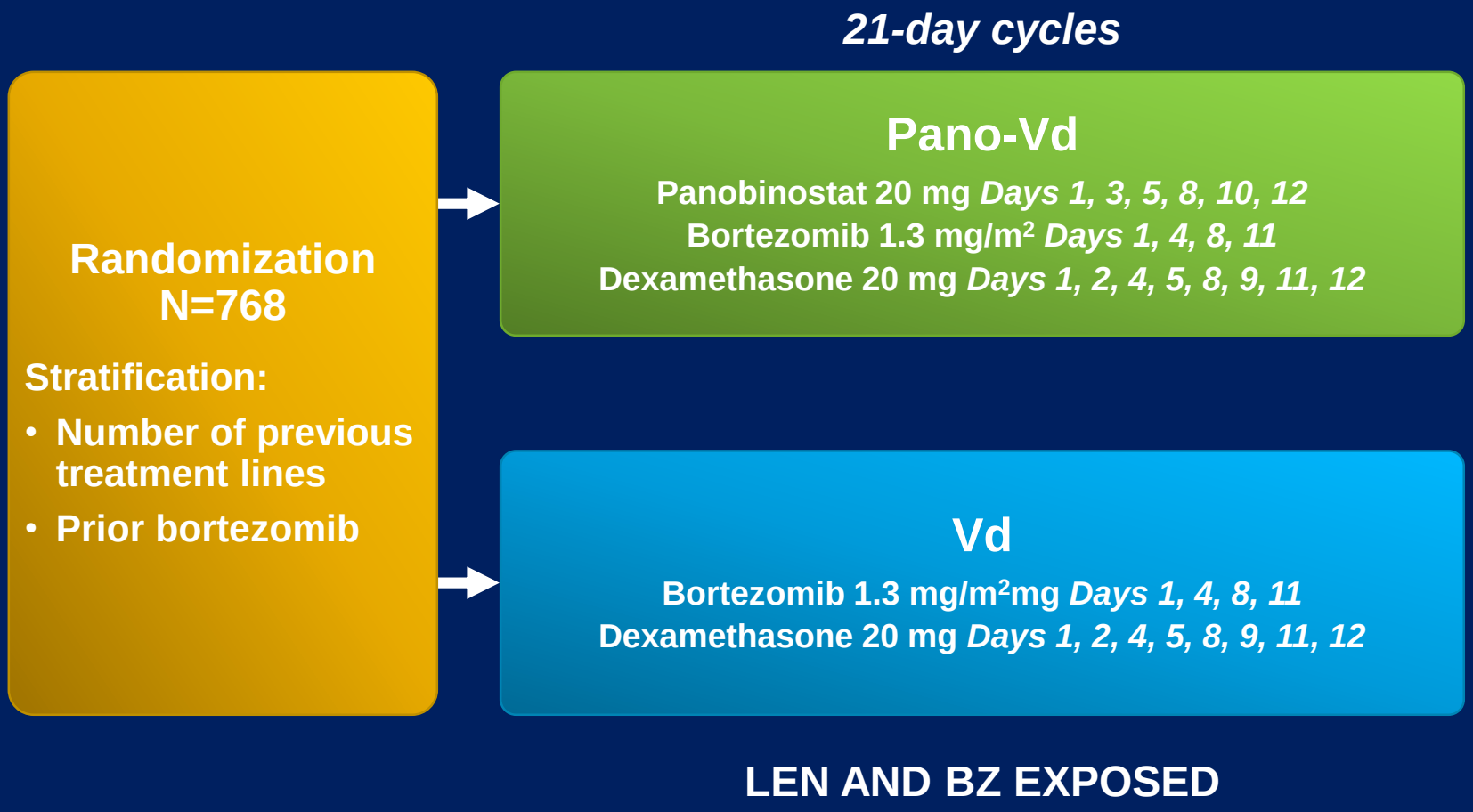
ENDEAVOR Results

	Kd (n=464)	Vd (n=465)	HR	*P* Value
Median PFS, mos	18.7	9.4	0.53	<0.0001
≥CR, %	12.5	6.2	—	—
≥VGPR, %	54.3	28.6	—	—
Discontinuation	14.0	15.7	—	—
AEs, %				
≥G3 Hypertension	8.9	2.6	—	—
≥G3 Dyspnea	5.6	2.2	—	—
≥G3 Cardiac failure	4.8	1.8	—	—
≥G3 Acute renal failure	4.1	2.6	—	—
≥G2 PN	6.3	32.0	—	<0.0001

No benefit observed in patients refractory to lenalidomide

Dimopoulos MA et al. *J Clin Oncol*. 2015;33. Abstract 8509.

PANORAMA1 Study Design



San Miguel JF et al. *Lancet Oncol*. 2014;15:1195.

PANORAMA1 Results

	Pano-Vd (n=387)	Vd (n=381)	HR	*P* Value
Median PFS, mos	12	8.1	0.63	<0.0001
ORR, %	60.7	54.6	—	0.09
≥nCR, %	27.6	15.7	—	<0.001
IMiD + bortezomib, mos	10.6	5.8	--	--
IMiD + bortezomib + ≥2 prior lines, mos	12.5	4.7	--	--
AEs, %				
≥G3 Diarrhea	25	7	—	—
≥G3 Asthenia	24	12	—	—
≥G3 PN	17	15	—	—

Benefit less pronounced in women and patients > 65 years BUT more evident in patients who with previous exposure to bortezomib and immunomodulatory agent.

San Miguel JF et al. *Lancet Oncol*. 2014;15:1195.

Treatment Approaches in Relapsed/Refractory MM

First relapse

Participate in clinical trials with novel agents

IMiD-based regimen

- Underlying PN
- Prior IMiD use with durable/deep response
- Prior bortezomib use

PI-based regimen

- Prior IMiD use
- Prior bortezomib use with durable/deep response
- Translocation (4;14)

Autologous transplant

- Long remission post 1st transplant (>18–24 months)
- Transplant not part of primary therapy

Len-naïve

KRd, IRd
Elo-Rd (high risk)

Bor-naïve

Kd, KRd, IRd

Len/Bor-exposed

Pano-Vd

Usmani SZ, Lonial S. *Clin Lymphoma Myeloma Leuk*. 2014;14 Suppl:S71.

Treatment Approaches in Relapsed/Refractory MM

≥ second relapse

Participate in clinical trials with novel agents

Chemotherapy for rapid relapse

- VTD-PACE, DT-PACE, DCEP
- Especially for extramedullary disease, secondary plasma cell leukemia

IMiD- or PI-based regimen

- Carfilzomib/ Dex ± IMiD
- Pomalidomide/ Dex ± PI
- PI preference for translocation (4;14)

Transplant

- Autologous: usually a short-term fix
- Allogeneic: for select group, in a clinical trial setting

Double-Refractory, ≥3 Prior Lines

Daratumumab

Usmani SZ, Lonial S. *Clin Lymphoma Myeloma Leuk*. 2014;14 Suppl:S71.

Summary of PI Combination Therapy

Regimen	Phase	N	Outcomes, %				Notes
			ORR	CR	VGPR	PR	
Carfilzomib + lenalidomide + LoDex[1]	2	84	69	4.8	35.7	28.6	ORR similar in bor- or len-refractory pts
Bortezomib+ pomalidomide + LoDex[2]	1	28	70	7	37	26	
Carfilzomib + pomalidomide + dexamethasone[3]	2	79	70	–	27	43	PFS: 9.7 mos
Carfilzomib + cyclophosphamide + thalidomide + dexamethasone[4]	1b/2	64*	91	5	51	22	PFS 76% (24 mos)

*In newly diagnosed MM

CR, complete response; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

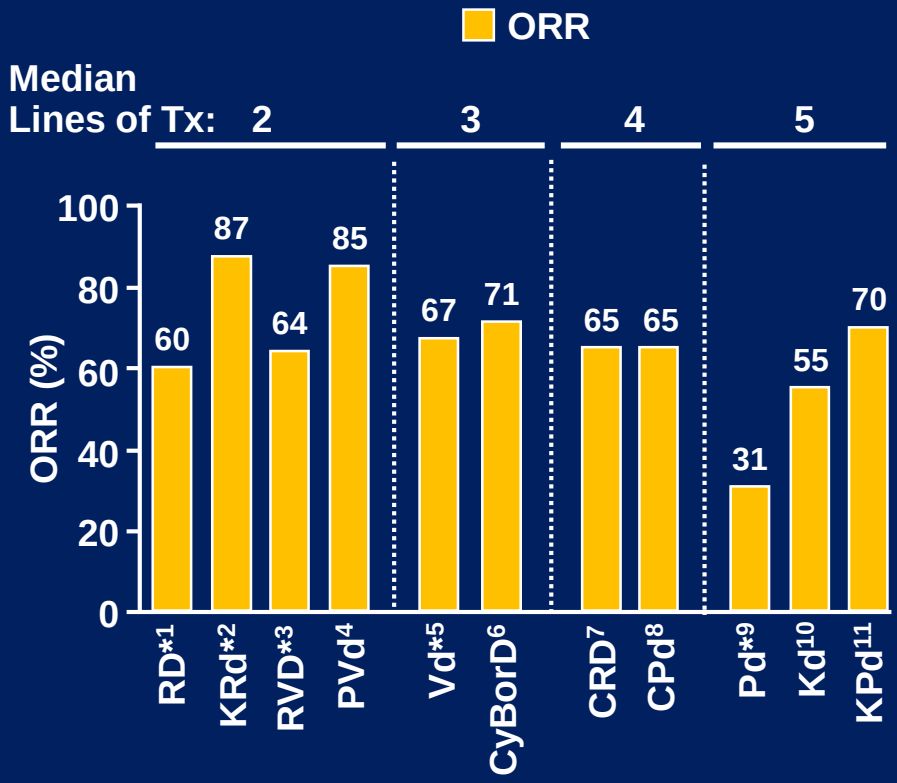
1. Wang M et al. *Blood*. 2013;122:3122.
2. Richardson PG et al. *J Clin Oncol*. 2014;32. Abstract 8589.
3. Shah JJ et al. *Blood*. 2013;122. Abstract 690.
4. Mikhael JR et al. *Br J Haematol*. 2015;169:219.

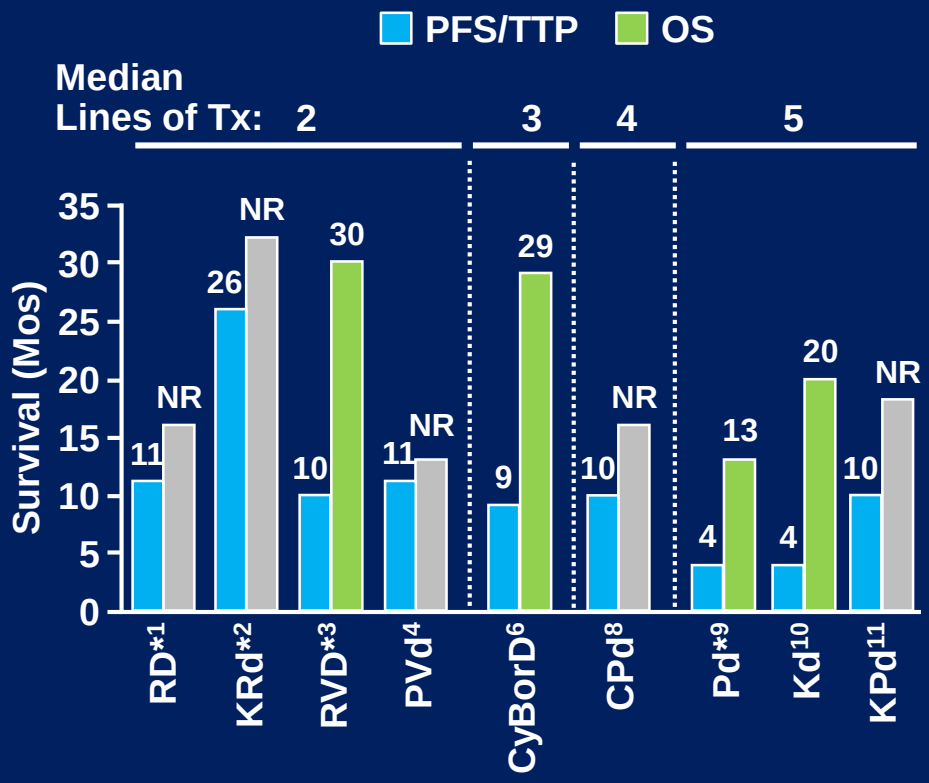
Summary of Other Notable Combination Therapy

Regimen	Phase (N)	Outcomes	
		ORR	CBR
Panobinostat + carfilzomib + dexamtheasone[1]	1 (36)	77%	88% (1 pt CR, 10 pts VGPR, 16 pts PR, 4 pts MR, 4 pts SD)
Daratumumab + lenalidomide + dexamtheasone[2]	1/2 (32)	88%	–
Daratumumab + pomalidomide + dexamtheasone[3]	1b (77)	58.5%	–
Ricolinostat ± bortezomib + dexamethasone[4]	1 (20)	25% (heavily pretreated)	60% (2 pts VGPR, 3 pts PR, 2 pts MR, 5 pts SD)
Ricolinostat + lenalidomide + dexamethasone[5]	1 (22)	64%	100% (1 pt CR, 5 pts VGPR, 8 pts PR, 3 pts MR, 5 pts SD)

1. Berdeja JG et al. J Clin Oncol. 2015;33. Abstract 8513.
2. Plesner T et al. Presented at: 57th ASH Annual Meeting & Exhibition. Orlando, FL; December 2015. Abstract 507.
3. Chari A et al. Presented at: 57th ASH Annual Meeting & Exhibition. Orlando, FL; December 2015. Abstract 508.
4. Raje N et al. *Blood*. 2013;122. Abstract 759.
5. Raje N et al. EHA 2014. Abstract P358.

Summary of Combination Therapy





*Data from phase 3 trials, all others from phase 1 or 2 trials

1. Dimopoulos M et al. *N Engl J Med*. 2007;357:2123. 2. Stewart AK et al. *N Engl J Med*. 2015;372:142.
3. Richardson PG et al. *Blood*. 2014;123:1461. 4. Lacy MQ et al. *Blood*. 2014. Abstract 304.
5. Mikhael JR et al. *Br J Haematol*. 2009;144:169. 6. Monge J et al. *J Clin Oncol*. 2014. Abstract 8586.
7. Morgan GJ et al. *Br J Haematol*. 2007;137:268. 8. Baz R et al. *Blood*. 2014. Abstract 303.
9. San Miguel J et al. *Lancet Oncol*. 2013;14:1055. 10. Lendvai N et al. *Blood*. 2014;124:899.
11. Shah JJ et al. *Blood*. 2013. Abstract 690.

Salvage Autologous Stem Cell Transplant

- Option for:
  - Patients who deferred autologous stem cell transplant for first relapse
  - ≥18 month PFS benefit from first autologous stem cell transplant
  - Special considerations: improve cytopenias and bridge to clinical trial or allogeneic stem cell transplant

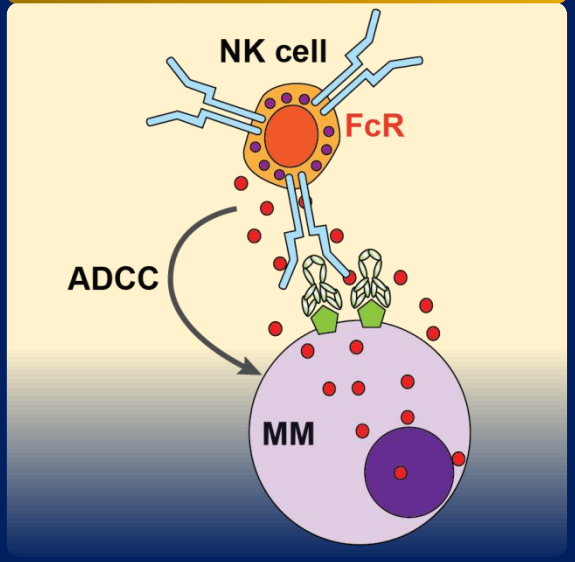
Giralt S et al. *Biol Blood Marrow Transplant*. 2015;21:2039.

Salvage Allogeneic Stem Cell Transplant

- Nonrandomized experience showing long-term disease control in some patients
- Randomized tandem auto-SCT vs auto-SCT/allo-SCT: nonrelapse mortality higher, survival similar
- Option for young, fit MM patients, BMT-CTN 1302 phase 2 trial accruing for high-risk patients

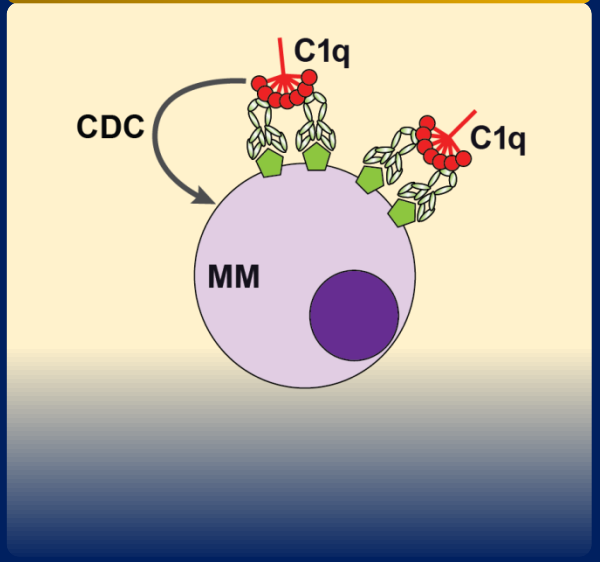
Monoclonal Antibody–Based Therapeutic Targeting of MM

Antibody-dependent cellular cytotoxicity (ADCC)



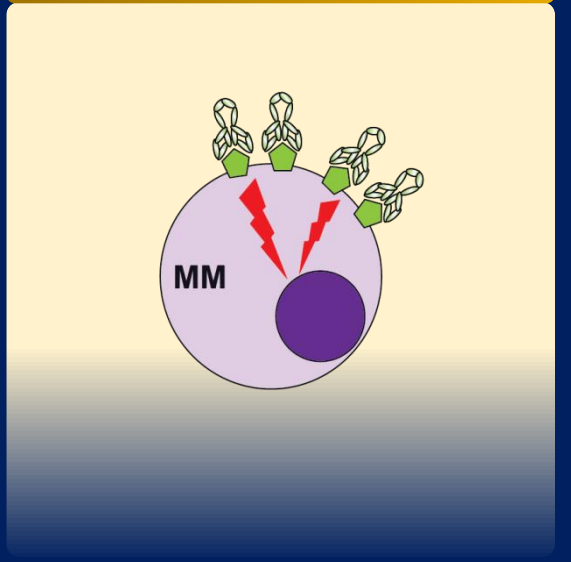
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent cytotoxicity (CDC)



- Daratumumab (CD38)

Apoptosis/growth arrest via targeting signaling pathways



- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Tai YT, Anderson KC. *Bone Marrow Res*. 2011;2011:924058.

Thank you for your attention!

LCI-Pineville

LCI-Northeast

LCI-Main

LCI-Lincoln

AnMed

CMC

LCI-Union

LCI-Mercy

Blue Ridge

Cleveland Regional

Stanly Regional

Roper St. Francis

LCI-University