Living Well with Myeloma Teleconference Series

Thursday, March 24th 2016

4:00 PM Pacific/5:00 PM Mountain

6:00 PM Central/7:00 PM Eastern

imf
International Myeloma Foundation

International Myeloma Foundation
MARCH
MYELOMA ACTION MONTH
Myeloma Action Month is an initiative of the IMF

Speakers


Dr. Brian Durie

Dr. Brian Durie, IMF Chairman
Cedars Sinai Samuel Oschin Cancer Center
Los Angeles, CA


Dr. Rafat Abonour

Dr. Rafat Abonour
Indiana University Simon Cancer Center
Indiana, IN


Dr. Vincent Rajkumar

Dr. Vincent Rajkumar
Mayo Clinic
Rochester, MN

Top Questions Needing Answers Episode 1 !

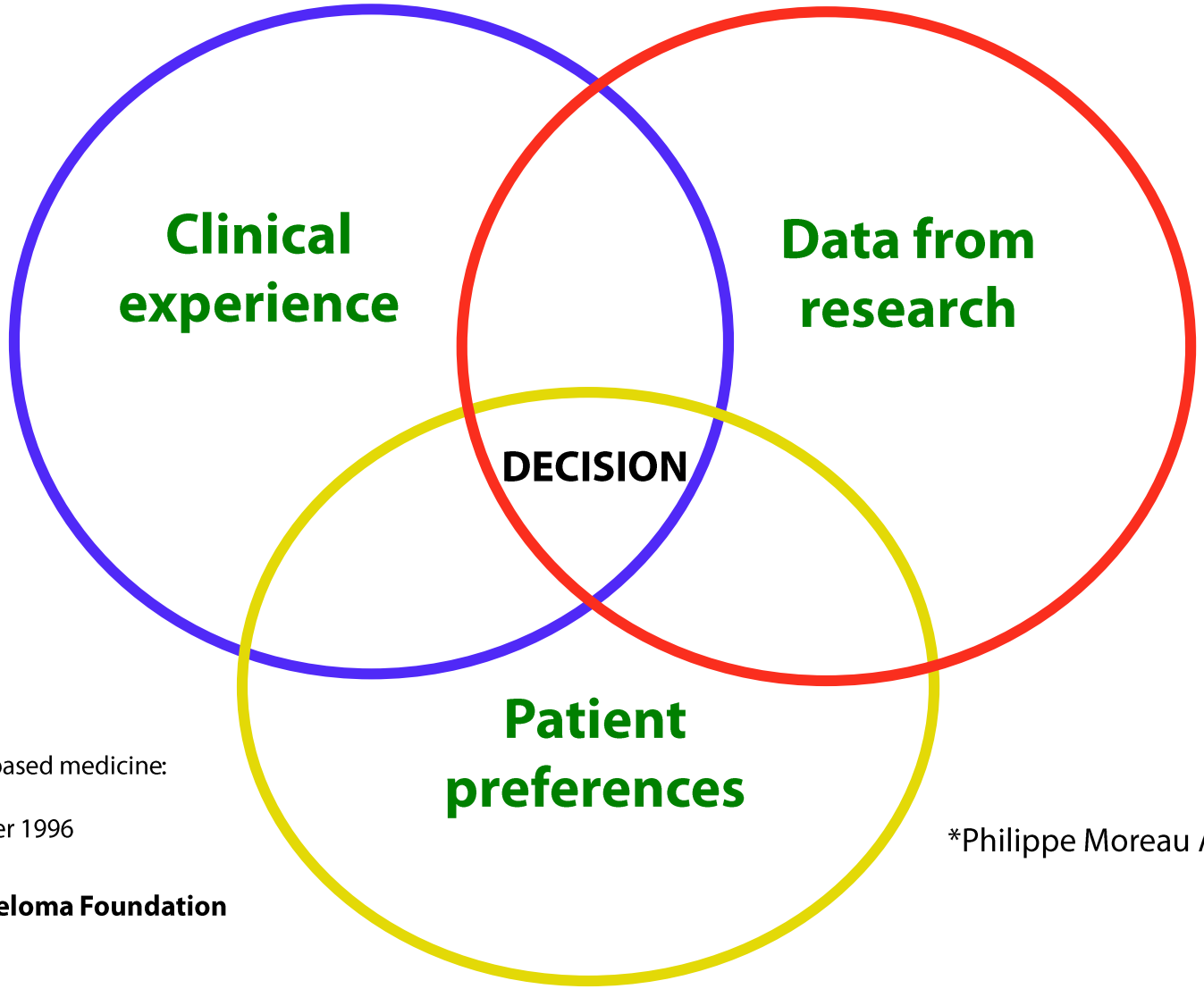
1. How to use newly approved agents:
    - Farydak® (panobinostat)
    - Darzalex® (daratumumab)
    - Ninlaro® (ixazomib)
    - Empliciti® (elotuzumab)

2. Are CAR-T cells the future best therapy?

Agents for Discussion Today

Agent	Use	Combination
Farydak® (panobinostat)	**Relapse/Refractory**	**+ Velcade®/ Dexamethasone**
Darzalex® (daratumumab)	**Relapse/Refractory**	**Single agent**
Ninlaro® (ixazomib)	**Relapse: >2 prior regimens**	**+ Revlimid®/ Dexamethasone**
Empliciti® (elotuzumab)	**Relapse: 1-3 prior regimens**	**+ Revlimid®/ Dexamethasone**

The Decision Process*



EVIDENCE-BASED MEDICINE
Sackett DL & al., « Evidence based medicine: what it is and what it isn't »
BMJ, vol. 312, no 7023, janvier 1996

*Philippe Moreau ASH 2015

Treatment Approaches in Relapsed/Refractory MM

First relapse

Participate in clinical trials with novel agents

IMiD-based regimen	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 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

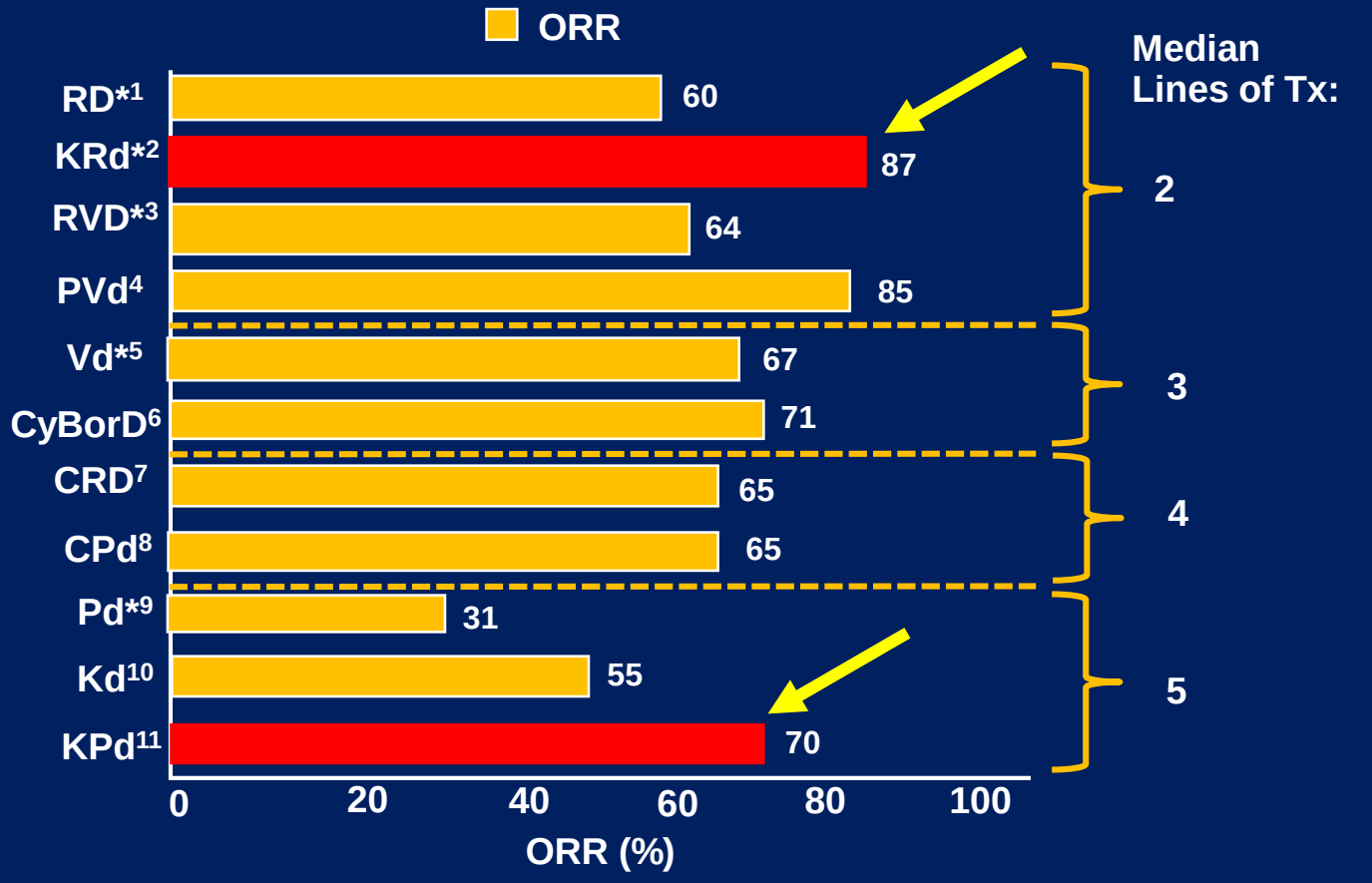
Chemotherapy for rapid relapse	IMiD- or PI-based regimen	Transplant
• VTD-PACE, DT-PACE, DCEP • Especially for extramedullary disease, secondary plasma cell leukemia	• Carfilzomib/ Dex ± IMiD • Pomalidomide/ Dex ± PI • PI preference for translocation (4;14)	• Autologous: usually a short-term fix • Allogeneic: for select group, in a clinical trial setting

Dual (Len/Bor) refractory OR ≥3 prior Lines

Daratumumab

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

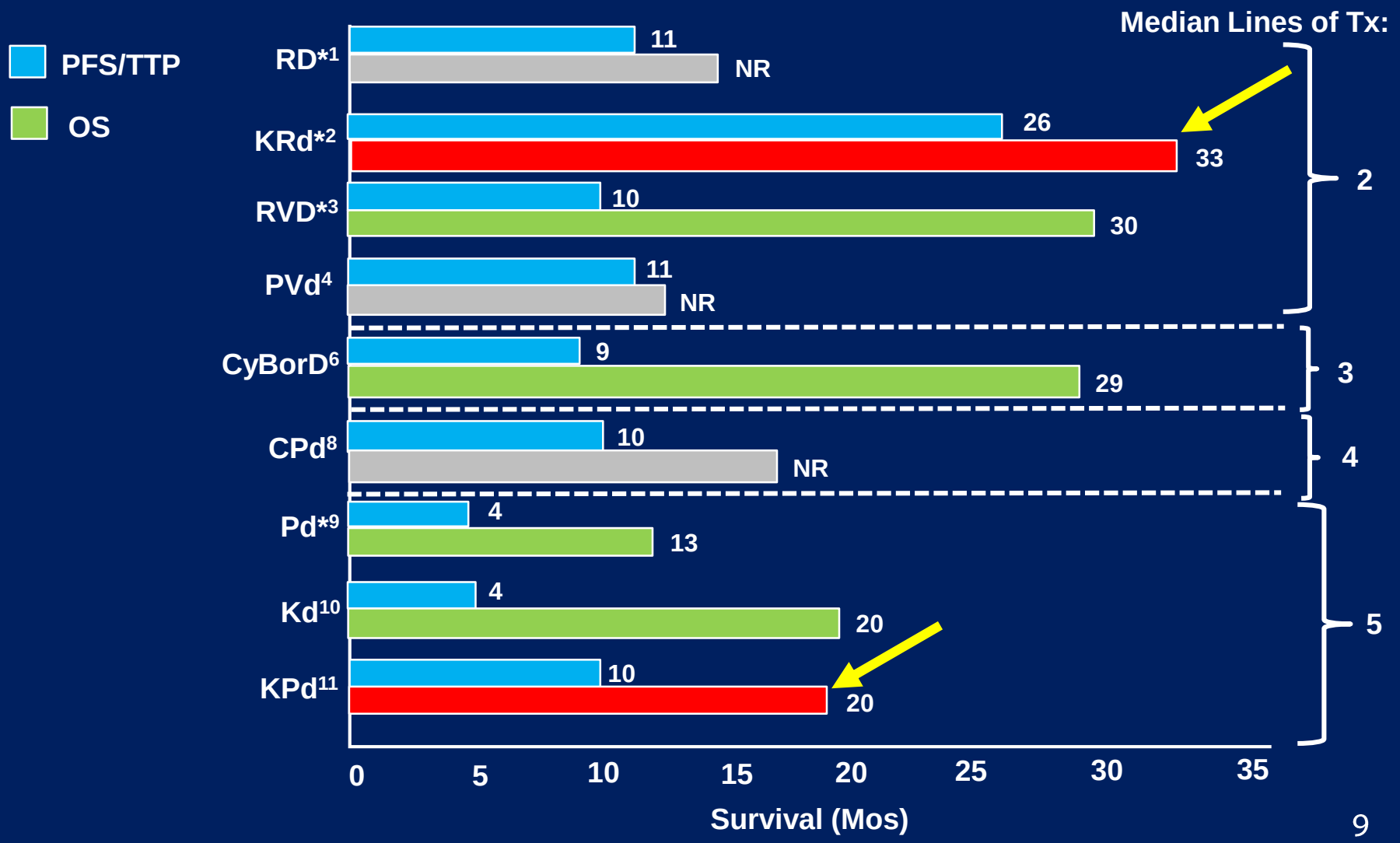
Summary of Combination Therapy at Relapse



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.

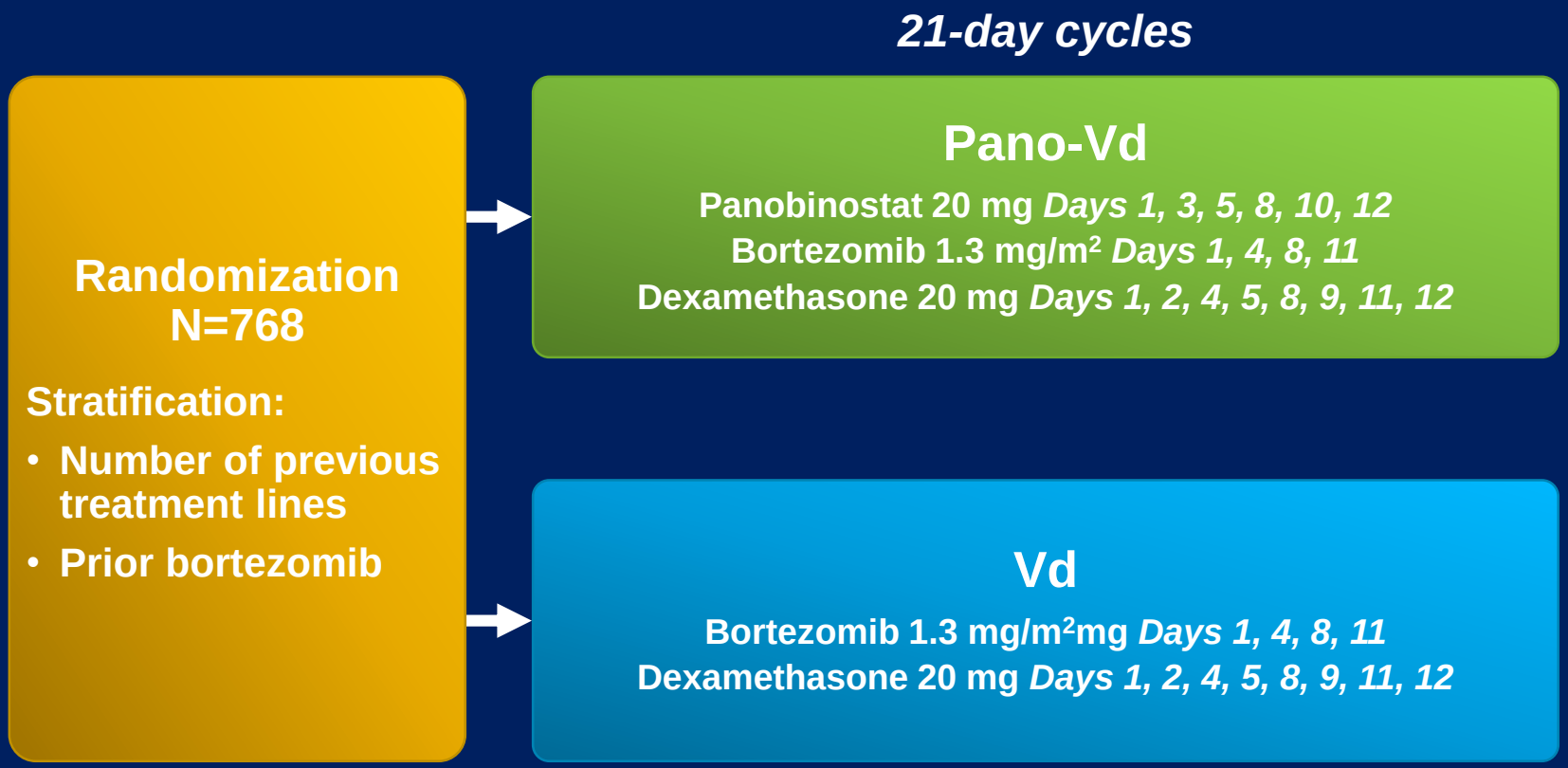
***Data from phase 3 trials, all others from phase 1 or 2 trials**

Summary of Combination Therapy at Relapse



How to use Farydak® (panobinostat)

PANORAMA1 Study Design



BOR NAÏVE OR BOR SENSITIVE

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.

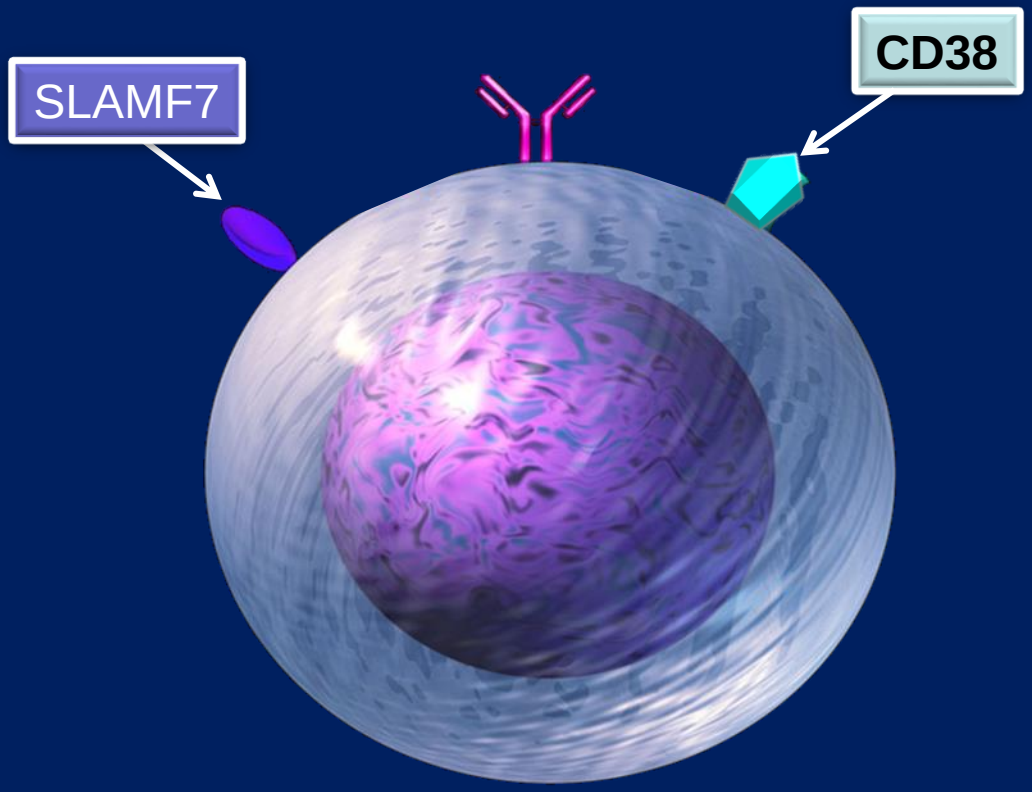
Summary of Other Notable HDAC Combinations

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

1. Raje N et al. *Blood*. 2013;122. Abstract 759.
2. Raje N et al. EHA 2014. Abstract P358.
3. Berdeja JG et al. *J Clin Oncol*. 2015;33. Abstract 8513.

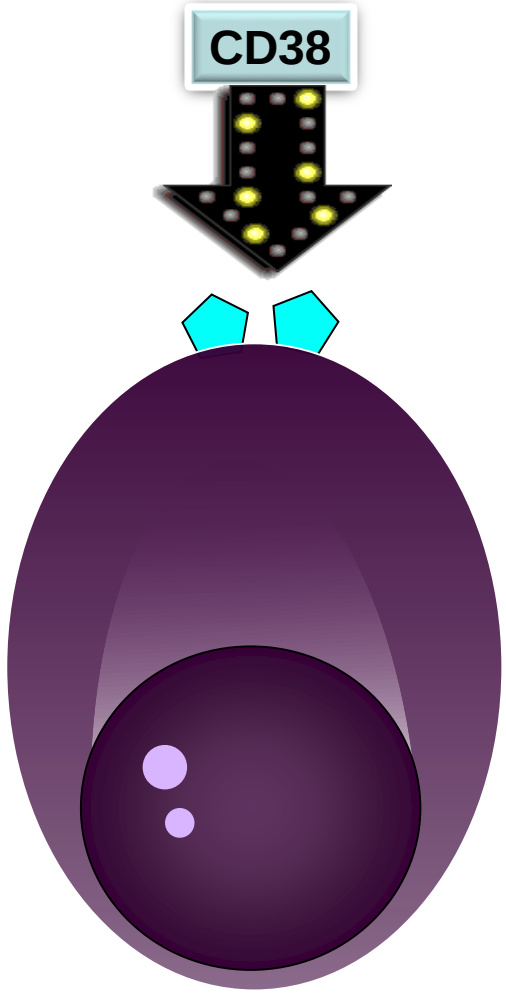
When do you recommend panobinostat?

Targets on the Myeloma Cell Surface

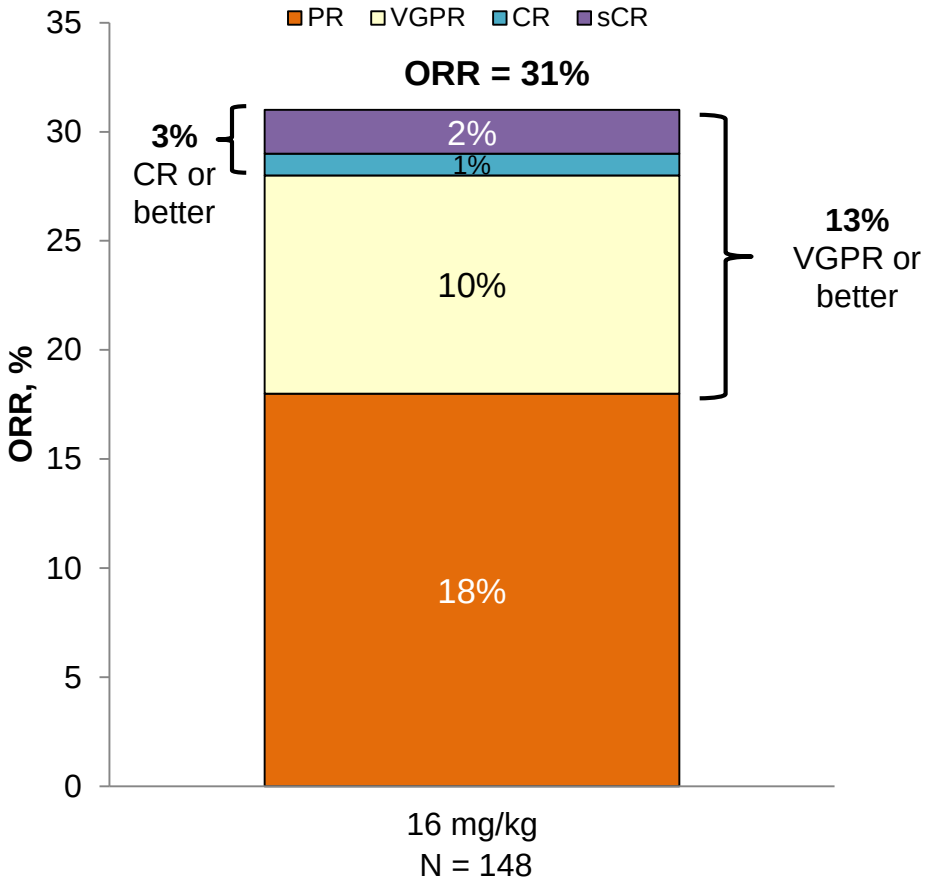


What's "Dara"?

- Daratumumab is an IV human IgG manufactured antibody
- It is a targeted immunotherapy which binds to CD38

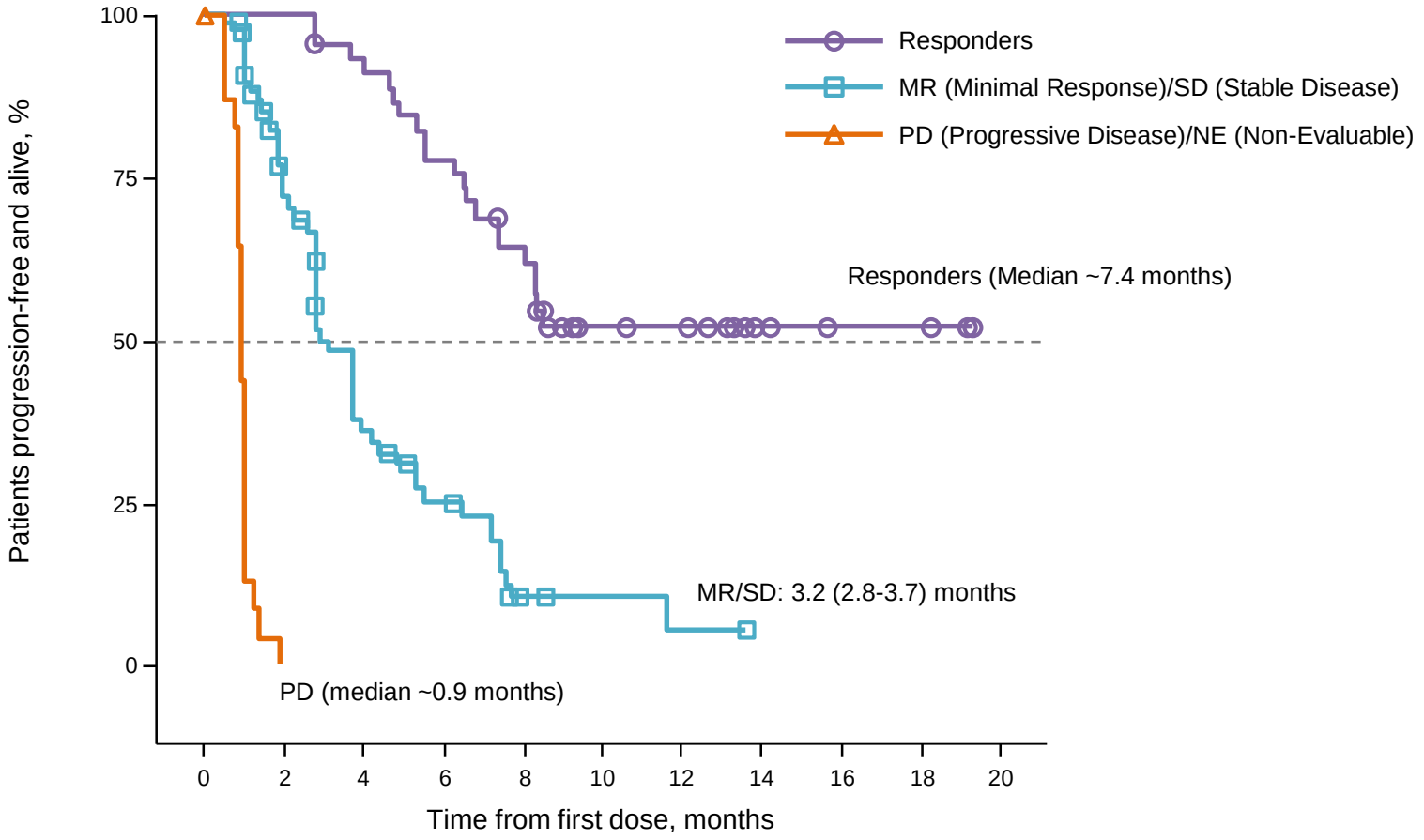


Efficacy in Combined Analysis



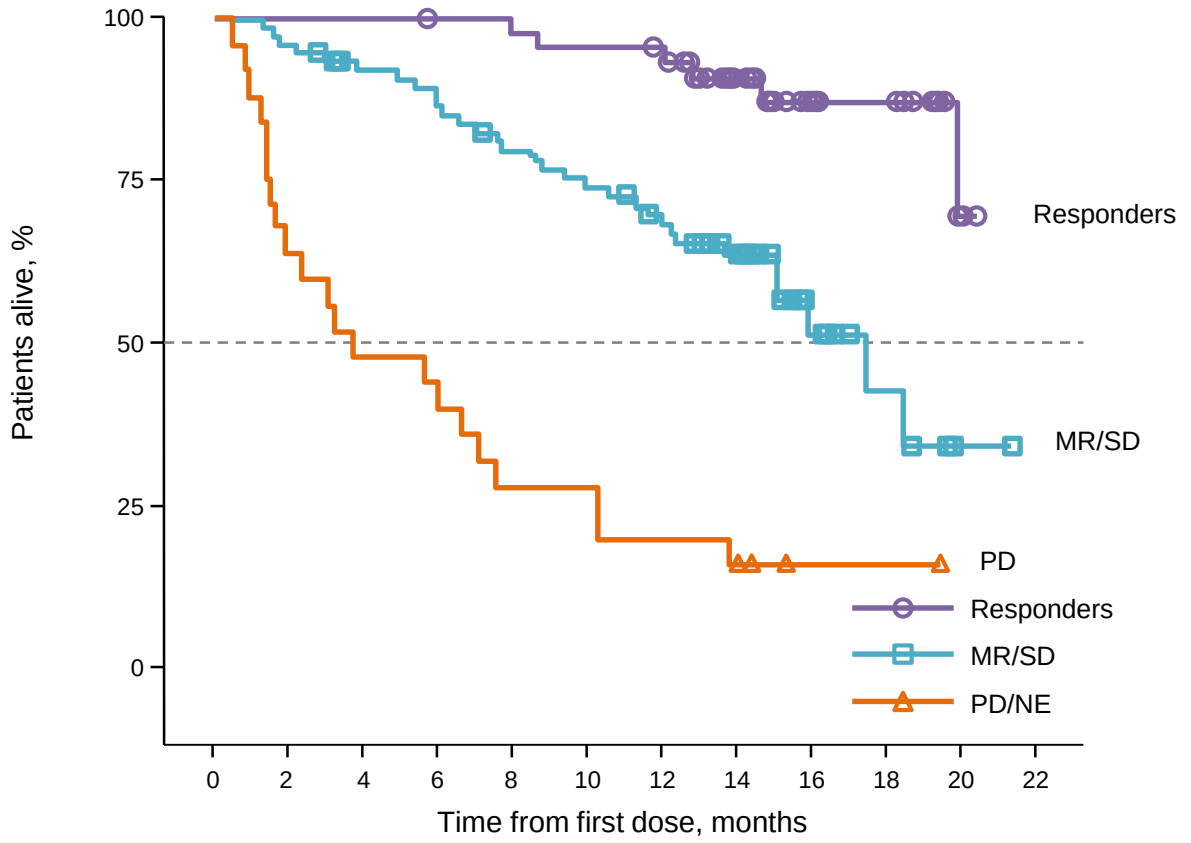
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Progression-free Survival



Patients at risk											
Responders	46	46	41	35	27	14	13	5	3	3	0
MR/SD	77	45	21	13	3	2	1	0	0	0	0
PD/NE	25	0	0	0	0	0	0	0	0	0	0

Overall Survival



Patients at risk												
Responders	46	46	46	45	44	43	42	29	15	13	3	0
MR/SD	77	74	67	63	57	53	47	37	10	5	1	0
PD/NE	25	16	12	11	7	7	5	4	1	1	0	0

For the combined analysis, median OS = 19.9 months

1-year overall survival rate = 69% (95% CI, 60.4-75.6)

When do you recommend “DARA”?

What about Ixazomib (Ninlaro®)?

TOURMALINE-MM1 Study Design

28-day cycles

Randomization
N=722

Stratification:

- Number of prior therapies
- PI exposure
- ISS stage

IRd

Ixazomib 4 mg *Days 1, 8, 15*
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

Rd

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

LEN NAÏVE OR LEN SENSITIVE

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	—	—

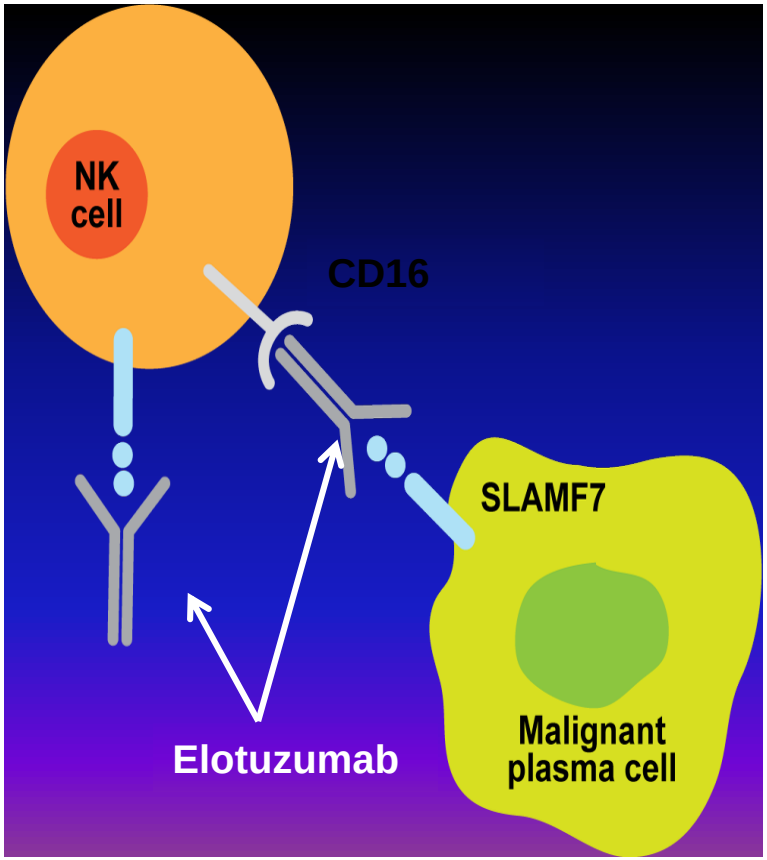
Benefit with IRd was also noted in pts with high-risk cytogenetics.

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

When do you recommend Ixazomib (Ninlaro®)?

What's "Elo"?

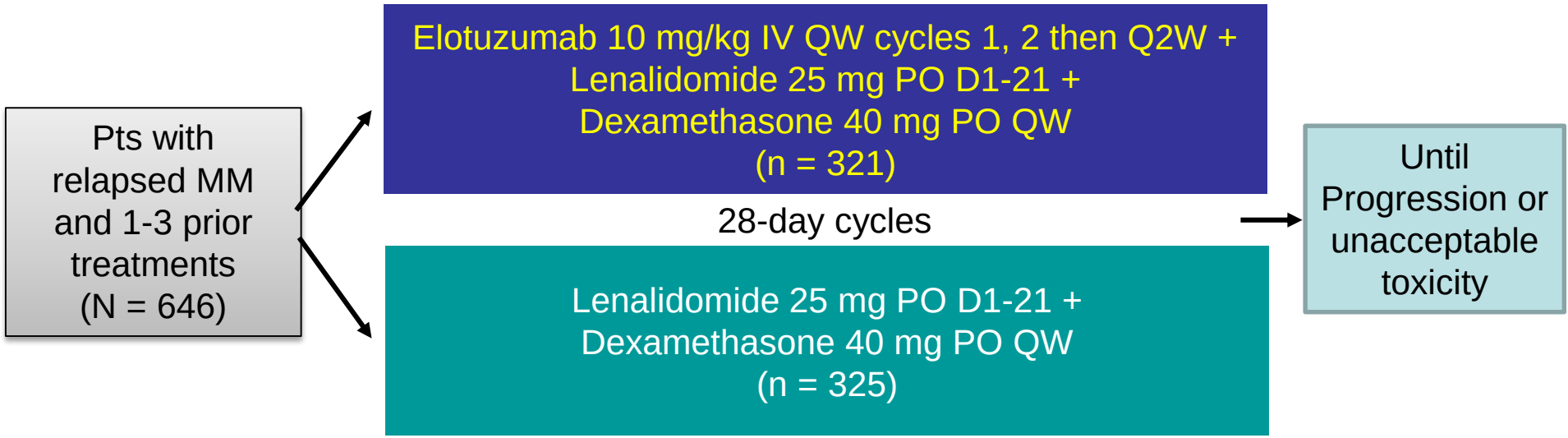
Elotuzumab (HuLuc63) is an IV humanized monoclonal antibody targeting human SLAMF7, a cell surface glycoprotein.



Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784. Tai YT et al. Blood. 2008;112:1329-1337.
van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624. Lonial S et al. Blood. 2009;114:432. Richardson PG, et al. ASH 2014. Abstract 302

ELOQUENT-2: Elotuzumab With Lenalidomide/Dexamethasone R/R MM

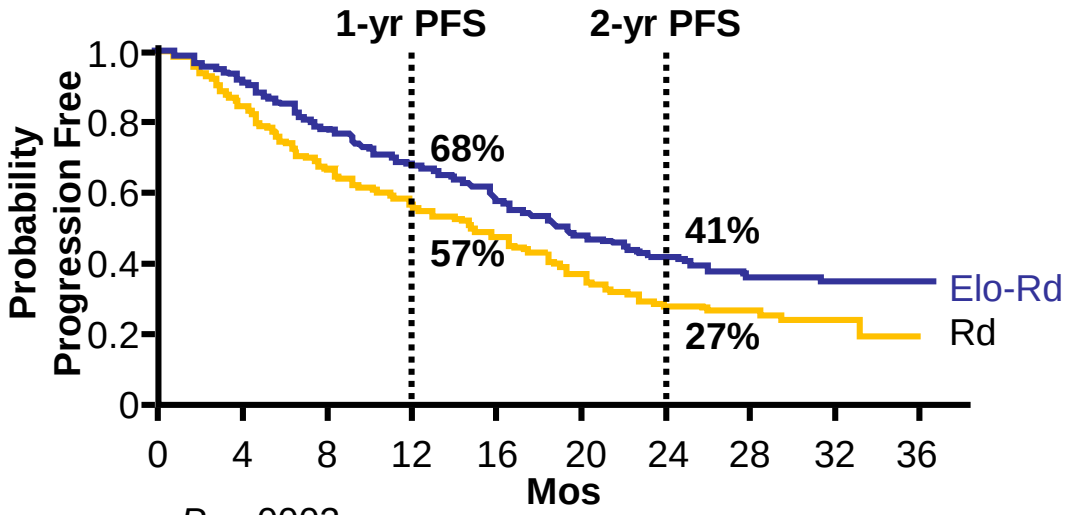
- Randomized, open-label, multicenter phase III trial



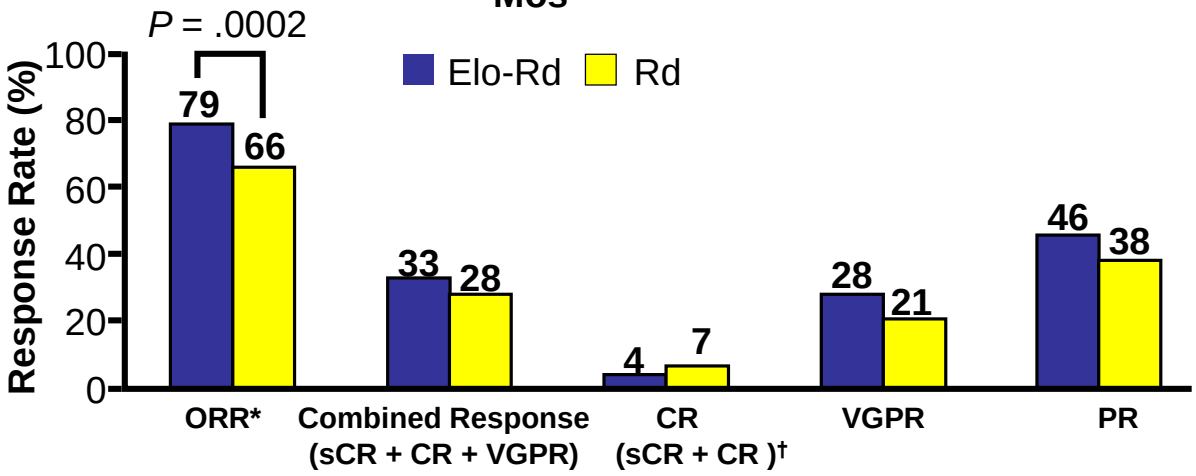
- Primary endpoints: Progression Free time (PFS), Overall Response
- Secondary endpoints: Overall Survival, safety, health-related Quality of Life

Dimopoulos MA, et al. ASH 2015. Abstract 28.

ELOQUENT-2: Progression Free and Overall Response



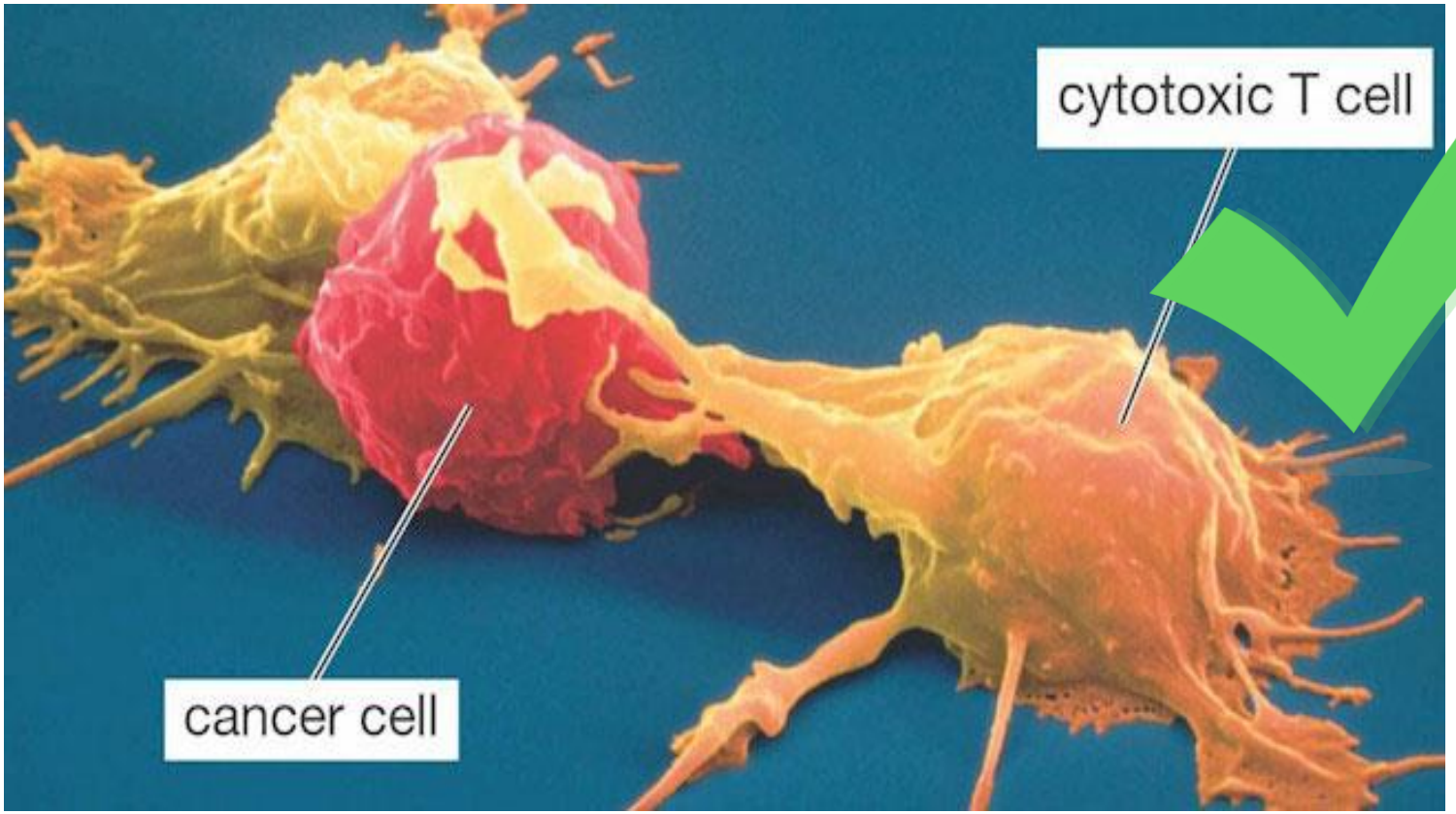
	Elo-Rd	Rd
Median PFS, mos (95% CI)	19.4 (16.6-22.2)	14.9 (12.1-17.2)



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

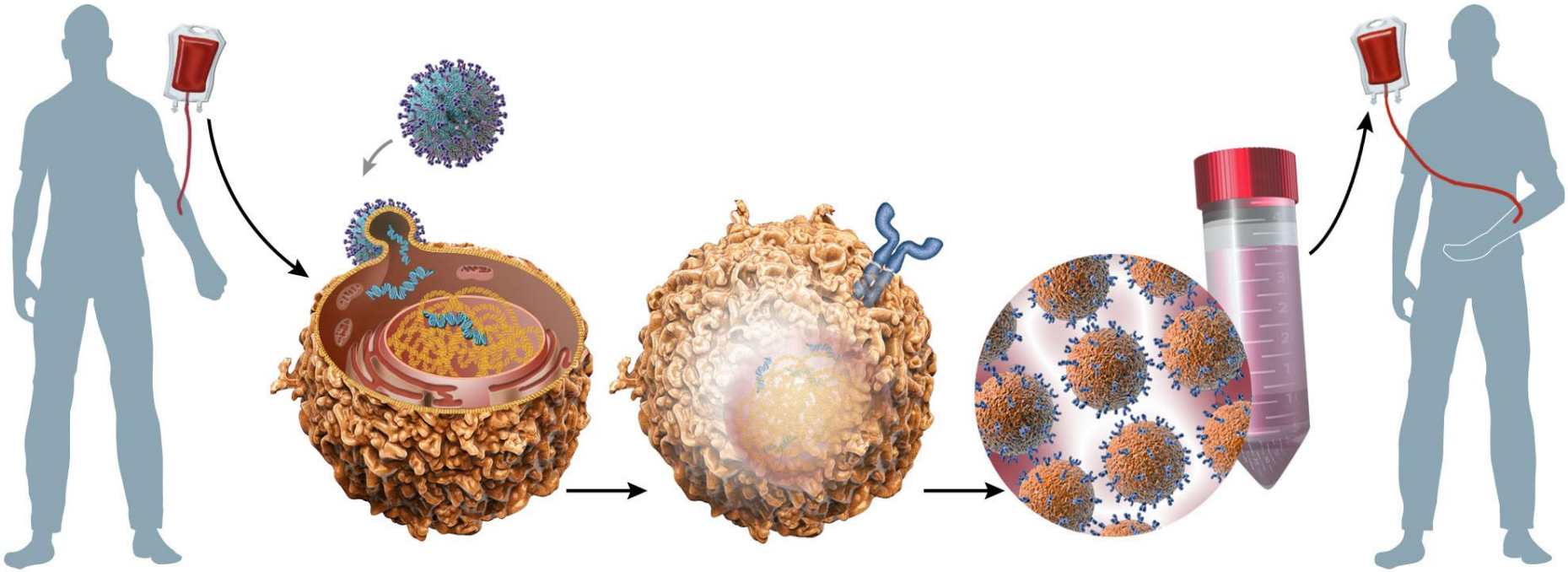
When do you recommend Elo?

CAR –T Immune Therapy



T cells are white blood cells that attack and kill viruses and cancer cells

Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells



1. T cells are collected from the patient. A machine removes the desired cells from the blood, then returns the rest back to the patient.

2. A modified virus (blue) is used to transfer DNA to the patient's T cells so they will produce CAR proteins.

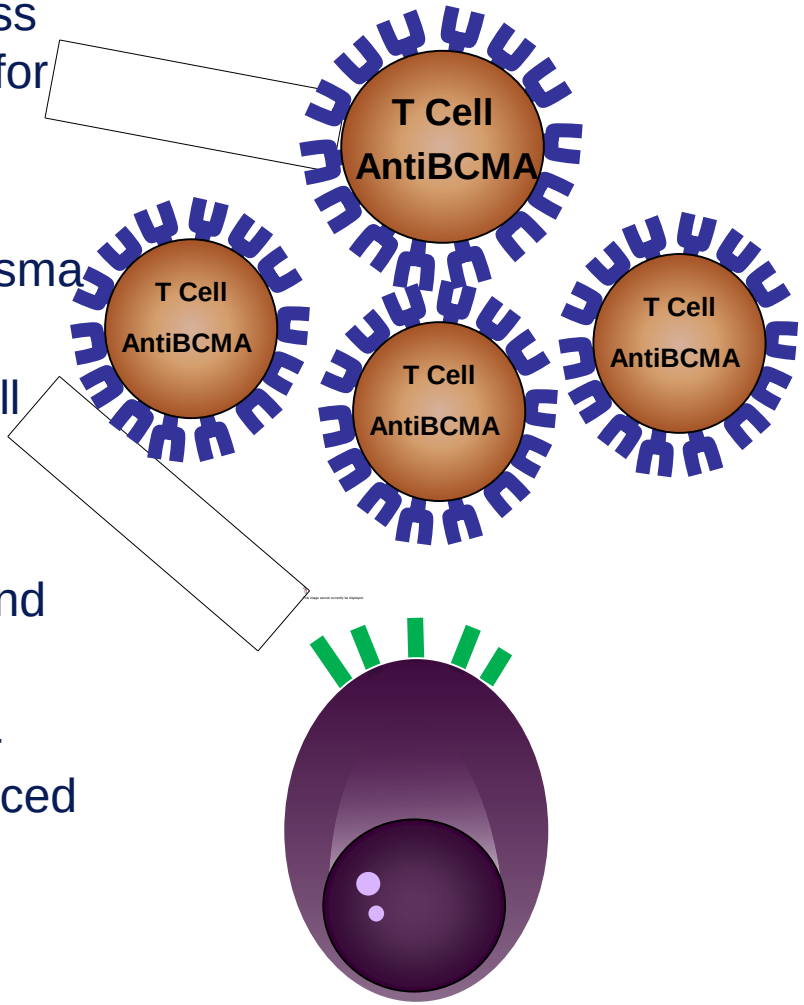
3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.

4. Once designed, millions of engineered CAR T cells are grown in the laboratory.

5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion

CAR-BCMA T Cells in Myeloma: Background

- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for malignancy-associated antigens
- B-cell maturation antigen (BCMA) is expressed by normal and malignant plasma cells.
  - BCMA is a potential target for CAR T-cell therapy for MM
- The patient's own T-cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion.
- Study presented ASH 2015 evaluated CAR-BCMA T cell infusion for treatment of advanced MM



1. Carpenter RO, et al. Clin Cancer Res. 2013;19:2048-2060. Ali SA, et al. ASH 2015. Abstract LBA-1.

CAR-BCMA T Cells in Myeloma: Study Design

- First-in-human phase I trial

- Pts with advanced relapsed/ refractory MM
- More than 3 prior lines of therapy;
  - BCMA expression on myeloma cells
- 12 patients enrolled

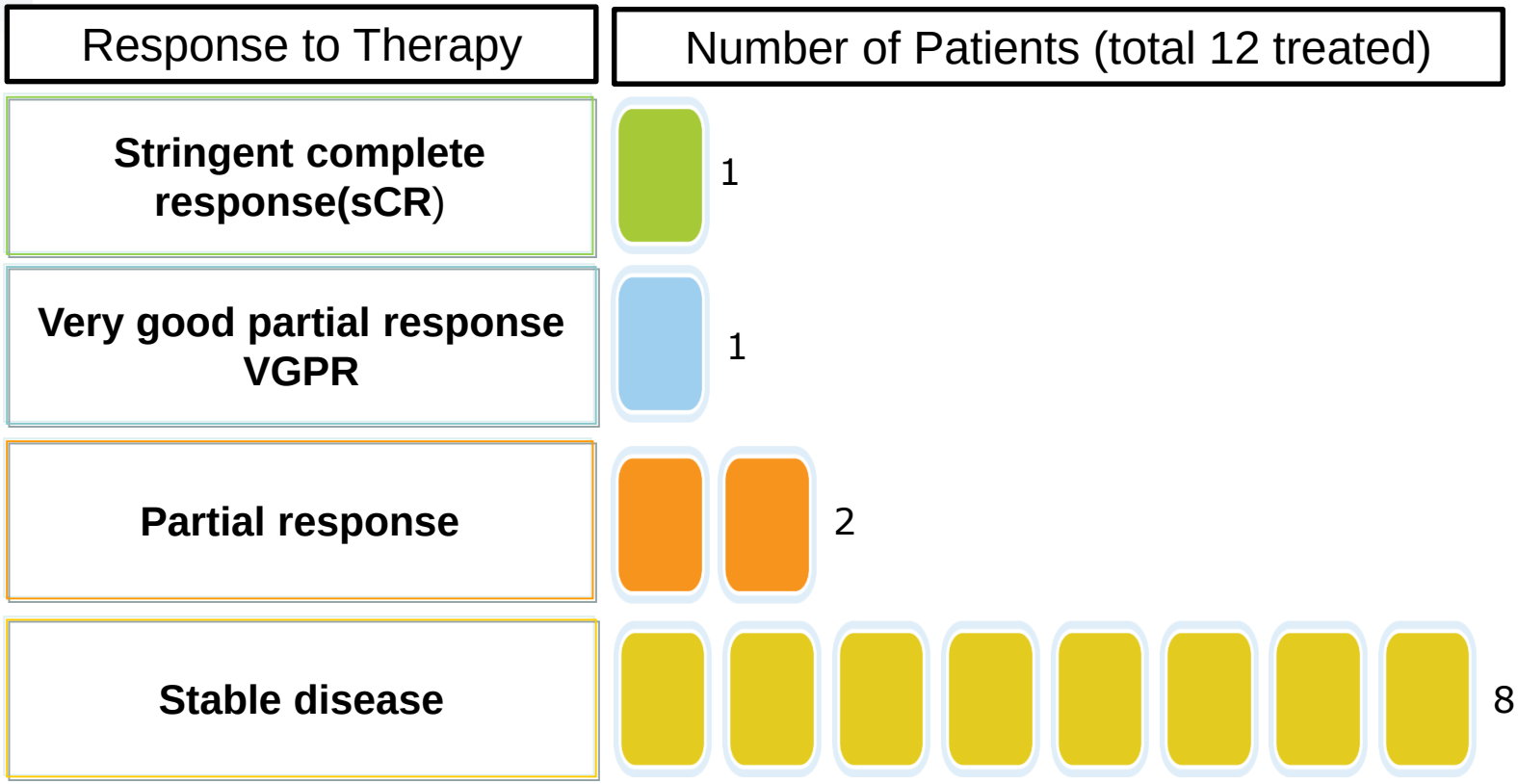
→ Cyclophosphamide 300 mg/m^2
Fludarabine 30 mg/m^2
QD for 3 days

→ CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg
0.3×10^6
1.0×10^6
3.0×10^6
9.0×10^6

Ali SA, et al. ASH 2015. Abstract LBA-1.

CAR-BCMA T Cells in Myeloma: Response to therapy



Ali SA et al. *Proc ASH* 2015;Abstract LBA1.

SO:

- **Are CAR-T cells worth all the hype?**

- **What other therapies can play an important role?**

Support

Bristol-Myers Squibb


imf
International Myeloma Foundation