Weighing the Options at First Relapse

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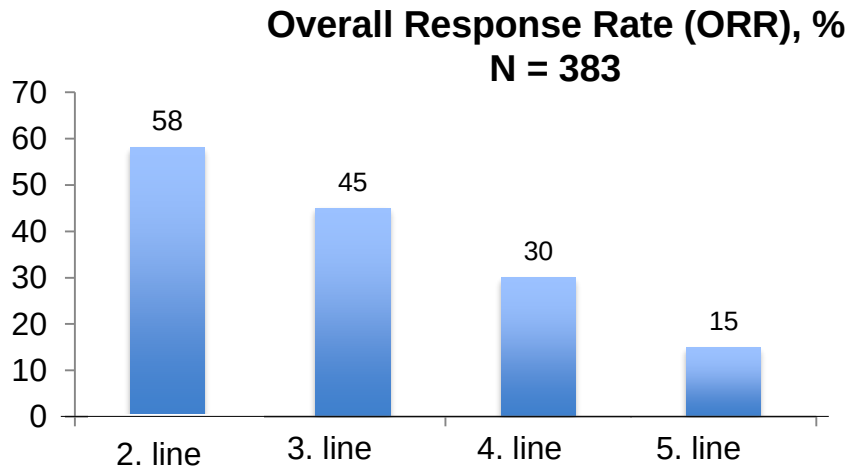
European Expert Perspective on Treatment at Disease Progression

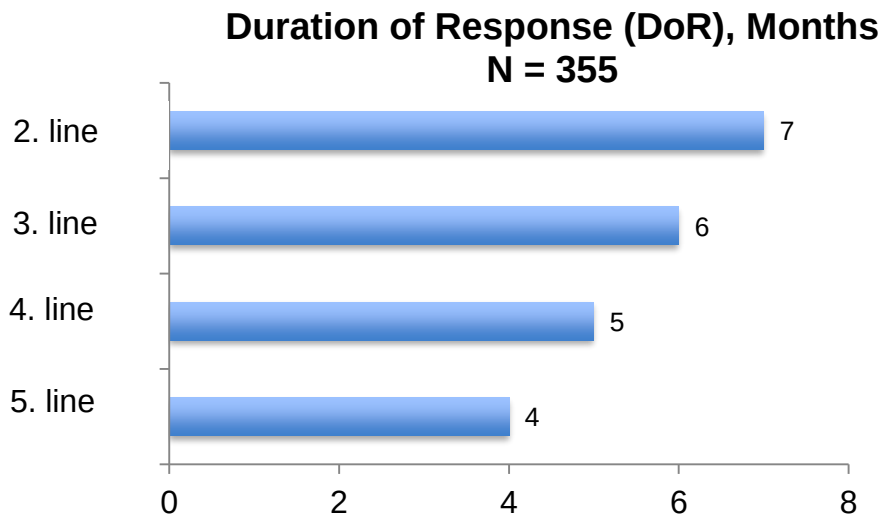
Definition	Treatment indication, if:
Clinical relapse	• Development of new soft-tissue plasmacytomas or bone lesions • Definite increase in size of existing plasmacytomas or bone lesions • Hypercalcemia (11.5 mg/dL; 2.65 mmol/L) • Decrease in hemoglobin of >2 g/dL (1.25 mmol/L), because of myeloma • Rise in serum creatinine by 2 mg/dL or more (177 mmol/L) or more), because of myeloma • Hyperviscosity requiring therapeutic intervention
Significant biochemical relapse in patients <u>without</u> clinical relapse *(IMW Paris 2011)*	• Doubling of the M-component in two consecutive measurements separated by <2 months with the reference value of 5 g/L, **<u>or</u>** • In two consecutive measurements any one of the following changes: – increase of the absolute levels of serum M protein by <u>≥</u>10 g/L – increase of urine M protein by <u>≥</u>500 mg per 24 hours – increase of involved FLC level by <u>≥</u>20 mg/dL (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

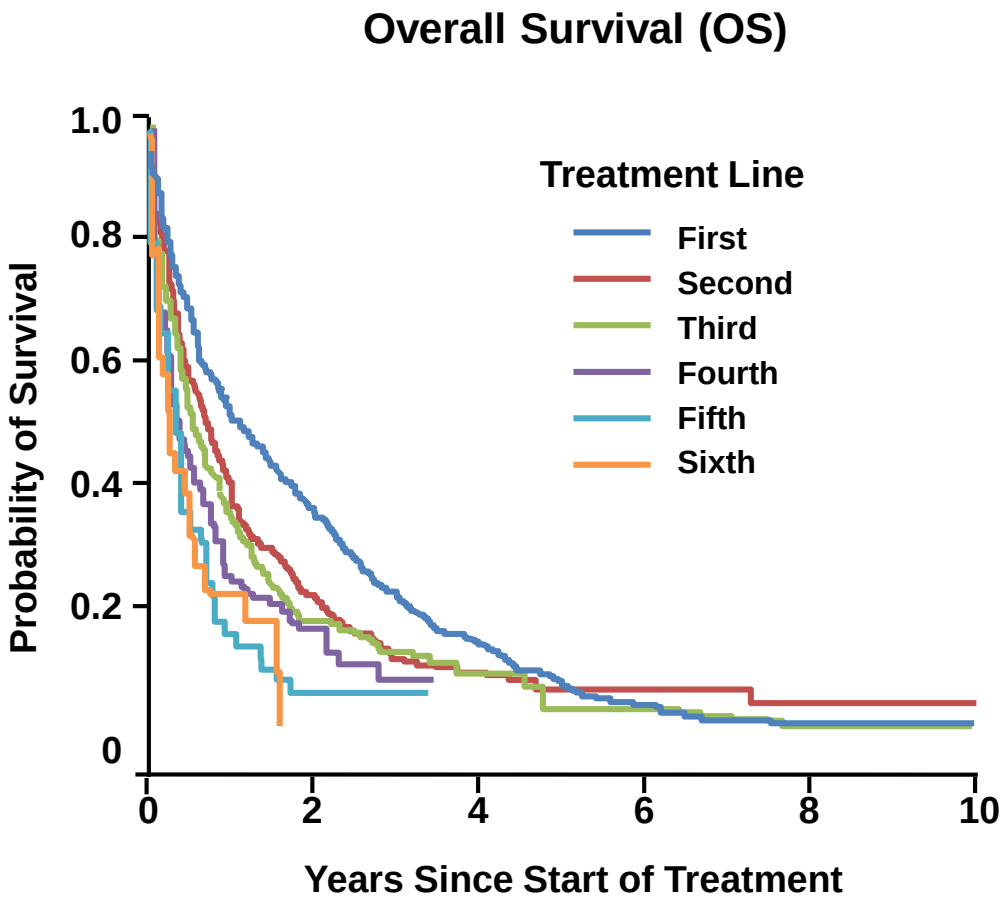
FLC, free light chain

Ludwig H, et al. *Oncologist*. 2014;19(8):829-844.

Reduction in Response Rate, Quality, and Duration With Each Additional Line of Treatment

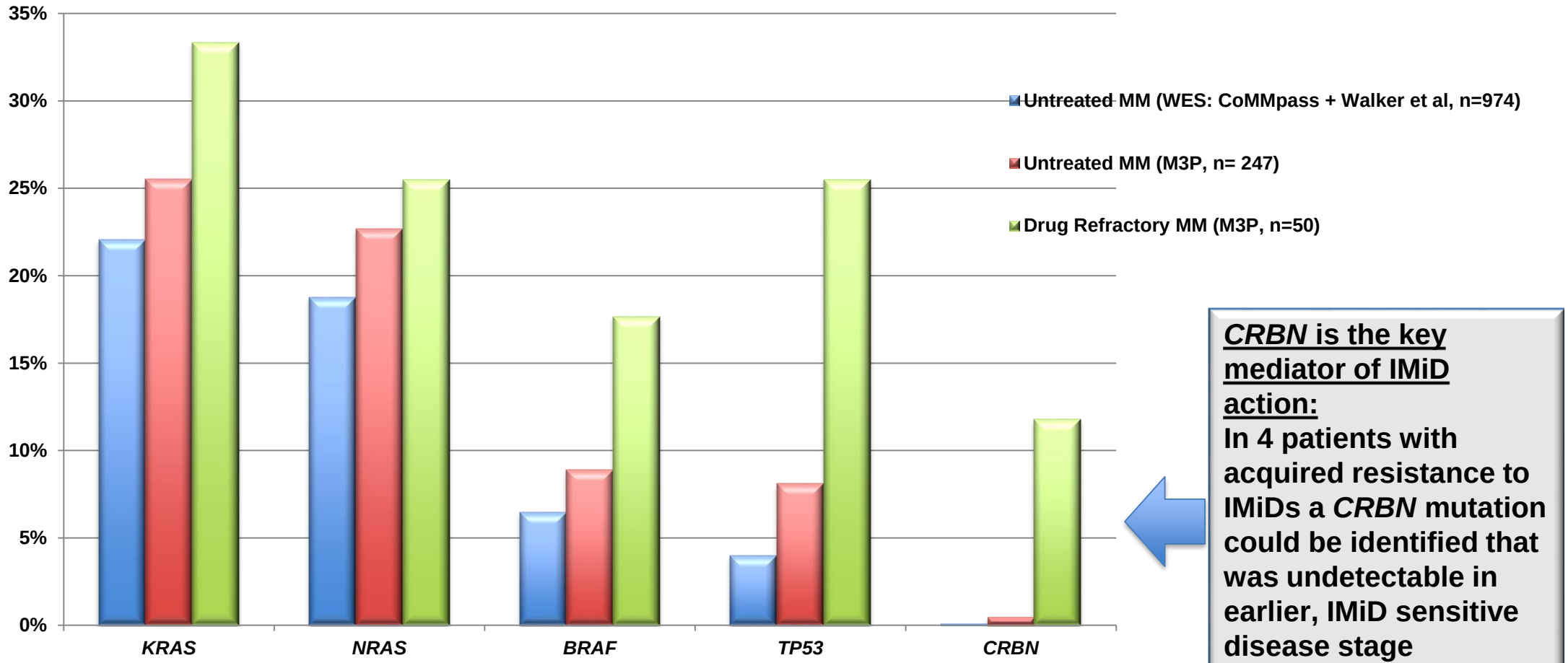






Kumar S – personal communication

Increasing Incidence of Mutations in the *MAPK* and *CRBN* Pathways, and *TP53* With the Duration of Therapy



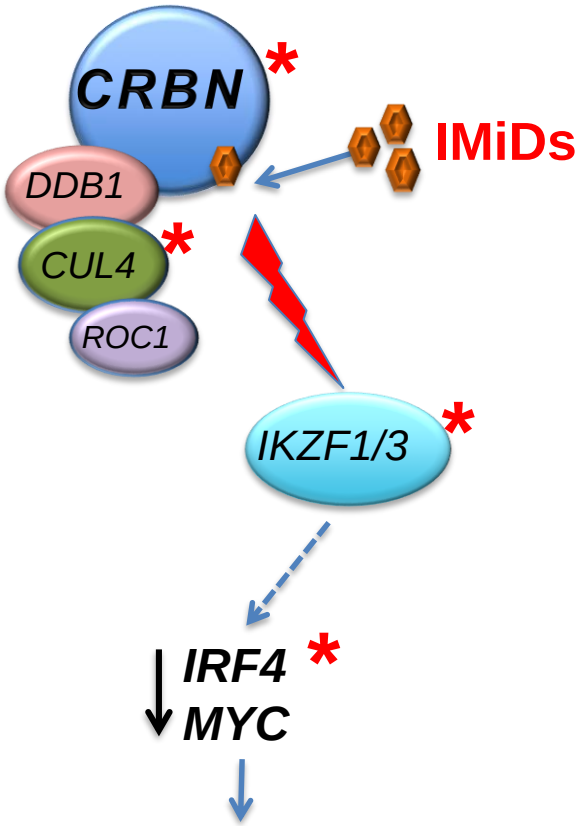
***CRBN* is the key mediator of IMiD action:**
In 4 patients with acquired resistance to IMiDs a *CRBN* mutation could be identified that was undetectable in earlier, IMiD sensitive disease stage

IMiD, immunomodulatory drug; MM, multiple myeloma

Kortüm M, et al. *Blood.* 2016;128(9):1226-1233.

Screening for Resistance Mechanisms

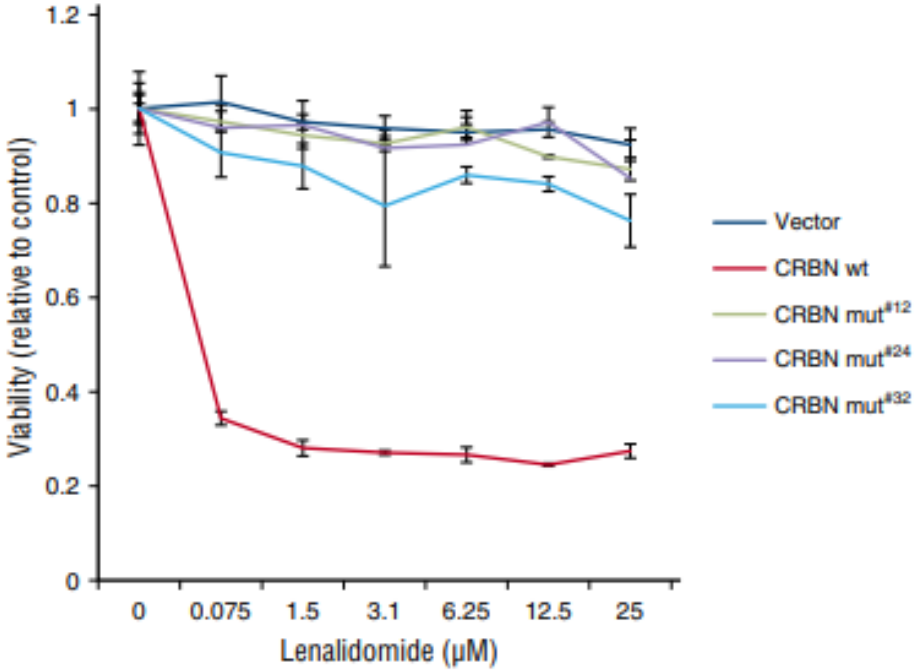
"Targeted sequencing of refractory myeloma reveals a high incidence of mutations in *CRBN* and *RAS* pathway genes in 50 R/R MM patients"



Frequency of Mutations

	CRBN	*CRBN* Pathway
de novo Myeloma	<1%	6%
R/R Myeloma	12%	22%

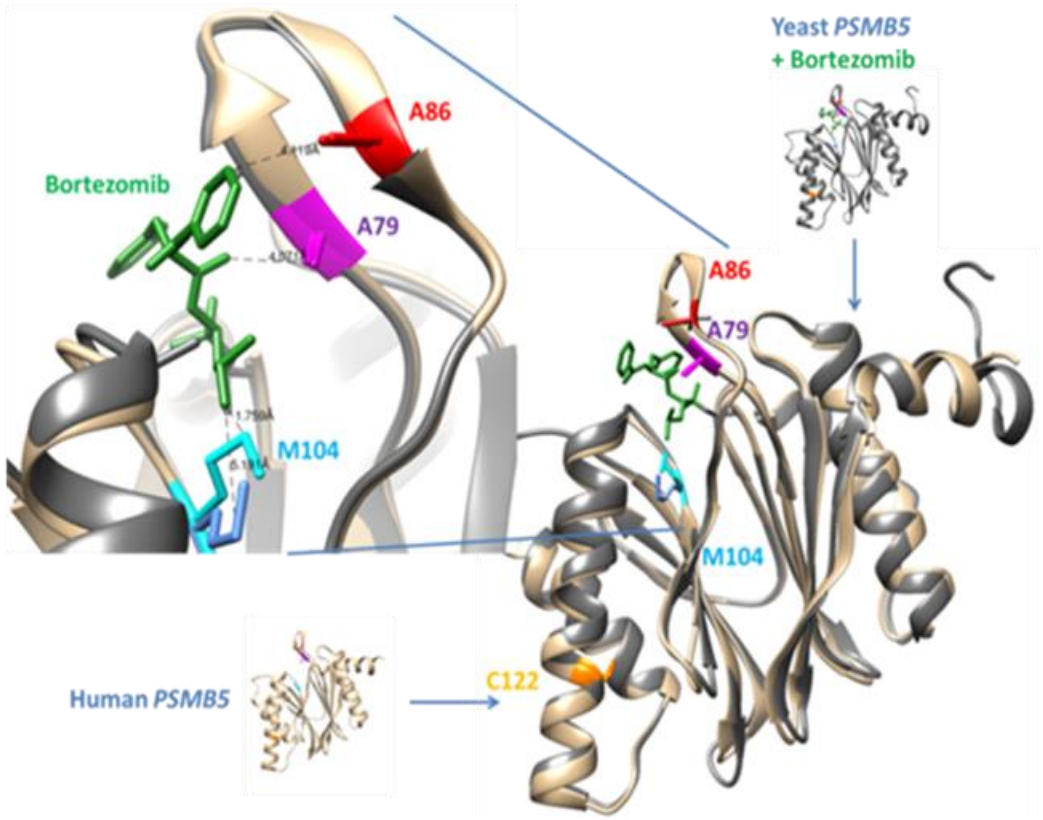
All *CRBN* mutations identified associated with potential impact on the CRBN-IMiD binding site!



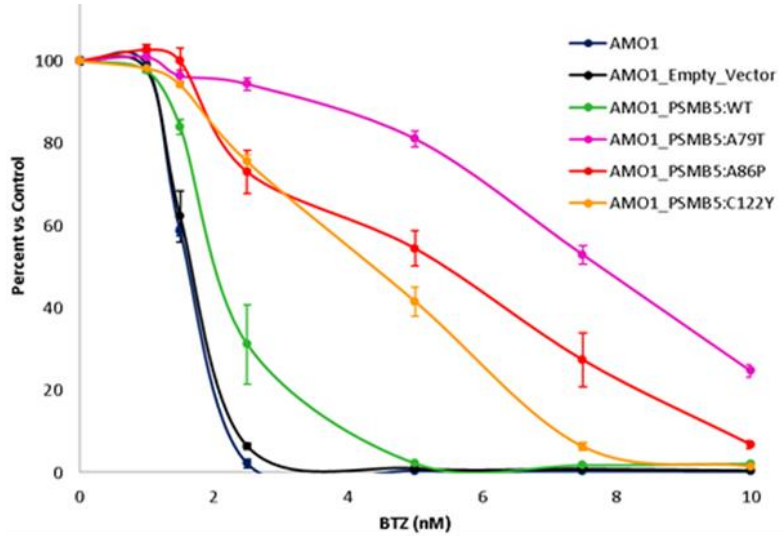
R/R, relapsed/refractory

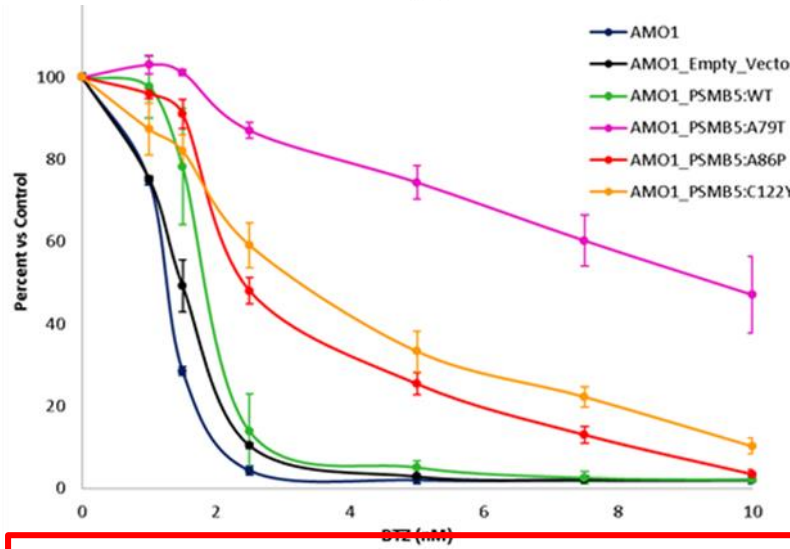
Kortüm M, et al. *Blood.* 2016;128(9):1226-1233.

Resistence Mechanisms Against Proteosome-Inhibitors



***PSMB5* mutations in the bindung pocket of proteosome inhibitors (PIs)**
→ Mutations with resistance against specific PIs





Thus, in first relapse optimal response quality should be aimed for!

Garcia SB, et al. *Blood.* 2017;130:Abstract 4347.

Case Report

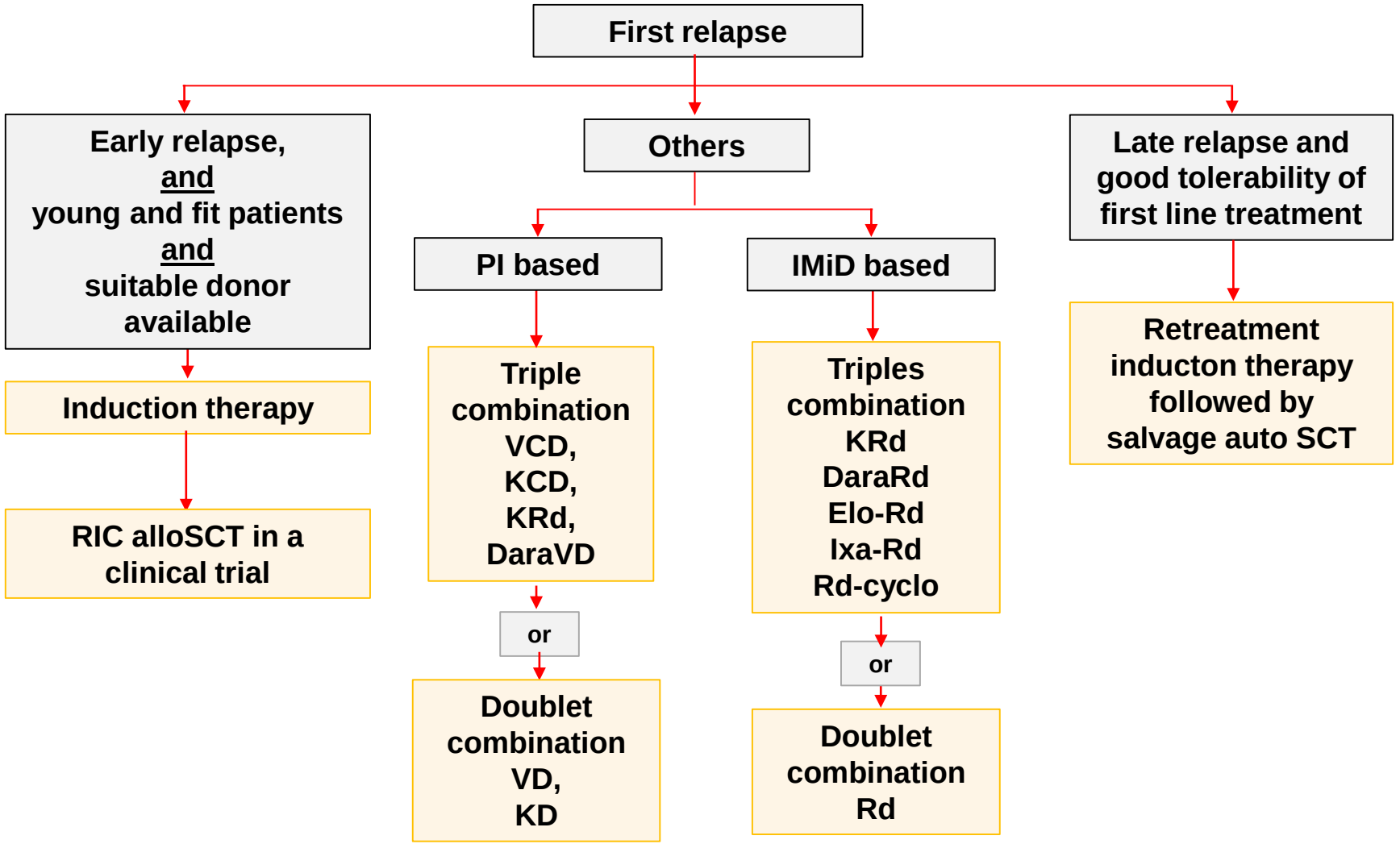
- 62-year-old woman with anemia and T12 compression fracture
- IgGλ MM with 45% marrow plasma cells, del13q, elevated LDH
- Treated with VRD induction, ASCT, and lenalidomide maintenance x 1 year, CR
- 3.5 years later, M-protein reappeared and increased slowly without detectable myeloma-related organ damage and no new cytogenetic changes
- Patient has good performance status and desires therapy

ASCT, autologous stem cell transplant; CR, complete response; LDH, lactate dehydrogenase; VRD, bortezomib + lenalidomide + and dexamethasone

What treatment would you recommend?

1. **Second ASCT without maintenance**
2. **Lenalidomide + dexamethasone (Rd)**
3. **Carfilzomib + dexamethasone**
4. **Cyclophosphamide + bortezomib + prednisone or dexamethasone**
5. **Monoclonal antibody (elotuzumab or daratumumab) + Rd**
6. **Lenalidomide + bortezomib + dexamethasone**

First Relapse



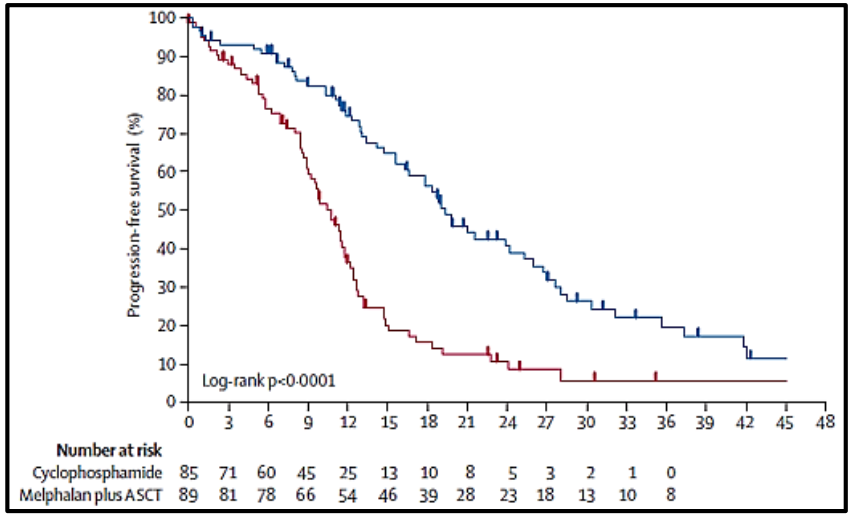
Onkopedia. www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@view/html/index.html#ID0E5ABG and www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@view/html/index.html. Accessed 19 April 2018.

ASCT vs Cyclophosphamide for Treatment of Relapse From Prior ASCT

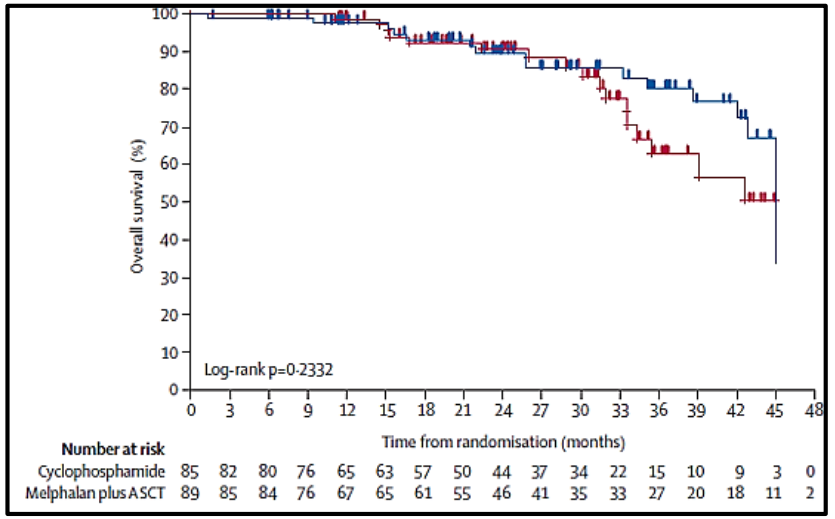
Transplantation vs Cyclophosphamide After First Relapse

Randomized, phase III study
Reinduction PAD x 4
ASCT vs cyclophosphamide 400 mg/week
PFS: 19 vs 11 months, *P*<.001
OS @ 3 years: 80.3% vs 62.9%
***P*<.233**

Progression-Free Survival



Overall Survival



Maintenance should be applied following salvage-ASCT

OS, overall survival; PAD, bortezomib + doxorubicin + dexamethasone; PFS, progression-free survival

Cook G, et al. *Lancet Oncol.* 2014;15(8):874-885. Cook G, et al. *Lancet Haematol.* 2016;3(7):e340-e351.

Consensus Guidelines for Salvage ASCT in R/R MM
(ASBMT, EBMT, BMT CTN, and IMWG)

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an ASCT, high-dose therapy with ASCT as part of salvage therapy should be considered standard

2. High-dose therapy and ASCT should be considered an appropriate therapy for any patients relapsing after primary therapy that includes an ASCT with initial remission duration of >18 months

3. High-dose therapy and ASCT can be used as a bridging strategy to ASCT

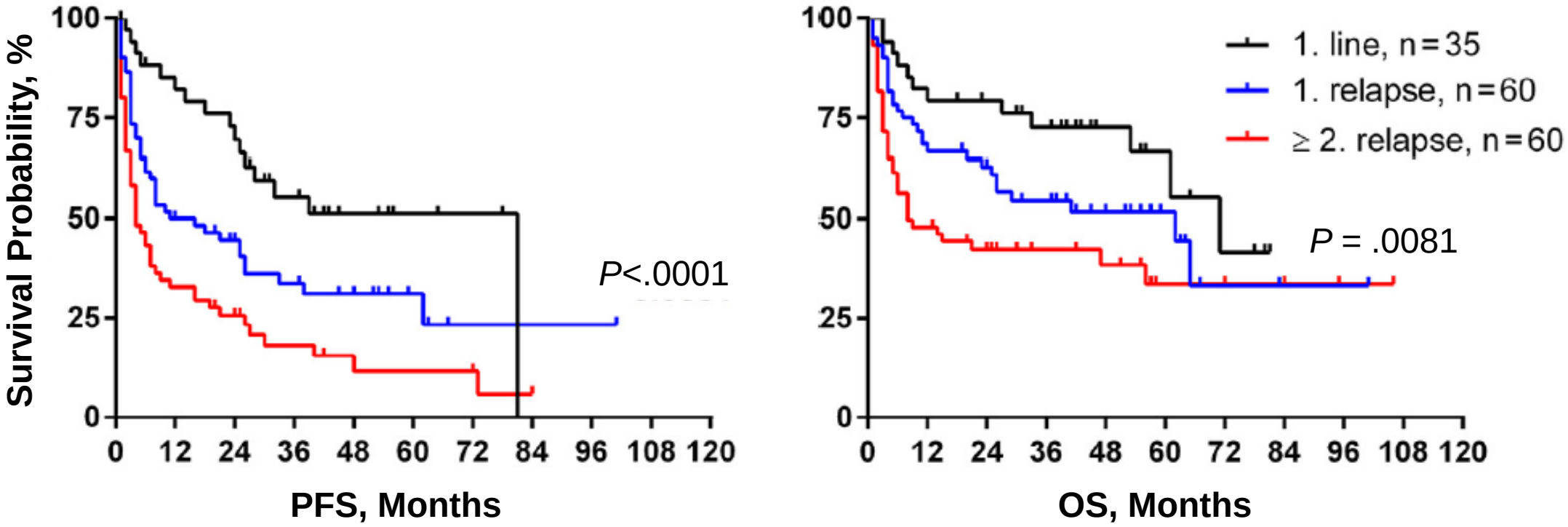
ASBMT, American Society for Blood and Marrow Transplantation; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; EBMT, European Group for Blood and Marrow Transplantation; HCT, hematopoietic cell transplantation; IMWG, International Myeloma Working Group

Giralt S, et al. *Biol Blood Marrow Transplant.* 2015;21(12):2039-2051.

Allogeneic SCT in Multiple Myeloma

Time-to-Event Data From 3 German Centers, N = 169

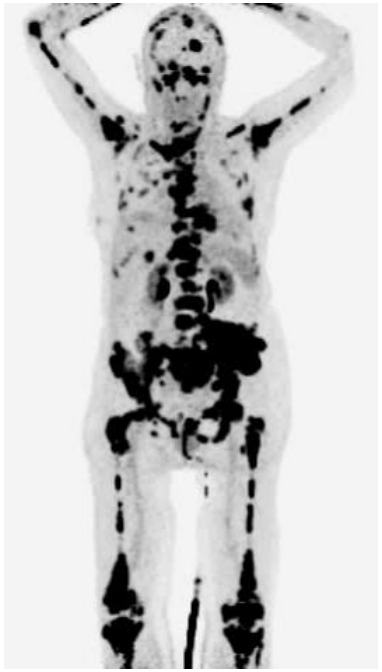
Impact of Duration of Pretreatment/Lines of Previous Therapy



Rasche L, et al. *Biol Blood Marrow Transplant.* 2016;22(11):1988-1996.

Extramedullary Disease: CXCR4-Directed Radionuclide Therapy

Imaging CXCR4 Expression



CXCR4 receptor expression in myeloma and normal marrow is visualized by PET using the receptor specific ligand ^{68}Ga-CPCR4-2

Outpatient

Step 1: Dosimetry
^{177}Lu-labeled CPCR4-2 (1 GBq)
at day -28 to -20

Inpatient

Step 2: Radionuclide-based therapy
^{177}Lu-labeled CPCR4-2 (8-16 GBq)
at day -21 to -14

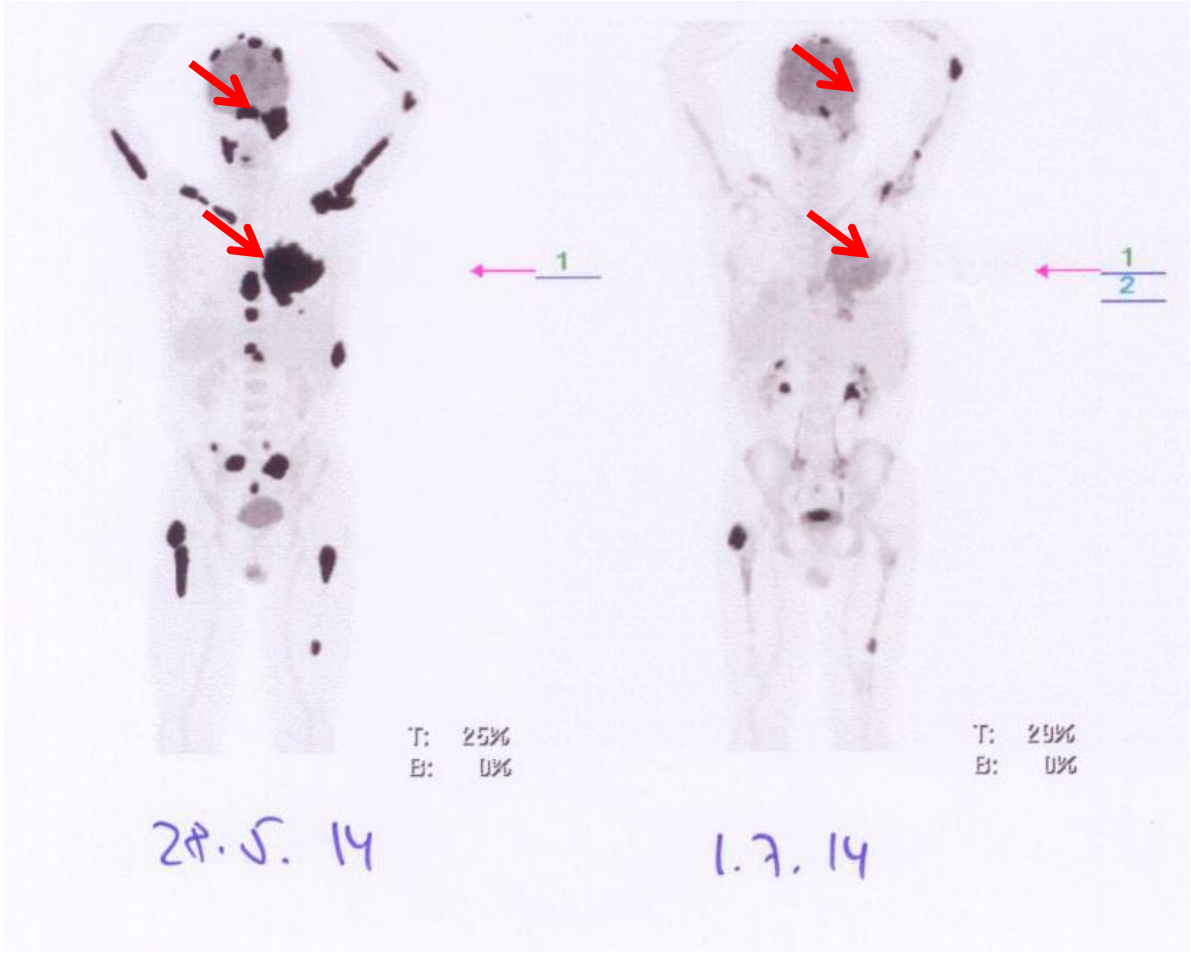
Step 3: Conditioning
Reduced intensity (eg, treosulfan 3x10 g/m^2)
at day -4 to -2

Step 4: Cell infusion
at day 0

PET, positive emission tomography

Stolzenburg A, et al. *Eur J Nucl Med Mol Imaging*. 2018 Apr 2. [Epub ahead of print].

CXCR4-Directed Radionuclide Therapy
Successful Application in EMD



EMD, extramedullary disease

Herrmann K, et al. *J Nucl Med.* 2016;57(2):248-251.

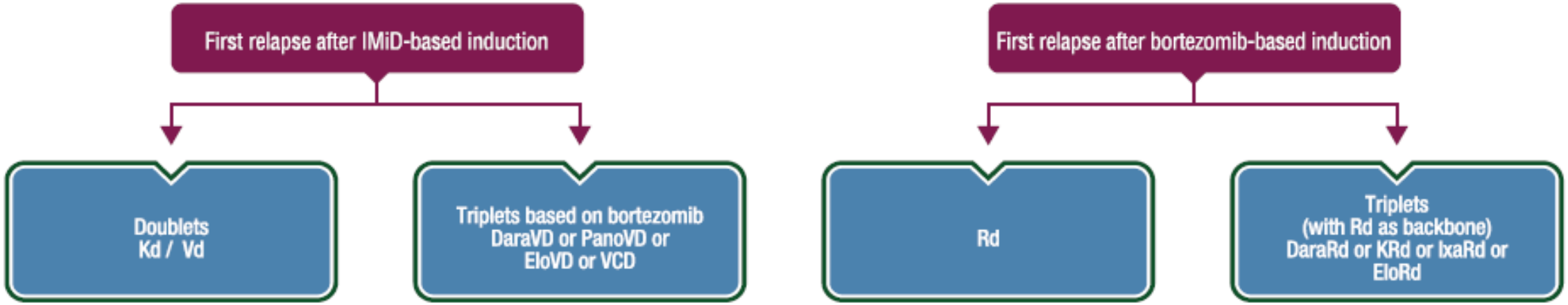
Older Regimens Used for Relapsed Myeloma

Regimen	Type of Study	# Cycles	N	Response Rate (CR Rate)	Median PFS, Months	Overall Survival†
Len + dex[1]	Phase III	To prog	353	**61% (15%)**	**13.4**	38 months
Len + dex[2]	Real world data	To prog	159	**83% (13%)**	**7.1**	22.7 months
RAD[3] **(Len +dex +doxorubicin)**	Phase I-II	6	69	**77% (14%)**	**5.7**	88% (1-year)†
CyBorP/D[4]	Real world data	8+	94	**69% (17%)**	**13.0**	23.5 months
RVD[5]	Phase I-II	8+	64	**64% (25%)†**	**9.5†**	86% (1-year)†
CyRD[6]	Phase I-II	9+	31	**94% (19%)†**	**16.1†**	27.6 months†
VDT-PACE[7]	Real world data	1 (Median; range 1-9)	141	**54% (10%)**	**3.1**	8.1 months

† Includes all dose levels

1. Dimopoulos MA, et al. *Leukemia.* 2009;23(11):2147-2152. 2. Reece D, et al. *Blood.* 2009;114(3):522-525. 3. Knop S, et al. *Blood.* 2009;113(18):4137-4143. 4. Reece D, et al. *Clin Lymphoma Myeloma Leuk*. 2016;16(7):387-394. 5. Richardson P, et al. *Blood*. 2010;116: Abstract 3049. 6. Reece DE, et al. *Br J Haematol*. 2015;168(1):46-54. 7. Lakshman A, et al. *Am J Hematol*. 2017 Oct 25. [Epub ahead of print].

Treatment of Relapse



Moreau P, et al. *Ann Oncol.* 2017;28(suppl_4):iv52–iv61.

Lenalidomide + Dex Versus Triplet Regimens

Relapsed/Refractory Myeloma After 1 to 3 Prior Regimens

Third Agent	% With Prior Len	% Bortezomib Refractory	% Bortezomib Exposed	% With High-Risk Cytogenetics	Response Rates for Triplet vs Doublet (%)	PFS for Triplet vs Doublet, Months	Interim OS for Triplet vs Doublet, Months
Proteasome inhibitors							
Carfilzomib[1]	19.8	No	66 vs 66	12 vs 13	87 vs 67	**26.3 vs 17.6** (*P* = .0001)	73% vs 65% (24 months)
Ixazomib[2]	12	No	69 vs 69	17 vs 21	78 vs 72	**20.6 vs 14.7** (*P* = .012)	--
Immunotherapy							
Elotuzumab[3]	6	22	68 vs 71	41 vs 42	79 vs 66	**19.4 vs 14.9** (*P* = .014)	43.7 vs 39.6 (*P* = .026)
Daratumumab[4]	18	18	86	15 vs 17	93 vs 76	**NR* vs 18.4** (*P*<.0001)	--

Triplets had higher response rates and superior PFS in all trials

*NR, not reached

1.Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152. 2. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634. 3. Lonial S, et al. N *Engl J Med*. 2015;373(7):621-631. 4. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.

Bortezomib + Dexamethasone vs Triplet Regimens

Relapsed/Refractory Myeloma After 1 to 3 Prior Regimens

Third Agent	N	% With Prior Len	% Len Refractory	% With High-Risk Cytogenetics (Composite)	Response Rates for New Regimen vs BTZ + Dex (%)	PFS for New Regimen vs BTZ + Dex, Months	OS for New Regimen vs BTZ + Dex, Months
CFZ (56 mg/m^2) + dex[#1]	929	38	25	23	77 vs 63	**18.7 vs 9.4**	47.6 vs 40
Panobinostat[2]	768	20	--	--	60.7 vs 54.6	**12 vs 8.1**	38.24 vs 35.38
Elotuzumab[§3]	152	75	33	NA	66 vs 63	**9.7 vs 6.9**	73% vs 66% (2 years)
Daratumumab[4]	498	68	33	23	83 vs 63	**16.7 vs 7.1**	NR vs NR

[#]Doublet vs doublet
[§]Phase II study
[+]NR, not reached

1. San Miguel SF, et al. *Lancet Oncol*. 2014;15(11):1195-206. 2. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38. 3. Jakubowiak A, et al. *Blood*. 2016;127(23):2833-2840. 4. Dimopoulos MA, et al. *Br J Haematol.* 2017;178(6):896-905. 5. Lentzsch S, et al. *J Clin Oncol*. 2017;35(Suppl): Abstract 8036.

Three-Drug Regimens for R/R MM After 1 to 3 Prior Lines

Based on previous exposure or refractoriness to bortezomib or lenalidomide (according to inclusion/exclusion criteria of respective studies)

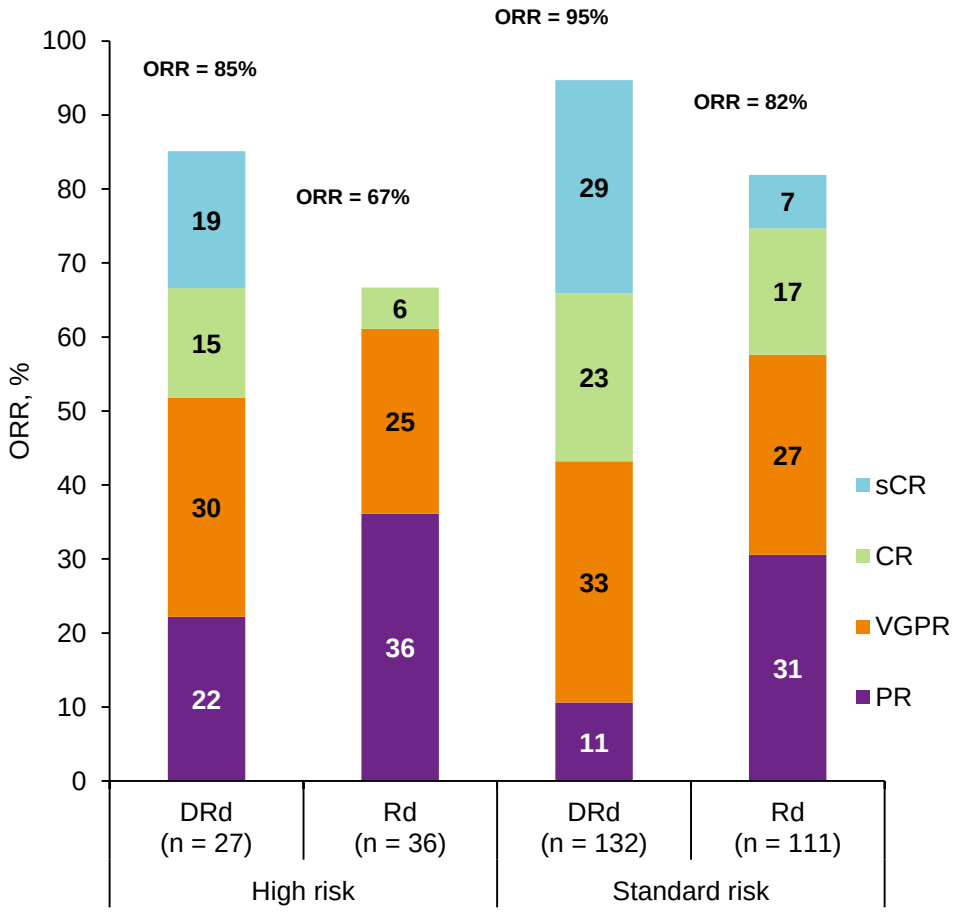
		KRD	KD	Elo-RD	IRD	DRd	DVd	Pano-VD
Bortezomib	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	-	+	-	+	-	-
Lenalidomide	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	+	-	-	-	+	+

What Would Your Preferred Regimen Be at Relapse?

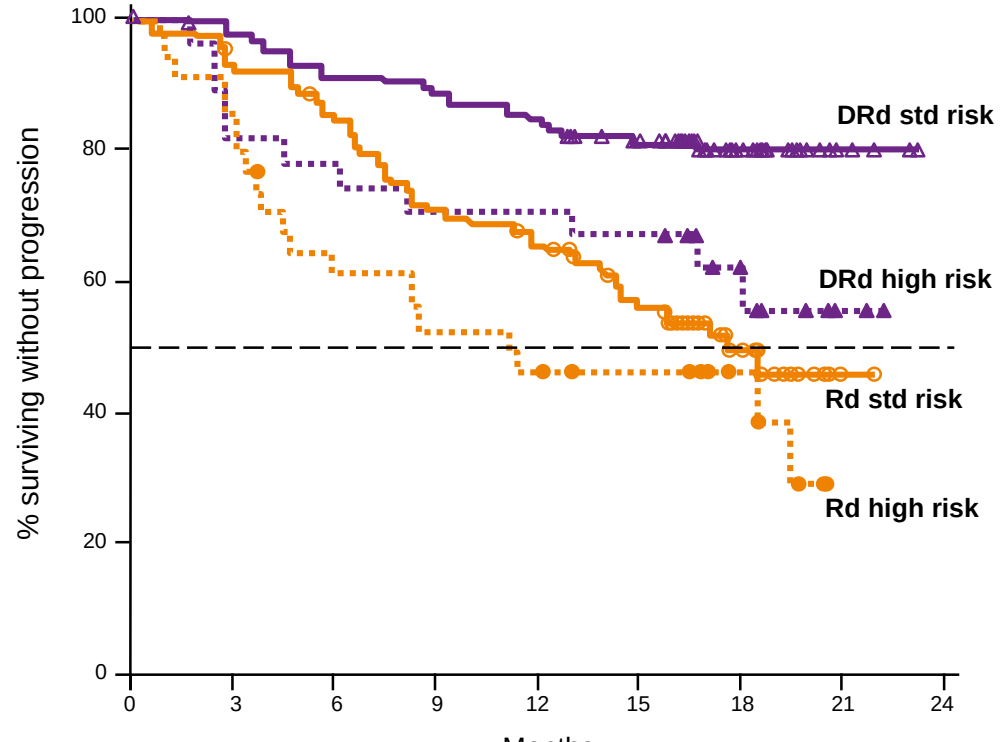
- According to previous lines of therapy
- If the patient has refractoriness to PIs or IMiDs?
- **If the patient has high-risk cytogenetics?**
- If the patient is elderly?

POLLUX: Responses and PFS By Cytogenetic Status

Total Population (Response Evaluable)



1 to 3 Prior Lines Population

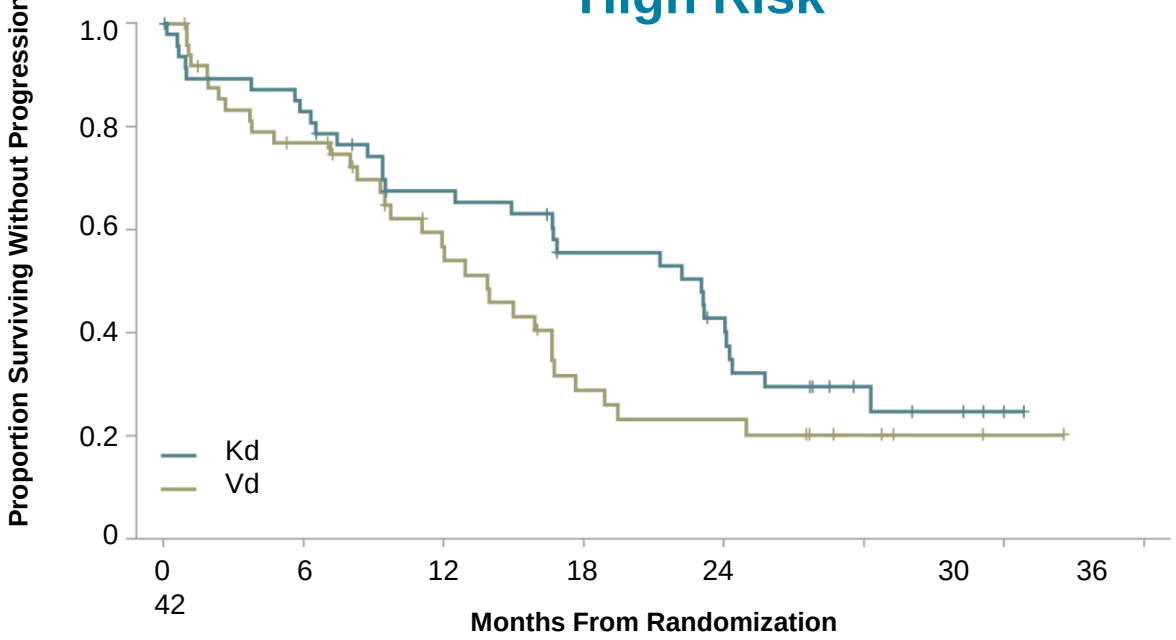


No. at risk									
Rd standard risk	103	95	86	71	65	51	18	1	0
DRd standard risk	124	119	111	108	103	93	38	4	0
Rd high risk	34	29	20	17	15	13	6	0	0
DRd high risk	28	22	21	19	19	18	9	2	0

Moreau P, et al. *Blood.* 2016;128: Abstract 489.

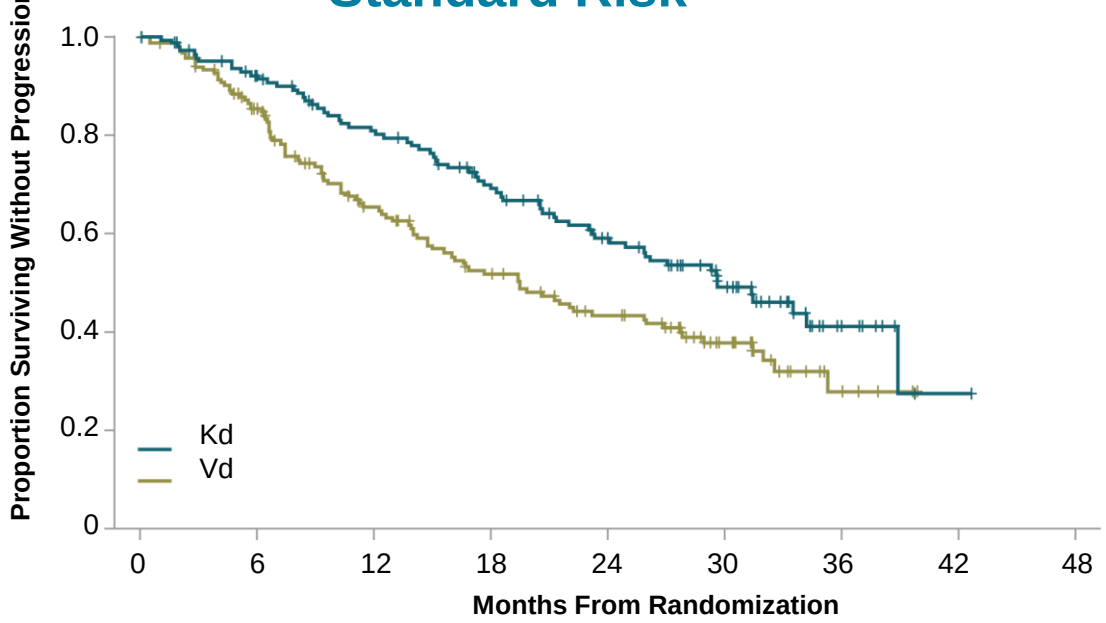
ASPIRE: KRd vs Rd
PFS By Cytogenetic Risk Status at Baseline

High Risk



	KRd n = 48	Rd n = 52
PFS, median months	23.1	13.9
Hazard ratio (95% CI)	0.703 (0.426–1.160)	
P value (1-sided)	.0829	

Standard Risk

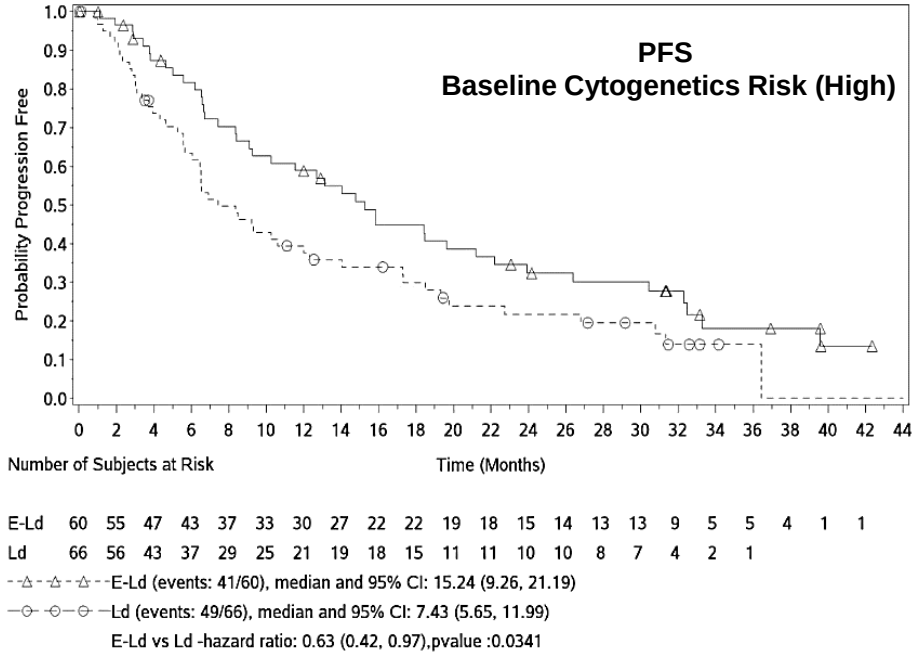


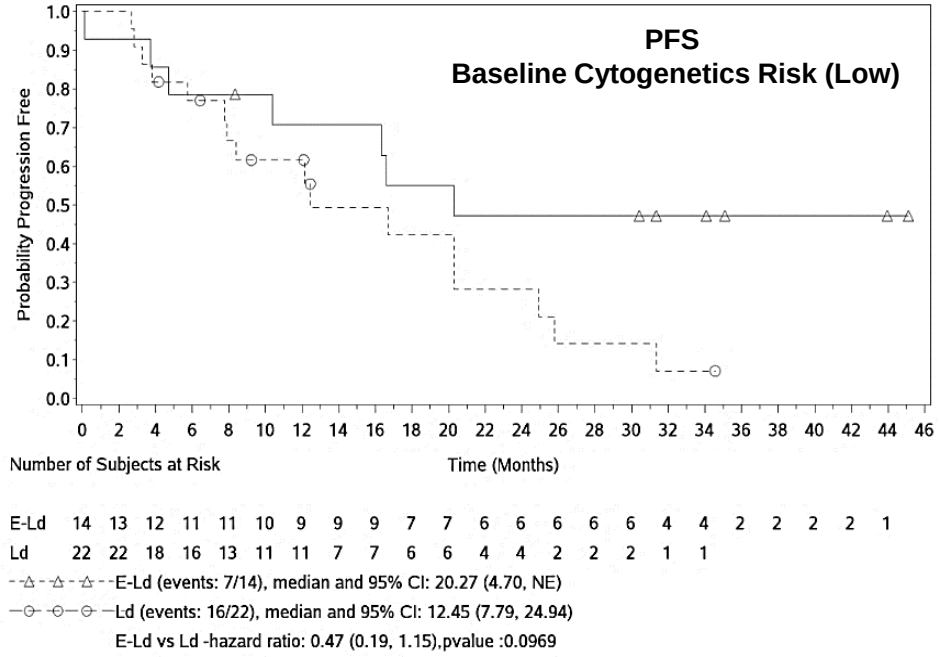
	KRd n = 147	Rd n = 170
PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.656 (0.480–0.897)	
P value (1-sided)	.0039	

Avet-Loiseau H, et al. *Blood.* 2016;128(9):1174–1180.

ELOQUENT-2 (Elo-Rd vs Rd): PFS in del(17p) and t(4;14)

del(17p)+	0.70 (0.49-0.99) *P* = .042	21.2 (16.6-27.5)	14.9 (10.6-18.5)
del(17p)–	0.73 (0.58-0.92) *P* = .007	18.5 (15.8-22.8)	14.8 (11.7-18.4)
t(4;14)+	0.52 (0.29-0.93) *P* = .027	15.8 (8.4-18.5)	5.6 (3.1-10.3)
t(4;14)–	0.74 (0.60-0.91) *P* = .004	20.3 (17.3-23.3)	15.7 (13.0-18.5)





EloRd improves the outcome of patients with high risk CA in comparison with Rd
High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥1% of plasma cells (PCs)

Moreau P, et al. *Blood.* 2015;126: Abstract 727.

TOURMALINE-MM1: Outcomes By Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, Months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

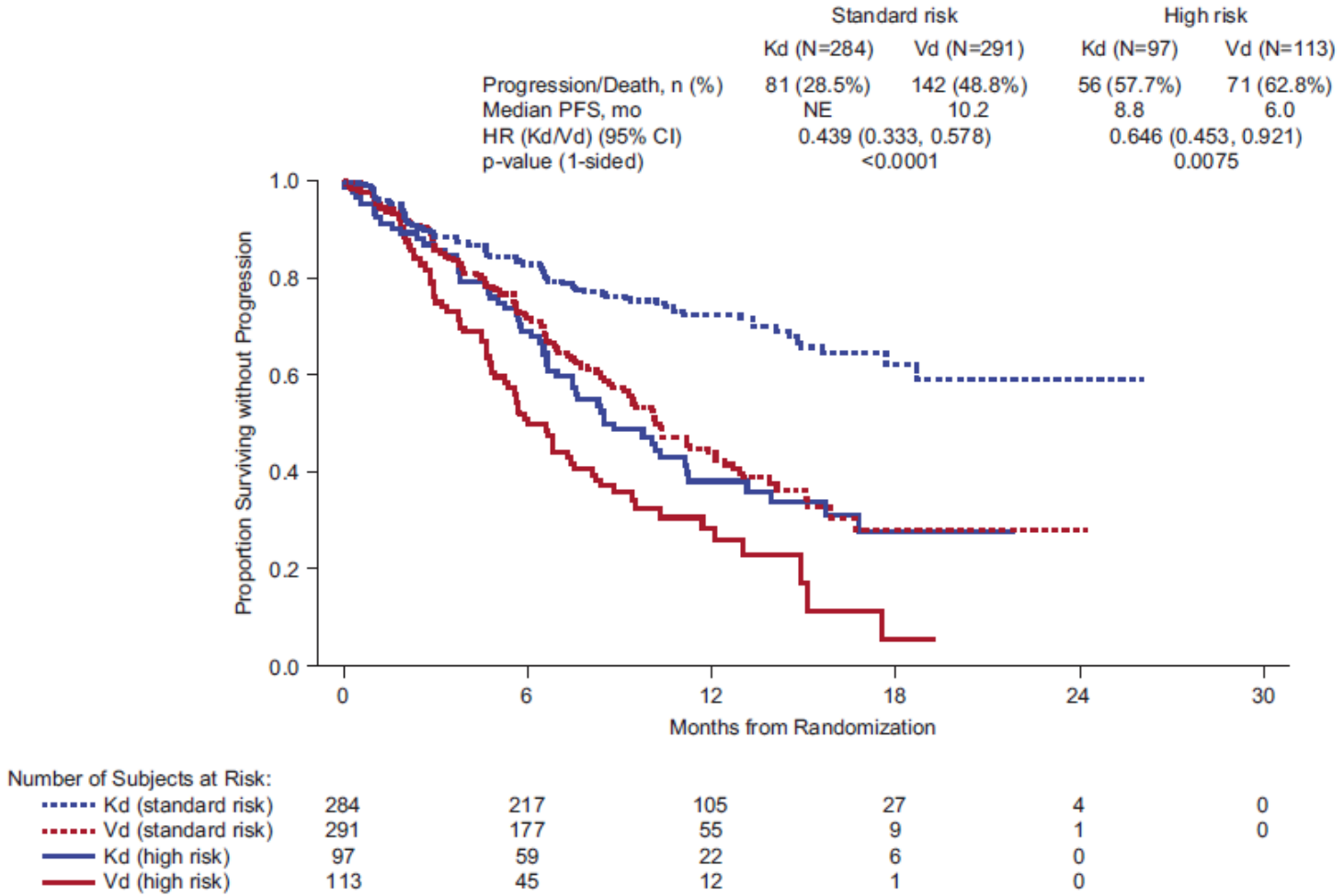
*P<.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16)
Data not included on patients with t(14:16) alone due to small numbers (n = 7)

- **In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics**
- **High risk was defined by t(4;14) or t(14;16) or del17p in ≥5% of PCs**

VGPR, very good partial response

Moreau P, et al. *Blood.* 2015; 126: Abstract 727.

Kd vs Vd: PFS By Cytogenetic Risk Status at Baseline
(Kd is not a good option for high-risk cytogenetics)



High Risk	Kd n = 97	Vd n = 113
PFS, median months (95% CI)	8.8 (6.9–11.3)	6.0 (4.9–8.1)
HR (95% CI)	0.646 (0.453–0.921)	
P value	.0075	

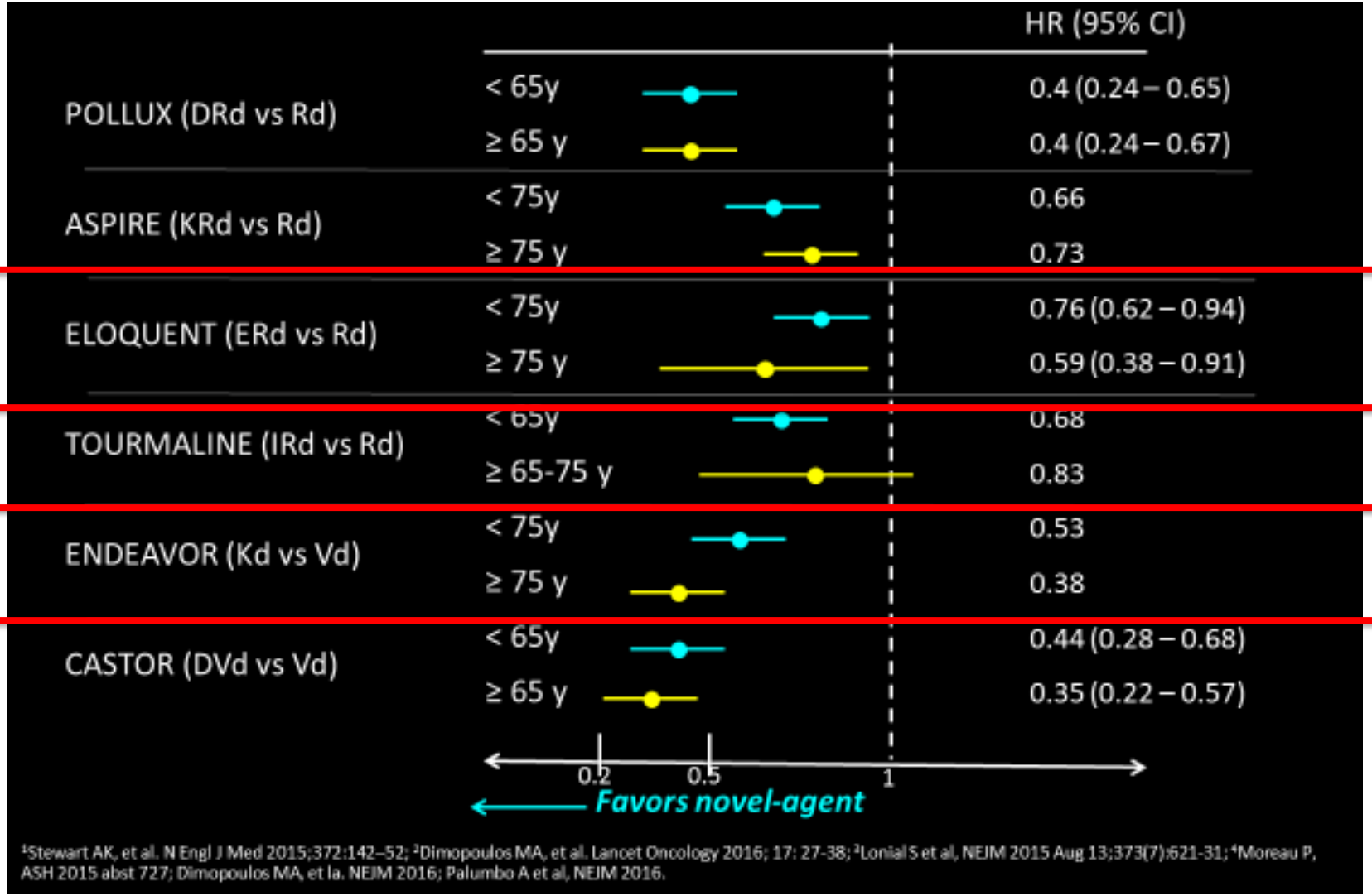
Standard Risk	Kd n = 284	Vd n = 291
PFS, median months (95% CI)	NE (18.7–NE)	10.2 (9.3–12.2)
HR (95% CI)	0.439 (0.333–0.578)	
P value	<.0001	

Chng WJ, et al. *Leukemia*. 2017;31(6):1368-1374.

What Would Your Preferred Regimen Be at Relapse?

- According to previous lines of therapy
- If the patient has refractoriness to PIs or IMiDs?
- If the patient has high-risk cytogenetics ?
- **If the patient is elderly?**

Impact of Age on Treatment Strategy



[1]Stewart AK, et al. N Engl J Med 2015;372:142–52; [2]Dimopoulos MA, et al. Lancet Oncology 2016; 17: 27-38; [3]Lonial S et al, NEJM 2015 Aug 13;373(7):621-31; [4]Moreau P, ASH 2015 abst 727; Dimopoulos MA, et la. NEJM 2016; Palumbo A et al, NEJM 2016.

Courtesy of: San Miguel J

Selected Toxicity of New Combinations

% of Patients With Grade 3 or 4 Toxicity

TRIAL	ASPIRE (KRd)	TOURMALINE-MM1 (IRd)	ELOQUENT-2 (EloRd)	POLLUX (DRd)	ENDEAVOR (Kd)	CASTOR (DVd)
Peripheral neuropathy	3%	2%	NA	NA	2%	5%
Acute renal failure	3%	3%	NA	NA	5%	NA
Cardiac toxicity	7%	6%	NA	NA	8%	NA
Pneumonia/ infections	2%	1%	NA	10%	8%	11%
Diarrhea	4%	6%	5%	5%	3%	4%

Brioli A, et al. *Expert Rev Hematol*. 2017;10(3):193-205. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

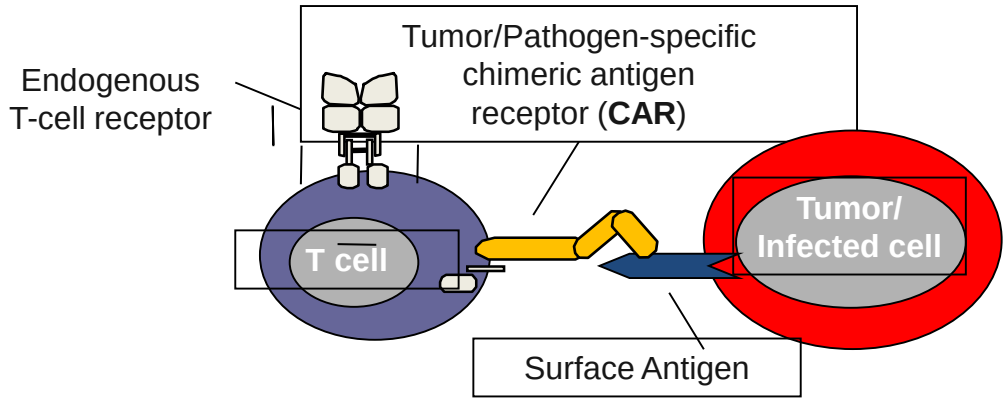
Toxicity and Convenience of Newer Agents for Relapsed Myeloma

Agent	Carfilzomib[1]	Elotuzumab[2]	Ixazomib[3]	Daratumumab[4]
Neutropenia	++	-	++	+
Thrombocytopenia	++	-	++	+
Hypertension	++	-	-	-
GI toxicity	+	-	++	+
Neuropathy	Occasional	-	+	-
Dyspnea/cough	++	-	-	+
Infusion reactions	+/-	+	-	+++
DC due to toxicity	15%	17%	8.7%	7%
Administration	6x/month IV	q 1 to 2 weeks IV	PO	IV q w x 8; q 2 w x 8; q 4 w

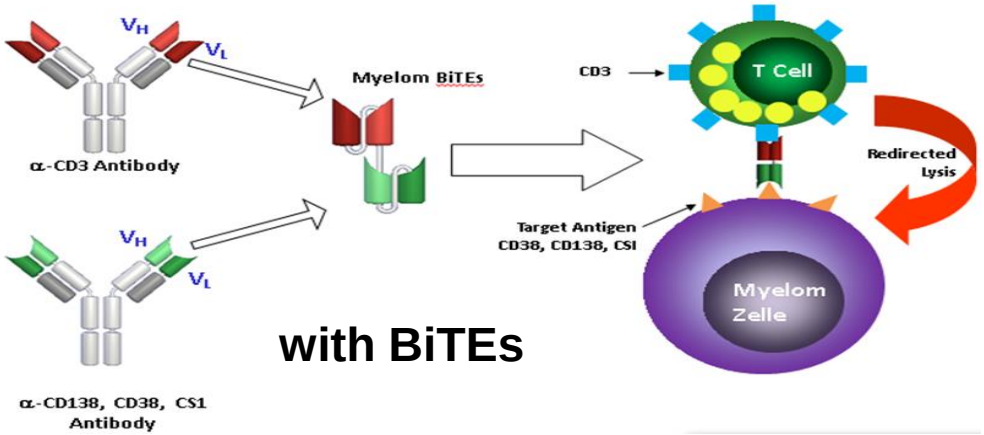
DC, discontinued; GI, gastrointestinal

1. Moreau P, et al. *Blood*. 2015;126: Abstract 72. 2. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631. 3. Moreau P, et al. *Blood*. 2015;126: Abstract 72. 4. Dimopoulos M, et al. *Haematologica*. 2016;101(Suppl 1): Abstract S456.

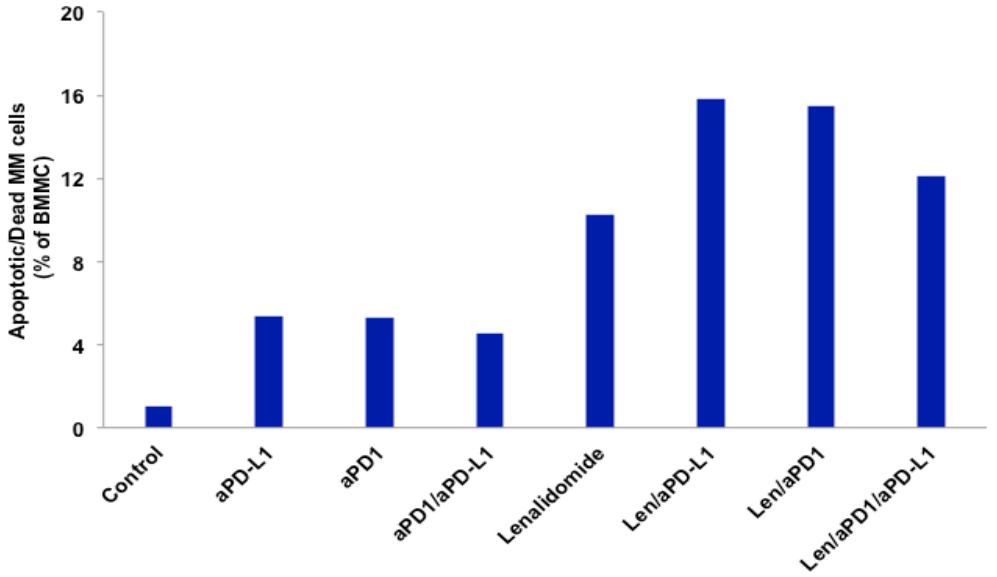
New Options for First Relapse?
How To Increase the Frequency of MM-Reactive T Cells?



with CAR T cells

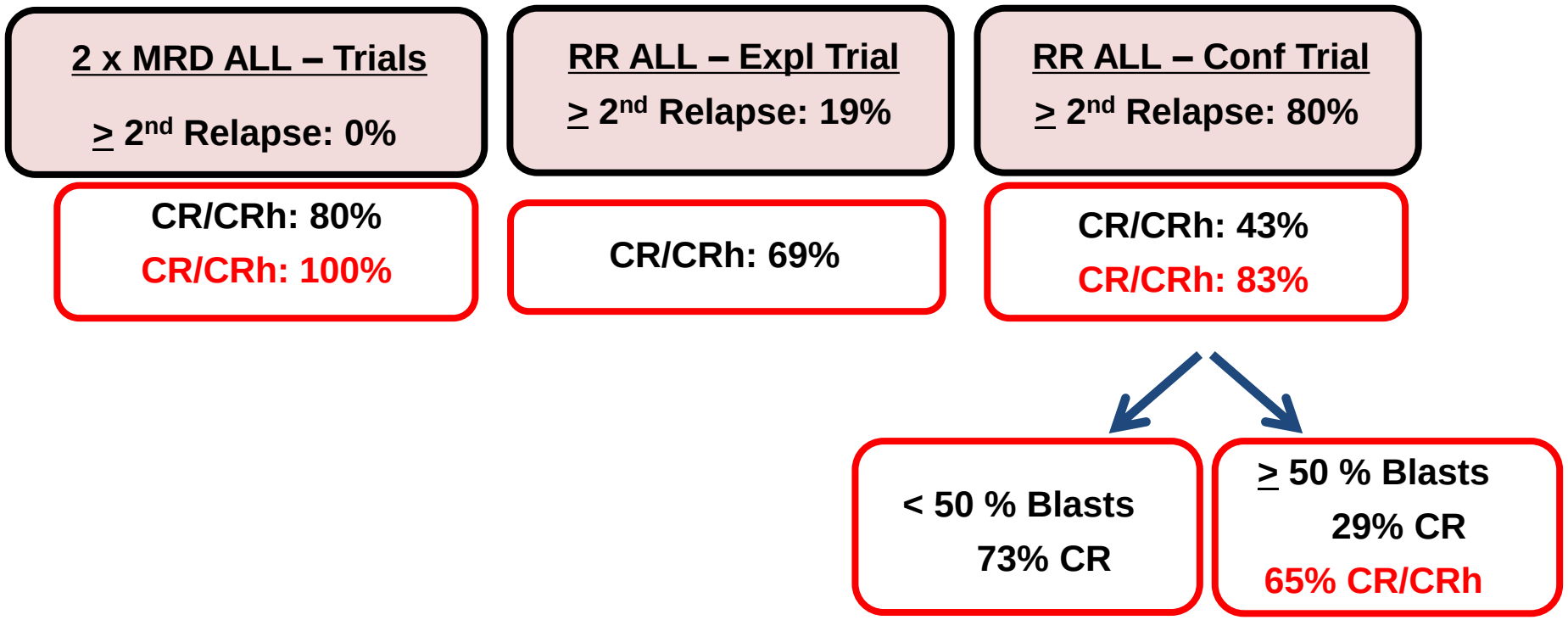


with BiTEs



with checkpoint blockers

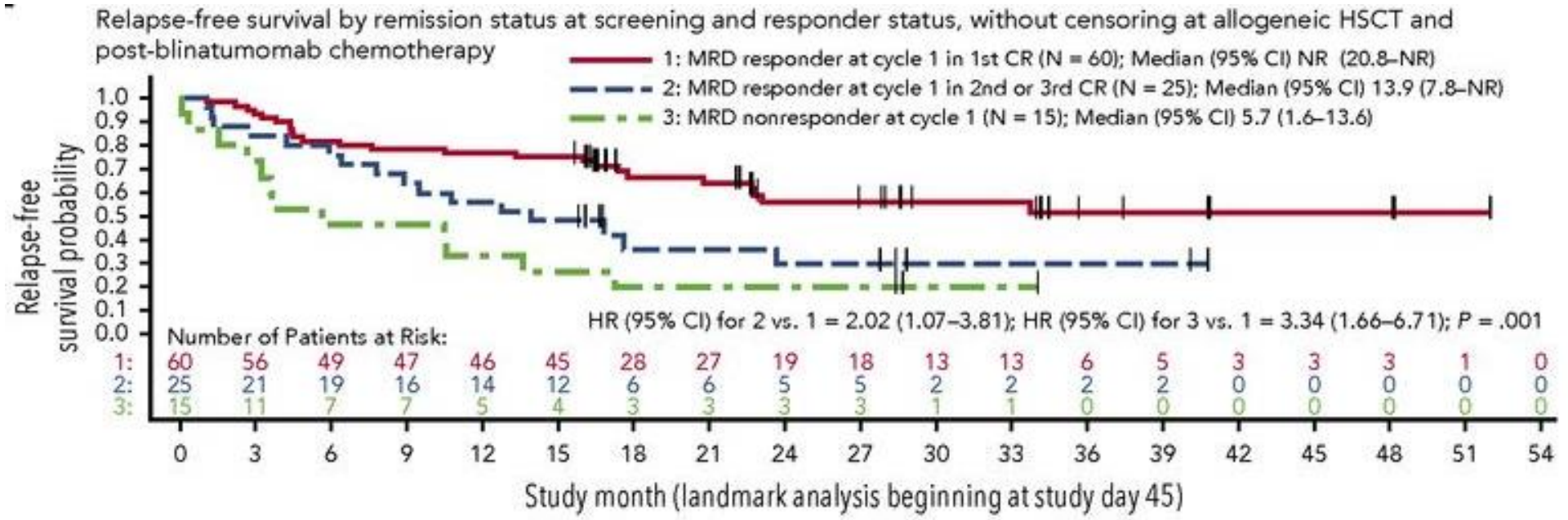
Efficacy of T-Cell Redirection Strategies (Bites, CAR T-Cells) Also Seems to Correlate With The Number of Previous Therapies And Tumor Load



Topp MS, et al. *J Clin Oncol.* 2014;32(26):4134-4140. Topp MS, et al. *Lancet Oncol.* 2015;16(1):57-66. Kantarjian H, et al. *N Engl J Med.* 2017;376(0):836-847.

Long-Term Disease Control by Bispecific Antibodies Depends on Pre-treatment

- **Inspite of a similar MRD clearance rate (78 vs 80%) patients who had already relapsed before had an inferior EFS/OS compared with those treated in first line for MRD+**



- **Thus, if redirection T-cell strategies should be curative – they should be applied in earlier treatment lines !!!**

Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531..

Case Report

- 62-yr old woman with anemia and T12 compression fracture
- IgGλ MM with 45% marrow plasma cells, del13q, elevated LDH
- Treated with VRD induction, ASCT, and lenalidomide maintenance x 1 year, CR
- 3.5 years later, M-protein reappeared and increased slowly without detectable myeloma-related organ damage and no new cytogenetic changes
- Patient has good performance status and desires therapy

What treatment would you recommend?

1. **Second ASCT without maintenance**
2. **Lenalidomide + dexamethasone (Rd)**
3. **Carfilzomib + dexamethasone**
4. **Cyclophosphamide + bortezomib + prednisone or dexamethasone**
5. **Monoclonal antibody (elotuzumab or daratumumab) + Rd**
6. **Lenalidomide + bortezomib + dexamethasone**

Treatment of Relapsed Myeloma

Potential Strategies

- Start all patients on a triplet regimen
  - All phase III trials have shown superiority of including a 3rd newer agent with either len + dex or BTZ + dex[4,5]
- Start selected patients on a doublet such as len + dex
  - Elderly/frail patients may tolerate doublet > triplet[1,2]
  - Some patients do very well with len + dex doublet
    - 14% of relapsed patients had a PFS ≥6 years in Mayo Clinic review, but could not be identified ahead of time[3]
  - Can add a third agent only "on demand" at next relapse
    - Limited data suggests efficacy; could reduce toxicity/cost
- In the future, novel immunotherapies are moving in earlier lines of treatment, also in first relapse

1. Larocca A, et al. *Leukemia*. 2016;30(6):1320-1326. 2. Magarotto V, et al. *Blood*. 2016;127(9):1102-1108. 3. Nijhof IS, et al. *Blood*. 2016;128(19):2297-2306. 4. Alahmadi M, et al. *Blood*. 2015;126: Abstract 1842. 5. Kaedbey R, et al. *Blood*. 2015;15(Suppl 3):e298.

Thanks For Your Attention!

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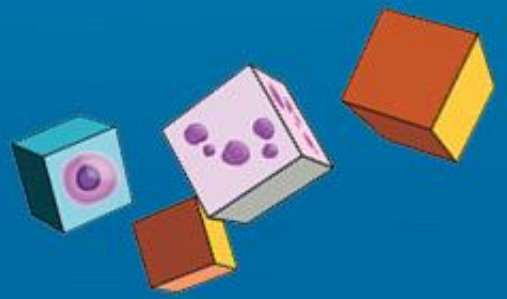
Treatment Decisions for Relapsed/Refractory Multiple Myeloma:



Fitting the Pieces Together