What's New in Multiple Myeloma?

Advances in Oncology, 2020

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Disclosures

- Speakers Bureau (unbranded)
  - Janssen, Millennium-Takeda
- Research
  - Amgen

- Bone Marrow Transplant Attending (probably more important than any of the above!)

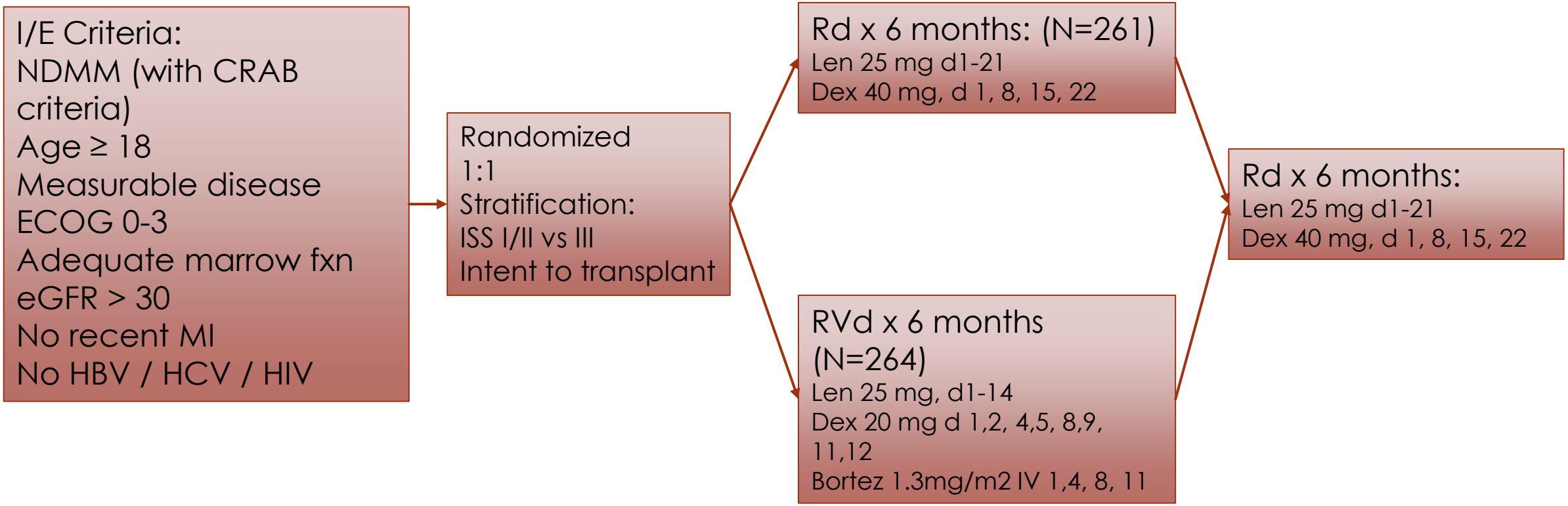
Outline

- Newly Diagnosed Multiple Myeloma
- New Treatments in 2020:
  - Belantamab Mafodotin
  - Selinexor with Bortez/Dex
- Survivorship in Myeloma
  - Second primary malignancies
  - Cardiovascular Endpoints

Newly Diagnosed Myeloma

WHAT IS THE CURRENT STANDARD OF CARE IN 2020?

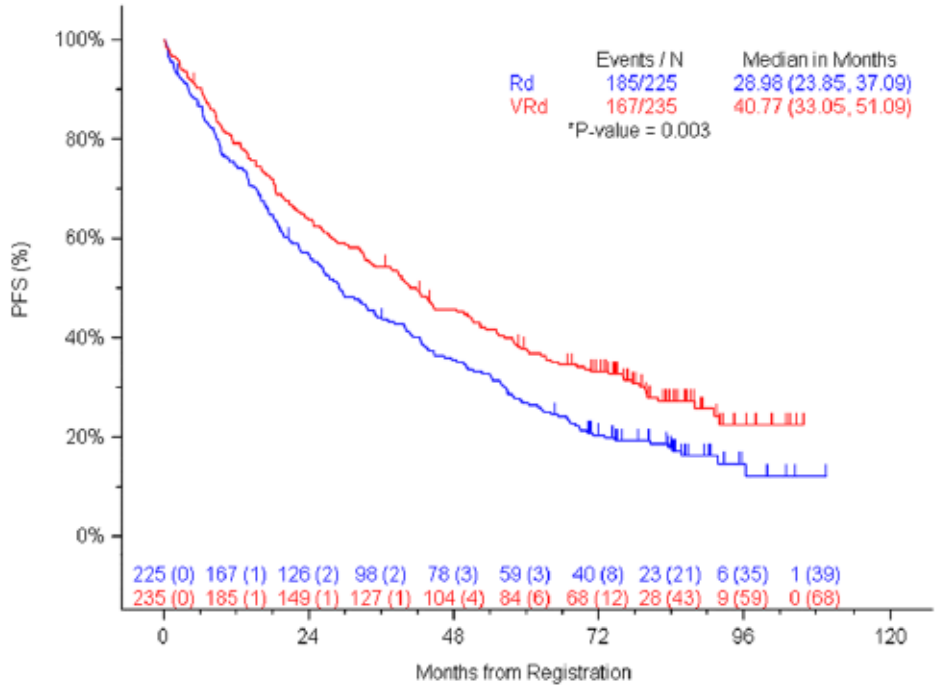
S0777: Trial Schema



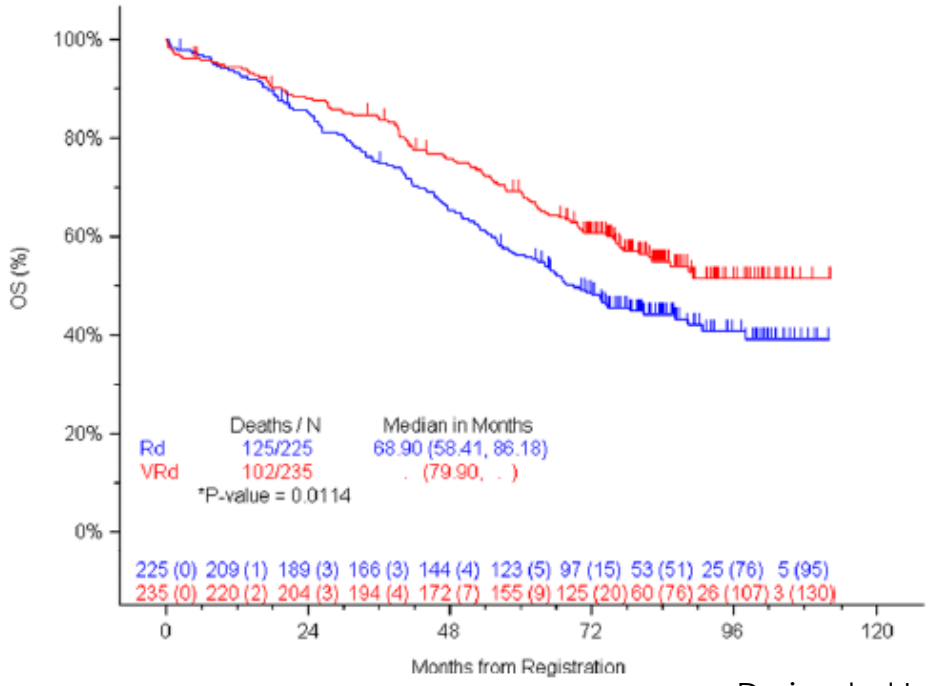
Durie et al Lancet 2017
Durie et al Blood Canc

S0777: PFS and OS

PFS



OS



Durie et al Lancet 2017
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S0777: Response Rates and Multivariable Analysis

Table 2 Confirmed best responses in assessable patients.

	VRd[a] ($n = 215$)	Rd[a] ($n = 207$)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	**74.9% (161)**	**53.2% (110)**
Partial response (PR)	15.3% (33)	25.6% (53)
Overall response rate (ORR)	**90.2% (194)**	**78.8% (163)**
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or Death	2.8% (6)	4.8% (10)

Table 3 Multivariate age-adjusted progression-free survival and overall survival.

	Variable	*n/N* (%)	PFS		OS	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Multivariate	RVd arm	235/460 (51%)	0.77 (0.62, 0.95)	0.013	0.75 (0.58, 0.98)	0.033
	ISS Stage III	155/460 (34%)	1.34 (1.01, 1.77)	0.041	1.98 (1.38, 2.86)	<.001
	ISS Stage II	179/460 (39%)	1.12 (0.86, 1.47)	0.398	1.36 (0.95, 1.97)	0.096
	Intent to Transplant	315/460 (68%)	0.95 (0.74, 1.23)	0.714	0.73 (0.54, 0.99)	0.043
	Age > =65 yr	197/460 (43%)	1.27 (1.00, 1.61)	0.048	1.63 (1.21, 2.19)	0.001

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S0777: Does Response Matter?

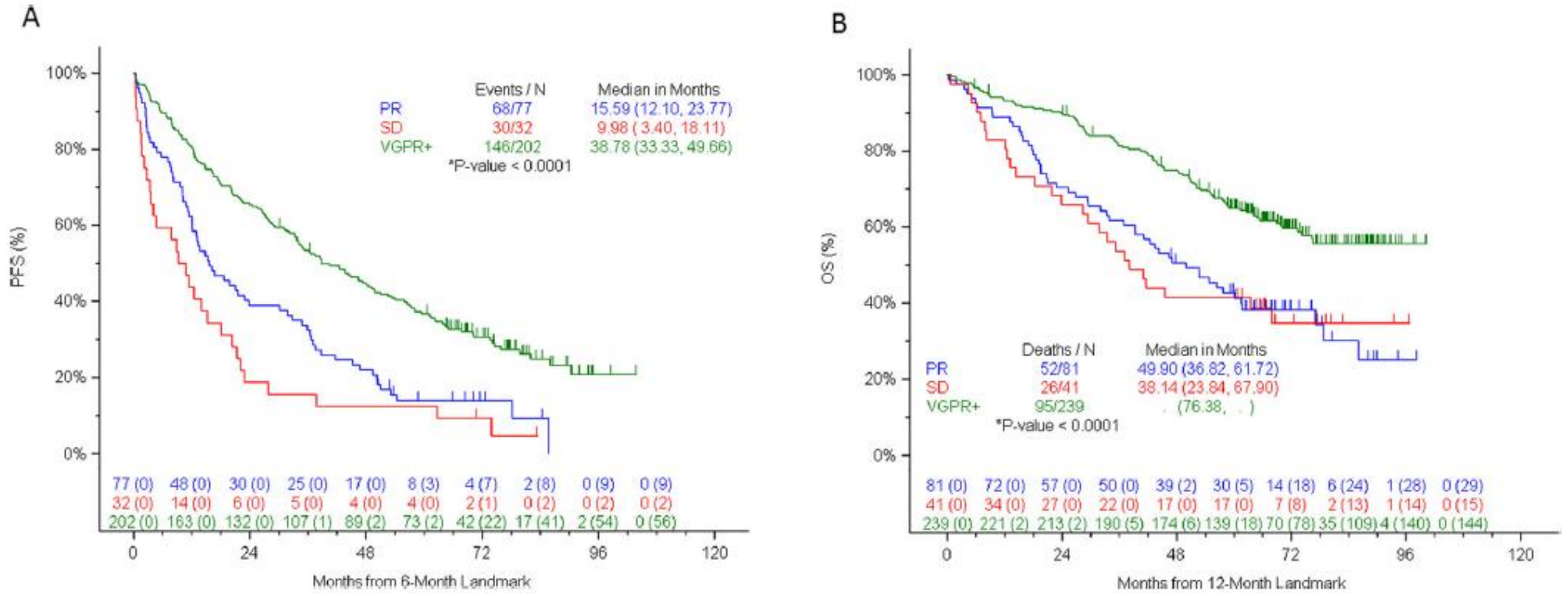

Fig. 2 Landmarked outcomes. a Progression-free Survival by best response at 6 months. **b** Overall Survival by best response at 12 months.

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Table 5 Adverse events at least possibly attributable to study drug by category.

Adverse event description	Revlimid/dexamethasone (*N* = 222)					Velcade/Revlimid/dexamethasone (*N* = 234)				
	1	2	3	4	5	1	2	3	4	5
Allergy/immunology	12 (5%)	5 (2%)				10 (4%)	4 (2%)	2 (<1%)		
Auditory/ear	1 (<1%)	16 (7%)				1 (<1%)	8 (3%)			
Blood/bone marrow	22 (10%)	53 (24%)	68 (31%)	39 (18%)		27 (12%)	52 (22%)	70 (30%)	44 (19%)	
Cardiac arrhythmia	5 (2%)	4 (2%)	4 (2%)			10 (4%)	3 (1%)	3 (1%)		
Cardiac general	13 (6%)	9 (4%)	8 (4%)			15 (6%)	17 (7%)	21 (9%)		
Coagulation	1 (<1%)		3 (1%)					5 (2%)		
Constitutional symptoms	61 (27%)	77 (35%)	38 (17%)			60 (26%)	84 (36%)	51 (22%)		
Death					1 (<1%)					2 (<1%)
Dermatology/skin	60 (27%)	23 (10%)	9 (4%)			50 (21%)	41 (18%)	7 (3%)	1 (<1%)	
Endocrine	11 (5%)	8 (4%)				7 (3%)	12 (5%)			
Gastrointestinal	77 (35%)	71 (32%)	19 (9%)			64 (27%)	79 (34%)	51 (22%)	2 (<1%)	1 (<1%)
Hemorrhage/bleeding	13 (6%)	2 (<1%)				9 (4%)	3 (1%)	8 (3%)		
Hepatobiliary/pancreas			2 (<1%)							
Infection	1 (<1%)	31 (14%)	27 (12%)	4 (2%)		1 (<1%)	33 (14%)	34 (15%)	7 (3%)	1 (<1%)
Lymphatics	58 (26%)	19 (9%)	1 (<1%)			73 (31%)	26 (11%)	4 (2%)		
Metabolic/laboratory	56 (25%)	58 (26%)	51 (23%)	13 (6%)		50 (21%)	58 (25%)	57 (24%)	8 (3%)	
Musculoskeletal/soft tissue	25 (11%)	25 (11%)	16 (7%)	1 (<1%)		15 (6%)	31 (13%)	24 (10%)		
Neurology	78 (35%)	44 (20%)	21 (9%)	3 (1%)	1 (<1%)	42 (18%)	70 (30%)	77 (33%)	4 (2%)	
Ocular/visual	21 (9%)	8 (4%)	11 (5%)			39 (17%)	17 (7%)	6 (3%)		
Pain	44 (20%)	29 (13%)	10 (5%)			55 (24%)	43 (18%)	28 (12%)		
Pulmonary/upper respiratory	42 (19%)	27 (12%)	9 (4%)	1 (<1%)		56 (24%)	17 (7%)	15 (6%)	5 (2%)	
Renal/genitourinary	3 (1%)	2 (<1%)	9 (4%)	1 (<1%)		10 (4%)	3 (1%)	6 (3%)		
Secondary malignancy			5 (2%)	1 (<1%)				5 (2%)	2 (<1%)	
Sexual/reproductive function	1 (<1%)	1 (<1%)	1 (<1%)			3 (1%)	1 (<1%)			
Syndromes			2 (<1%)			1 (<1%)	2 (<1%)	4 (2%)		
Vascular		7 (3%)	15 (7%)	6 (3%)		1 (<1%)	9 (4%)	20 (9%)	4 (2%)	

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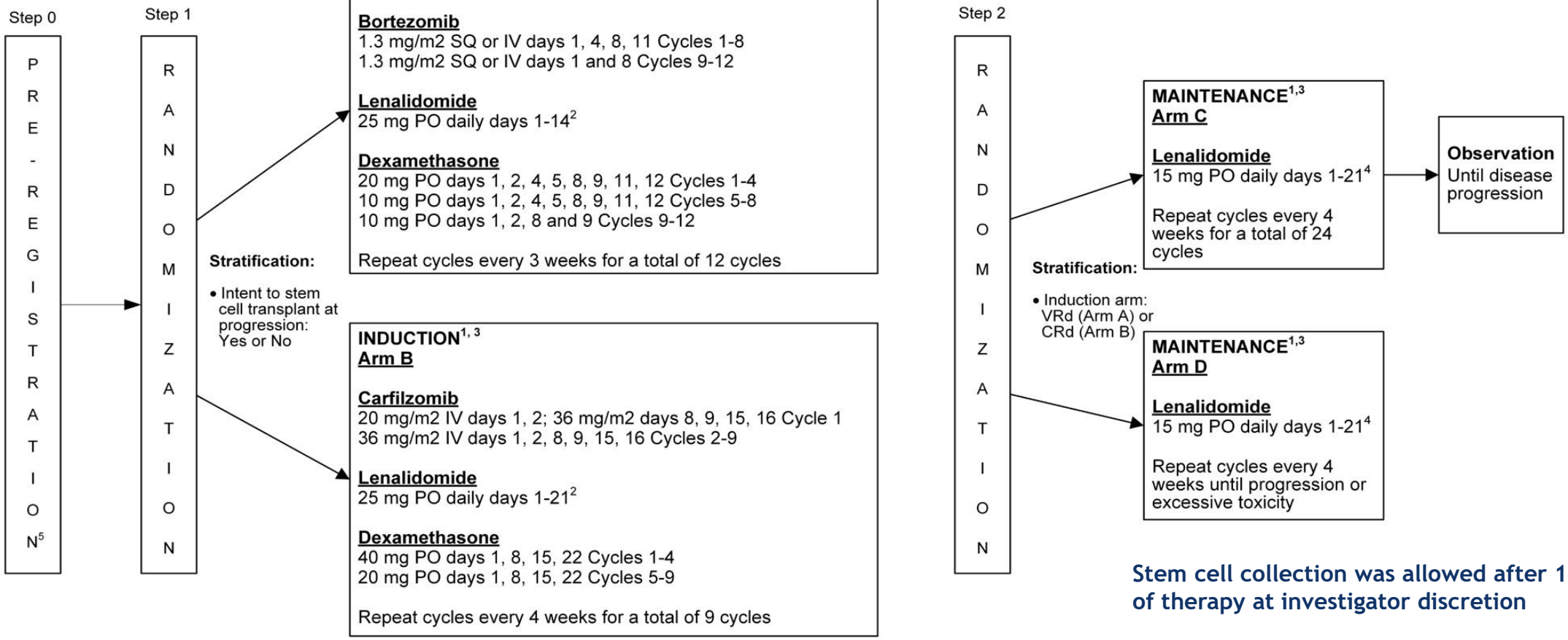
Can we do better than VRd?

Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

Shaji K Kumar, Susanna J Jacobus, Adam D Cohen, Matthias Weiss, Natalie Callander, Avina K Singh, Terri L Parker, Alexander Menter, Xuezhong Yang, Benjamin Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Rosenberg, Jeffrey A Zonder, Edward Faber Jr, Sagar Lonial, Kenneth C Anderson, Paul G Richardson, Robert Z Orlowski, Lynne I Waqner, S Vincent Rajkumar

Patient Randomization and Treatment Schedule



Stem cell collection was allowed after 12 weeks of therapy at investigator discretion

Key Eligibility Criteria

- Previously untreated MM with no intent for immediate (upfront) SCT
- **None of the following high-risk features (t(14;20), t(14;16), del17p, LDH > 2 X ULN, no plasma cell leukemia)**
- ECOG performance status 0, 1, or 2 (PS 3 if secondary to pain)
- Adequate hematological parameters and organ function
- Measurable disease in serum, urine, or bone marrow
- No grade ≥2 peripheral neuropathy
- NYHA III or IV heart failure or MI < 6 months were excluded

Baseline Demographics

Variable	Category	VRd (n=542) N (%)	KRd (n=545) N (%)	Total (n=1087) N (%)
Age (y), median (range)		64 (32-88)	65 (35-86)	65 (32-88)
	>/=70 years	167 (30.8)	177 (32.5)	344 (31.6)
	>/=65 years	264 (48.7)	288 (52.8)	552 (50.8)
Gender	Male	315 (58.1)	327 (60.0)	642 (59.1)
Race	White	443 (84.5)	448 (86.3)	891 (85.4)
	Black	68 (13.0)	59 (11.4)	127 (12.2)
	Other	13 (2.5)	12 (2.3)	25 (2.4)
ECOG PS	PS0	212 (39.1)	241 (44.2)	453 (41.7)
	PS1	270 (49.8)	249 (45.7)	519 (47.8)
	PS2-3	60 (11.1)	55 (10.1)	115 (10.5)
ISS Stage	I	144 (30.6)	157 (32.5)	301 (31.6)
	II	203 (43.1)	207 (42.9)	410 (43.0)
	III	124 (26.3)	119 (24.6)	243 (25.5)
Measurable Disease Type	SPEP&UPEP	115 (21.2)	114 (20.9)	229 (21.1)
	SPEP	305 (56.3)	296 (54.3)	601 (55.3)
	UPEP	57 (10.5)	79 (14.5)	136 (12.5)
	FLC	58 (10.7)	51 (9.4)	109 (10.0)
	Bone Marrow	4 (0.7)	4 (0.7)	8 (0.7)
	Not Measurable	3 (0.6)	1 (0.2)	4 (0.4)

Variable	VRd (n=542) median (IQR)	KRd (n=545) median (IQR)	Total (n=1087) median (IQR)
Bone marrow plasma cell (%)	52 (30-75)	50.5 (30-72)	51 (30-75)
Albumin (g/dL)	3.8 (3.4-4.2)	3.8 (3.4-4.2)	3.8 (3.4-4.2)
Beta 2 microglobulin (ug/mL)	3.6 (2.6-5.6)	3.9 (2.8-6)	3.8 (2.6-5.8)
Hemoglobin (g/dL)	11 (9.6-12.4)	11.2 (9.8-12.6)	11.1 (9.7-12.5)
Calcium (mg/dL)	9.3 (8.9-9.8)	9.4 (8.9-9.8)	9.3 (8.9-9.8)
Serum M Spike (g/dL)	3 (1.8-4.2)	2.9 (1.8-4.2)	3 (1.8-4.2)
Urine M Spike (mg/24hr)	297.8 (64.9-1099)	257.1 (49.4-1312.4)	275 (56.4-1157)
Creatinine (mg/dL)	1 (0.8-1.3)	1 (0.8-1.3)	1 (0.8-1.3)
Lactate Dehydrogenase (U/L)	171 (136-222)	166 (135-203)	168 (136-209)

Variable	Category	N (%)	N (%)	N (%)
Cytogenetics	Normal	326 (71.8)	331 (72.3)	657 (72.0)
	Abnormal	128 (28.2)	127 (27.7)	255 (28.0)
	Missing	88	67	175
t(11;14)	Abnormal	87 (20.6)	80 (18.7)	167 (19.7)
t(4;14)	Abnormal	44 (10.4)	36 (8.4)	80 (9.4)

Induction Treatment Status

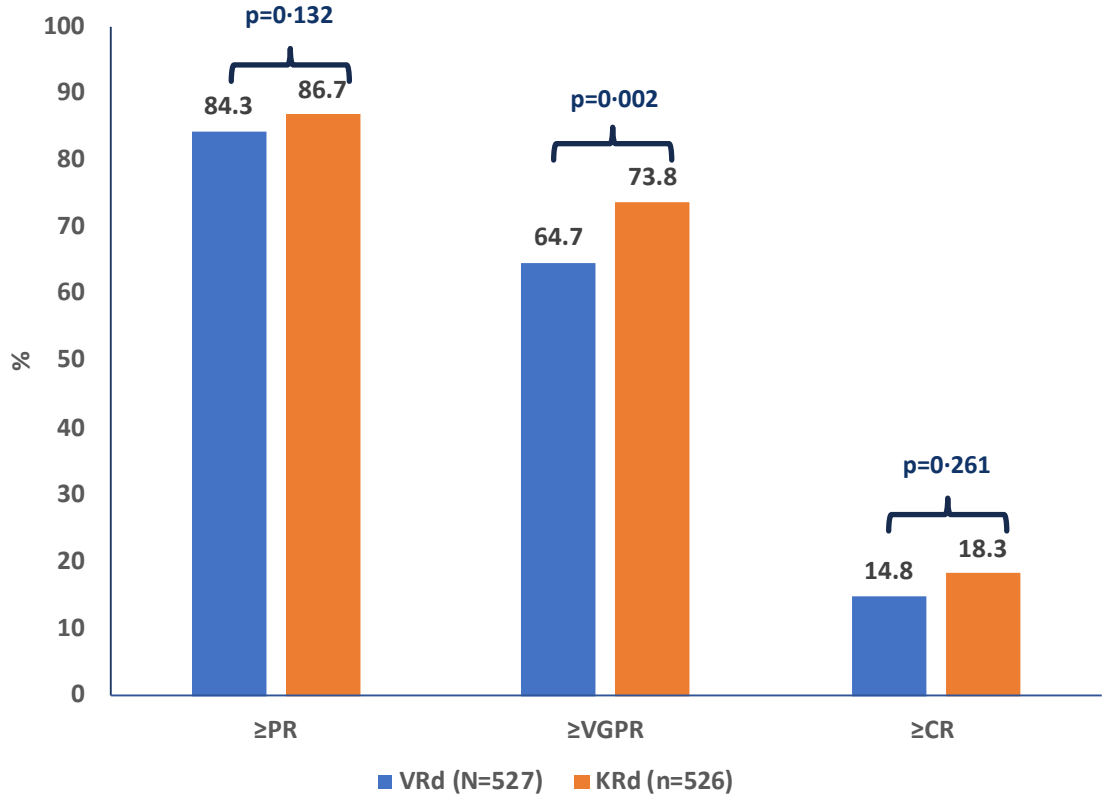
N=1053 starting assigned treatment

	VRd (n=527)	KRd (n=526)	Total (n=1053)
Reason	**N (%)**	**N (%)**	**N (%)**
Treatment Completed	228 (43.3)	324 (61.6)	552 (52.4)
Disease Progression	33 (6.3)	19 (3.6)	52 (4.9)
Adverse Events/ Complications	91 (17.3)	52 (9.9)	143 (13.6)
Death	6 (1.1)	15 (2.9)	21 (2.0)
Patient Withdrawal/ Refusal	39 (7.4)	22 (4.2)	61 (5.8)
Alternative Therapy	93 (17.7)	72 (13.7)	165 (15.7)
Other Complicating Disease	13 (2.5)	5 (1.0)	18 (1.7)
Non-Compliance	7 (1.3)	3 (0.6)	10 (1.0)
MD Decision	8 (1.5)	4 (0.8)	12 (1.1)
Other	9 (1.7)	10 (1.9)	19 (1.8)

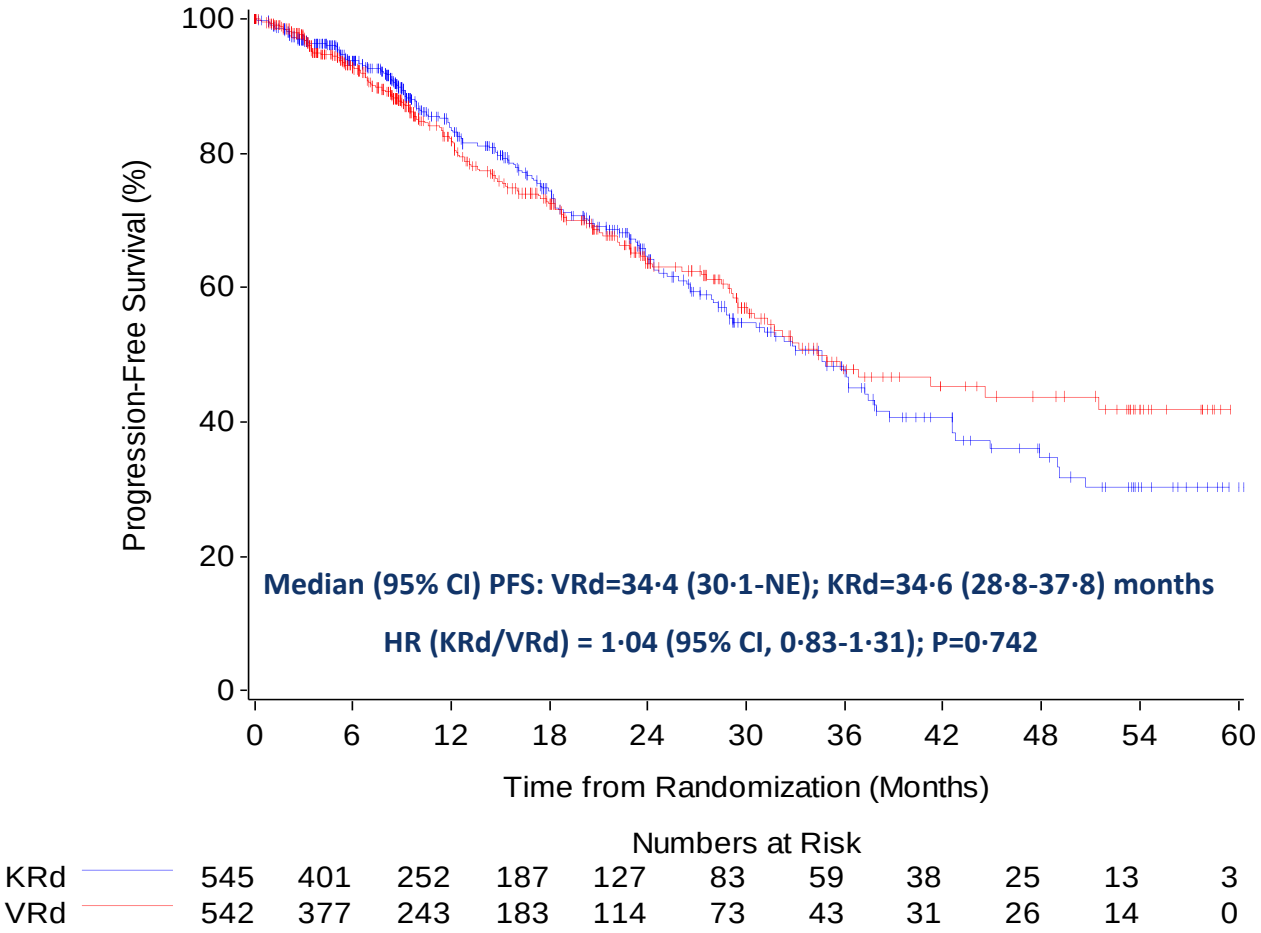
	VRd (n=542)	KRd (n=545)	Total (n=1087)
	N (%)	**N (%)**	**N (%)**
Received SCT	152 (28.0)	146 (26.8)	298 (27.4)
Median (range); months	6.5 (3.5-36.6)	8.9 (3.7-56.9)	
IQR	4.8-10.4	6.0-15.1	

Response To Induction

	VRd (n=527)	KRd (n=526)	Total (n=1053)
Category	N (%)	N (%)	N (%)
Stringent Complete Response	21 (4.0)	31 (5.9)	52 (4.9)
Complete Response	57 (10.8)	65 (12.4)	122 (11.6)
Very Good Partial Response	263 (49.9)	292 (55.5)	555 (52.7)
Partial Response	103 (19.5)	68 (12.9)	171 (16.2)
Stable Disease	40 (7.6)	34 (6.5)	74 (7.0)
Progressive Disease	1 (0.2)	0 (0.0)	1 (0.1)
Unevaluable/Insufficient	42 (8.0)	36 (6.8)	78 (7.4)



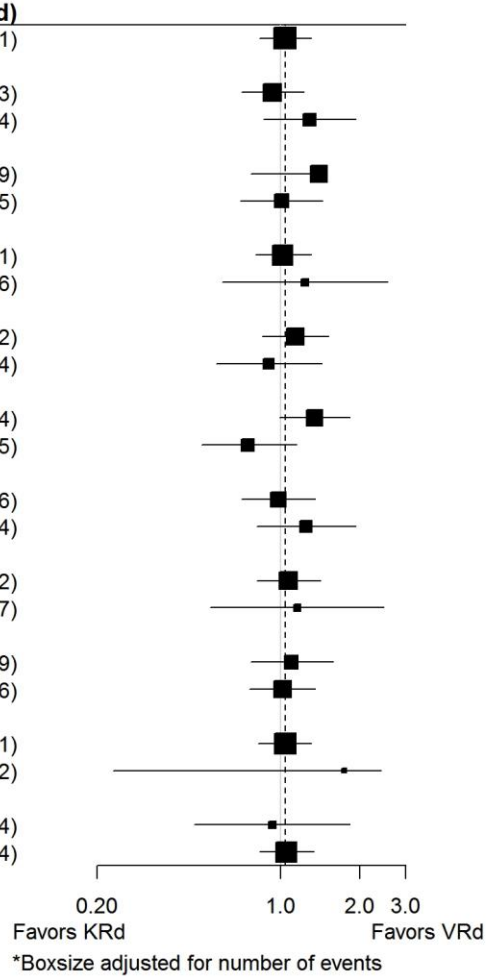
Progression Free Survival from Induction Randomization



- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31 ·7 (28 ·5-44 ·6) and KRd = 32 ·8 (27 ·2-37 ·5) months

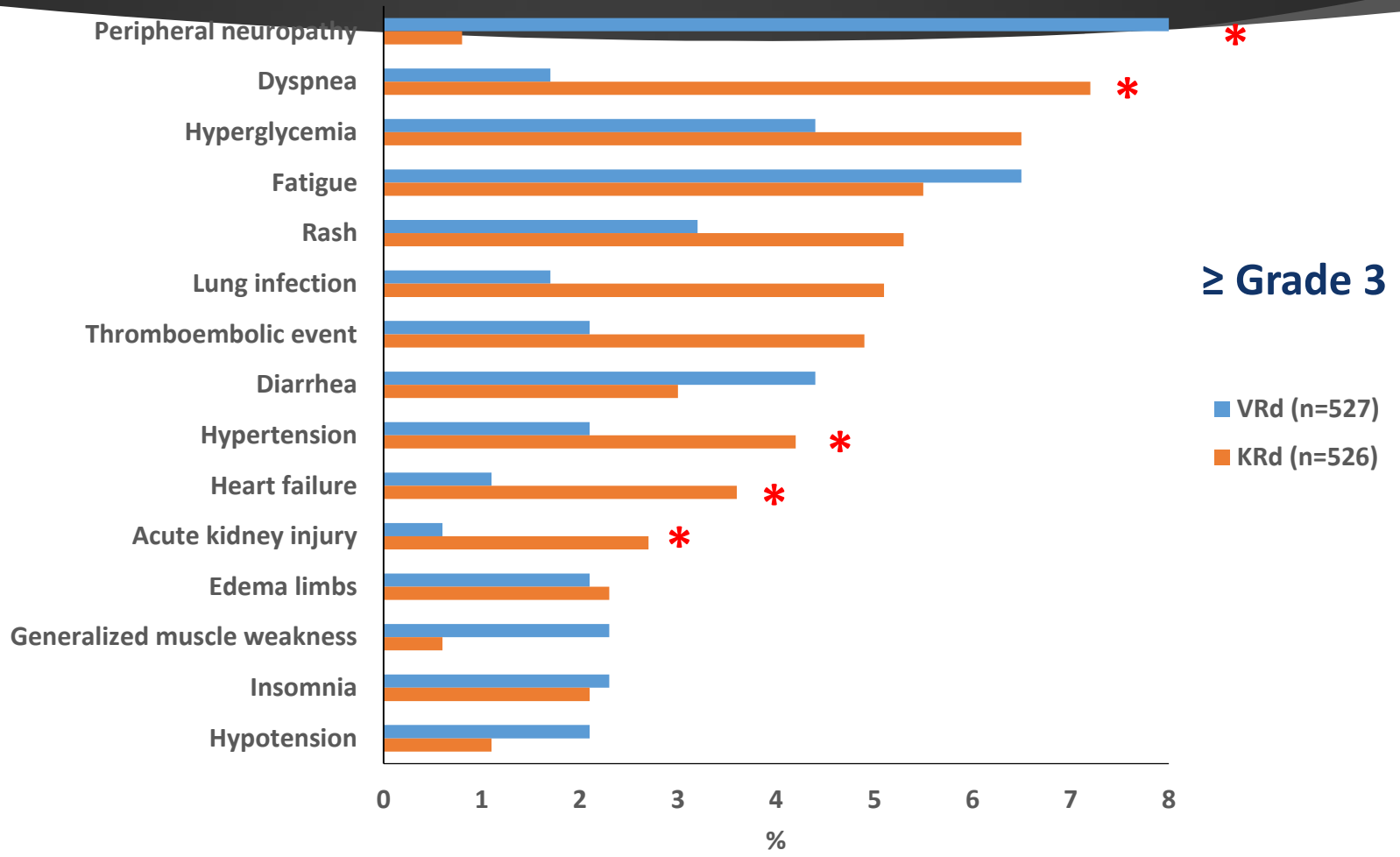
Progression Free Survival in Subgroups

Subgroup	N patients/events	Treatment HR (Krd/Vrd)
Overall	1087/298	1.04 (0.83-1.31)
Age		
<70y	743/199	0.93 (0.71-1.23)
>/=70y	344/99	1.29 (0.86-1.94)
Sex		
Male	642/182	1.04 (0.77-1.39)
Female	445/116	1.01 (0.70-1.45)
Race		
White	891/254	1.02 (0.80-1.31)
Non-white	152/31	1.24 (0.60-2.56)
ISS Stage		
I-II	711/186	1.14 (0.85-1.52)
III	243/71	0.90 (0.57-1.44)
Cytogenetics		
Normal	657/166	1.35 (0.99-1.84)
Abnormal	255/93	0.75 (0.50-1.15)
13q Status		
Absent	534/146	0.98 (0.71-1.36)
Present	316/85	1.25 (0.81-1.94)
t(4;14) Status		
Absent	770/203	1.07 (0.81-1.42)
Present	80/28	1.16 (0.54-2.47)
ECOG PS		
0	453/118	1.10 (0.77-1.59)
>0	634/180	1.02 (0.76-1.36)
Creatinine		
<2 mg/dL	1026/283	1.04 (0.82-1.31)
>/=2 mg/dL	61/15	0.75 (0.23-2.42)
Measurable Disease Type		
Light Chain MM	109/35	0.93 (0.47-1.84)
Non-Light Chain MM	978/263	1.05 (0.83-1.34)



*Boxsize adjusted for number of events

Non-hematologic: Treatment-Related AEs (≥2%)

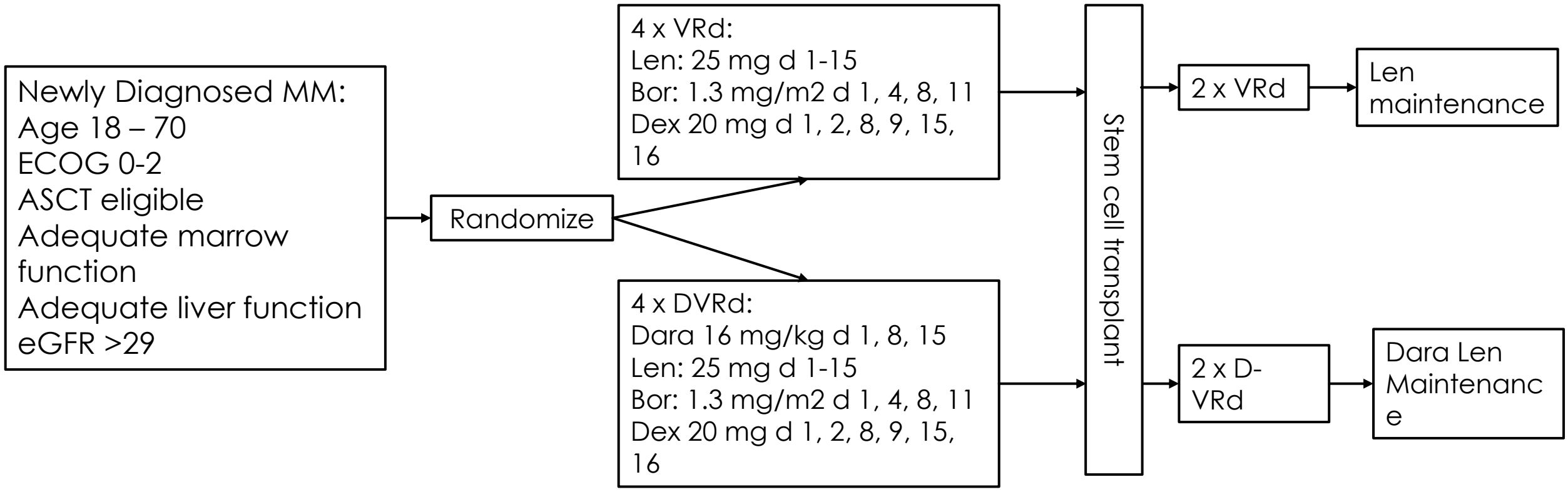


Can we do better than VRd?

Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial

Peter M. Voorhees,[1] Jonathan L. Kaufman,[2] Jacob Laubach,[3] Douglas W. Sborov,[4] Brandi Reeves,[5] Cesar Rodriguez,[6] Ajai Chari,[7] Rebecca Silbermann,[8] Luciano J. Costa,[9] Larry D. Anderson Jr,[10] Nitya Nathwani,[11] Nina Shah,[12] Yvonne A. Efebera,[13] Sarah A. Holstein,[14] Caitlin Costello,[15] Andrzej Jakubowiak,[16] Tanya M. Wildes,[17] Robert Z. Orlowski,[18] Kenneth H. Shain,[19] Andrew J. Cowan,[20] Sean Murphy,[21] Yana Lutska,[21] Huiling Pei,[22] Jon Ukropec,[23] Jessica Vermeulen,[24] Carla de Boer,[24] Daniela Hoehn,[21] Thomas S. Lin,[21] and Paul G. Richardson,[3] for the GRIFFIN Trial Investigators

Design



Voorhees et al Blood

GRIFFIN: Demographics and Toxicity

Table 1. Patient demographic and disease characteristics in the intent-to-treat population at baseline

	D-RVd	RVd
Age, y	n = 104	n = 103
Median (range)	59 (29-70)	61 (40-70)
Category, n (%)		
<65	76 (73.1)	75 (72.8)
≥65	28 (26.9)	28 (27.2)
Sex, n (%)	n = 104	n = 103
Male	58 (55.8)	60 (58.3)
Female	46 (44.2)	43 (41.7)
ECOG performance status, n (%)*	n = 101	n = 102
0	39 (38.6)	40 (39.2)
1	51 (50.5)	52 (51.0)
2	11 (10.9)	10 (9.8)
ISS disease stage, n (%)†	n = 104	n = 103
I	49 (47.1)	50 (48.5)
II	40 (38.5)	37 (35.9)
III	14 (13.5)	14 (13.6)
Missing	1 (1.0)	2 (1.9)
Baseline creatinine clearance, mL/min, n (%)	n = 104	n = 103
30-50	9 (8.7)	9 (8.7)
>50	95 (91.3)	94 (91.3)
Cytogenetic risk profile, n (%)‡	n = 98	n = 97
Standard	82 (83.7)	83 (85.6)
High risk	16 (16.3)	14 (14.4)
Time since diagnosis of MM, mo	n = 103	n = 102
Median (range)	0.7 (0-12)	0.9 (0-61)

t(4;14), t(14;16), del(17p)

Adverse event, n (%)	D-RVd, n = 99		RVd, n = 102	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic				
Neutropenia	57 (57.6)	41 (41.4)	36 (35.3)	22 (21.6)
Thrombocytopenia	43 (43.4)	16 (16.2)	36 (35.3)	9 (8.8)
Leukopenia	36 (36.4)	16 (16.2)	29 (28.4)	7 (6.9)
Anemia	35 (35.4)	9 (9.1)	33 (32.4)	6 (5.9)
Lymphopenia	30 (30.3)	23 (23.2)	28 (27.5)	22 (21.6)
Nonhematologic				
Fatigue	68 (68.7)	6 (6.1)	62 (60.8)	6 (5.9)
Upper respiratory tract infection	62 (62.6)	1 (1.0)	45 (44.1)	2 (2.0)
Peripheral neuropathy*	59 (59.6)	7 (7.1)	74 (72.5)	8 (7.8)
Diarrhea	59 (59.6)	7 (7.1)	51 (50.0)	4 (3.9)
Constipation	51 (51.5)	2 (2.0)	40 (39.2)	1 (1.0)
Cough	50 (50.5)	0	27 (26.5)	0
Nausea	49 (49.5)	2 (2.0)	50 (49.0)	1 (1.0)
Pyrexia	45 (45.5)	2 (2.0)	28 (27.5)	3 (2.9)
Insomnia	42 (42.4)	2 (2.0)	31 (30.4)	1 (1.0)
Back pain	36 (36.4)	1 (1.0)	34 (33.3)	4 (3.9)
Peripheral edema	34 (34.3)	2 (2.0)	35 (34.3)	3 (2.9)
Arthralgia	33 (33.3)	0	33 (32.4)	2 (2.0)
Infusion-related reaction	42 (42.4)	6 (6.1)†	NA	NA

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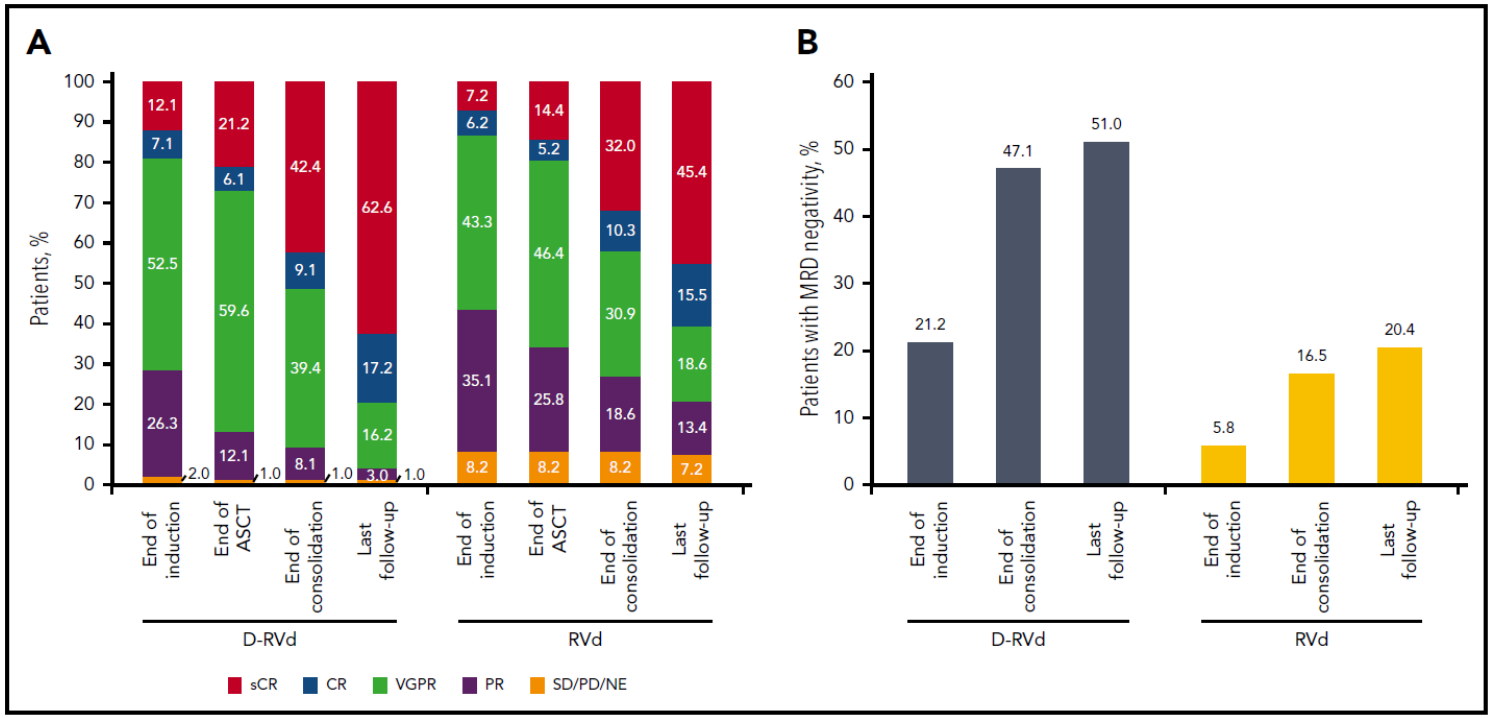
GRIFFIN: Responses deepen over time



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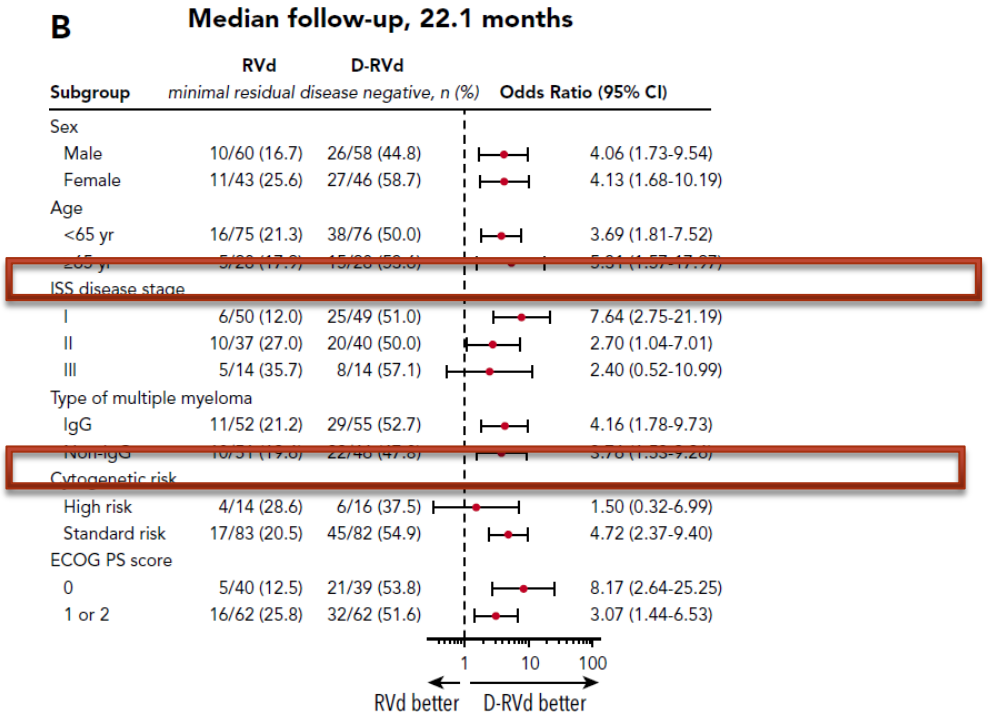
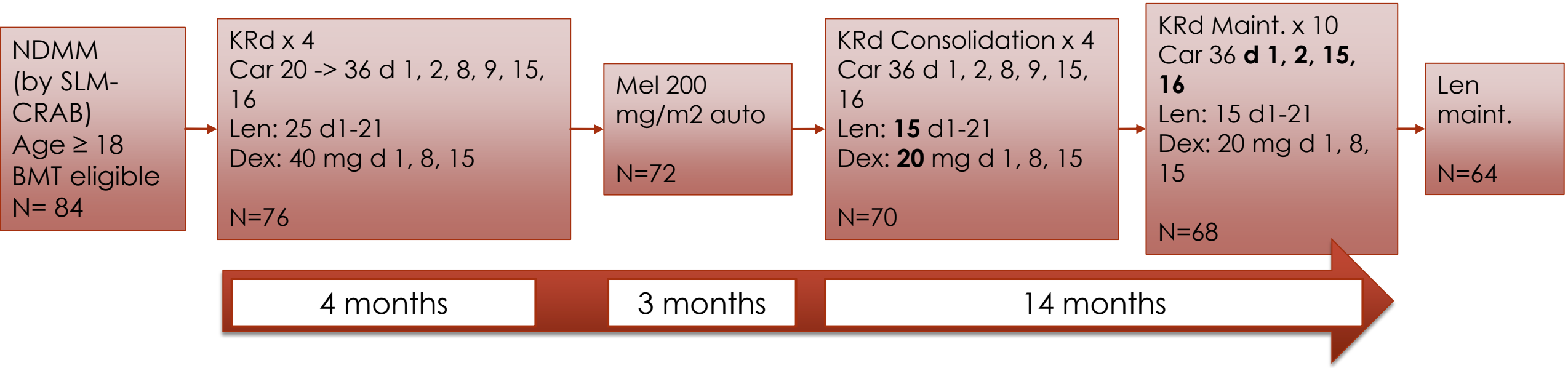
D-VRd: Subgroup analysis of sCR rates



Voorhees et al Blood

Is KRd really dead for NDMM? MMRC Extended KRd trial (The new total therapy?)



Jasielec Blood 2020

MMRC Extended KRd: Demographics and Toxicity

Characteristic	N=76
Age	
Median years (range)	59 (40–76)
≥65 years, n (%)	21 (27.6)
Sex, n (%)	
Male	45 (59.2)
Female	31 (40.8)
ECOG performance status, n (%)	
0–1	65 (85.5)
Unknown	11 (14.5)
ISS Stage, n (%)	
I	31 (40.8)
II	31 (40.8)
III	10 (13.2)
Unknown	4 (5.3)
Cytogenetic risk by FISH*, n (%)	
High	27 (35.5)
Deletion 17p	11 (14.5)
Ultra-high risk†	8 (10.5)
Standard	49 (64.5)
Serum $ß_2$-microglobulin, n (%)	
<3.5 mg/L	45 (59.2)
≥3.5 mg/L, %	24 (31.6
Unknown	7 (9.2)

*Defined per IMWG: t(4;14), del(17p), t(14;16), t(14;20), non-hyperdiploidy and gain(1q).

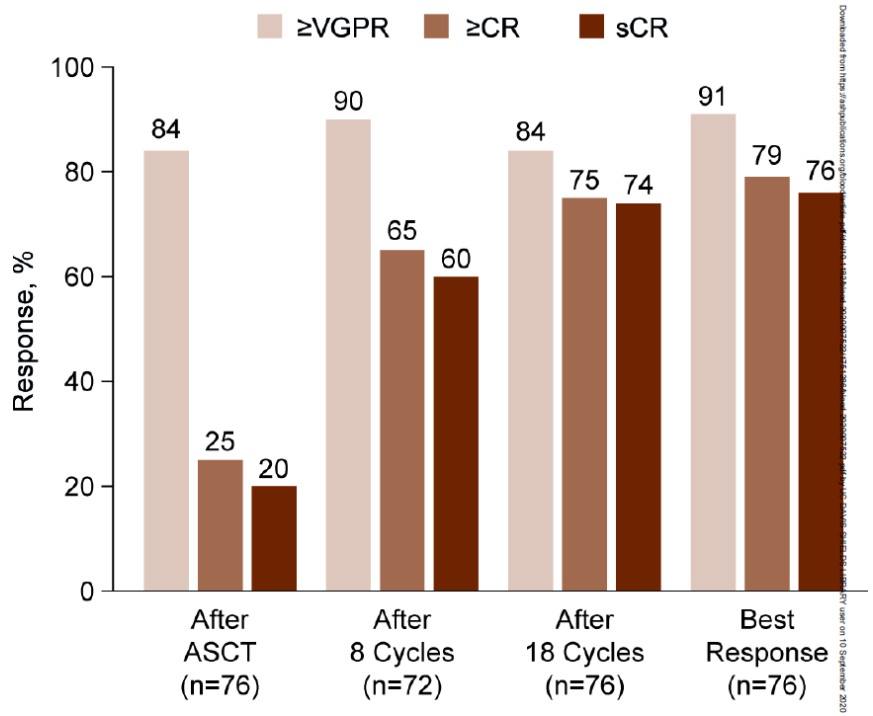
Table 3. Treatment-emergent adverse events during KRd*

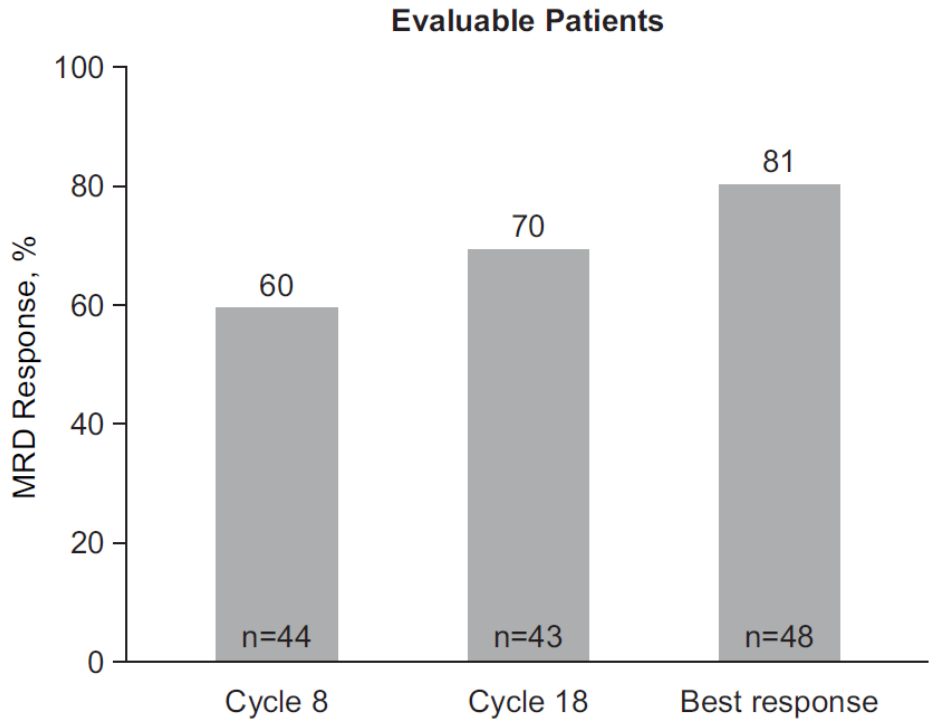
	KRd +ASCT N=76	
	All Grade, n (%)	Grade 3/4, n (%)
Hematologic		
Thrombocytopenia	47 (62)	11 (14)
Anemia	32 (42)	9 (12)
Lymphopenia	32 (42)	24 (32)
Neutropenia	30 (39)	26 (34)
Non-hematologic		
Infection	56 (74)	17 (22)
Fatigue	51 (67)	4 (5)
Diarrhea	39 (51)	7 (9)
Hyperglycemia	33 (43)	6 (8)
Dyspnoea	30 (39)	2 (3)
Peripheral neuropathy	32 (42)	0
Rash	33 (43)	4 (5)
Hypophosphatemia	22 (29)	11 (14)
Hypertension	15 (20)	4 (5)
Thromboembolic events	14 (18)	5 (7)
Cardiac events†	10 (13)	2 (3)

Jasielec Blood

MMRC Extended KRd: Responses improve throughout KRd exposure

MRD Negativity





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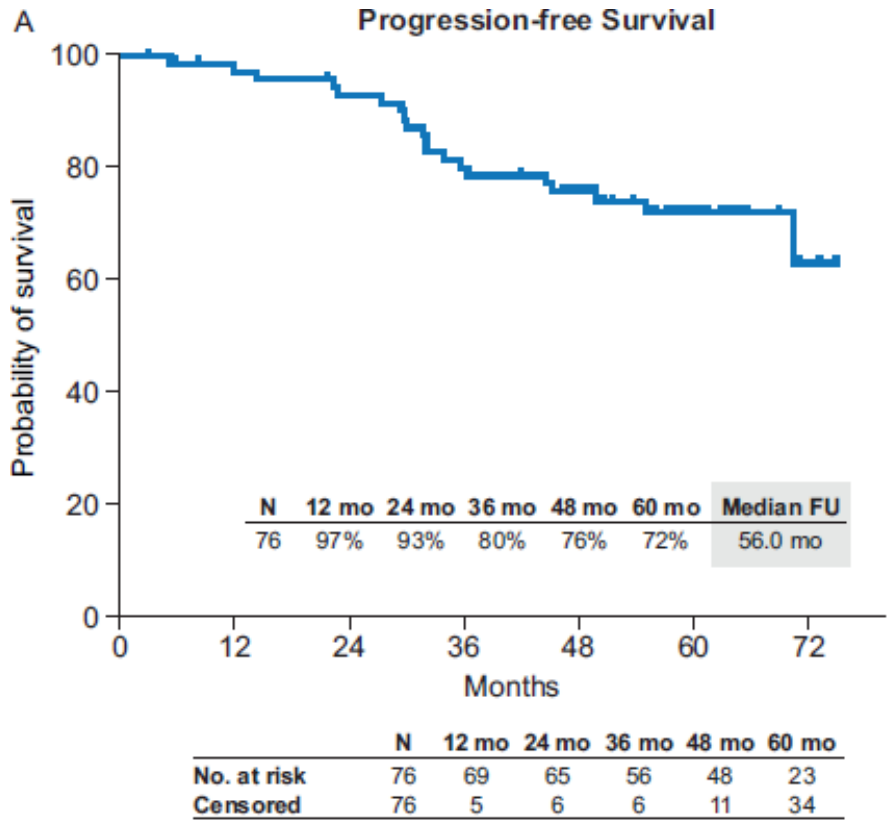
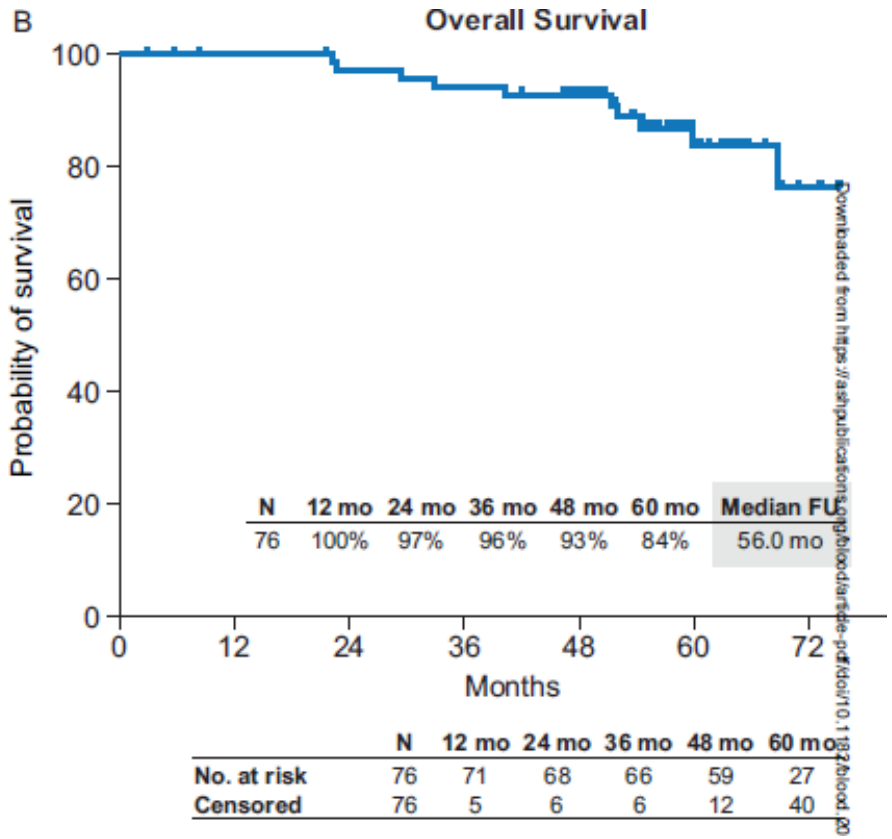
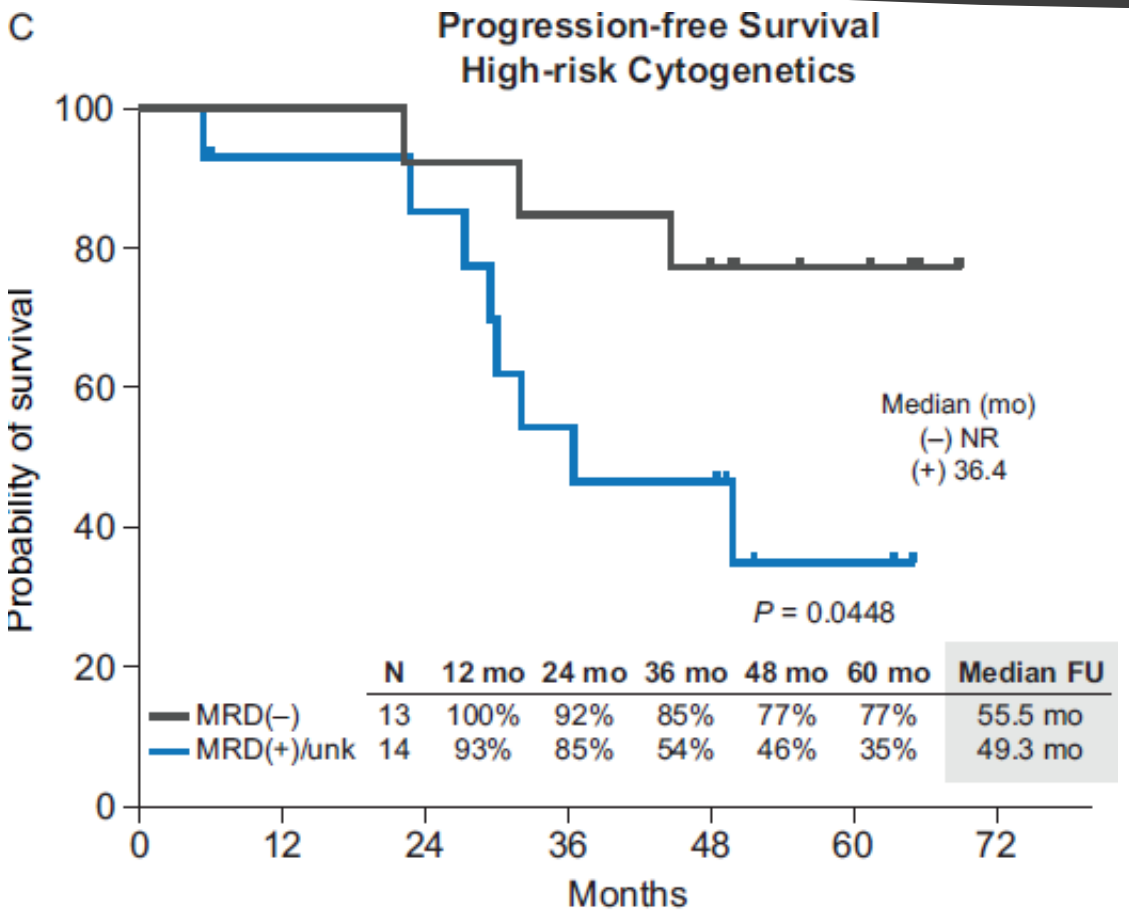
MMRC: Extended KRd PFS and OS

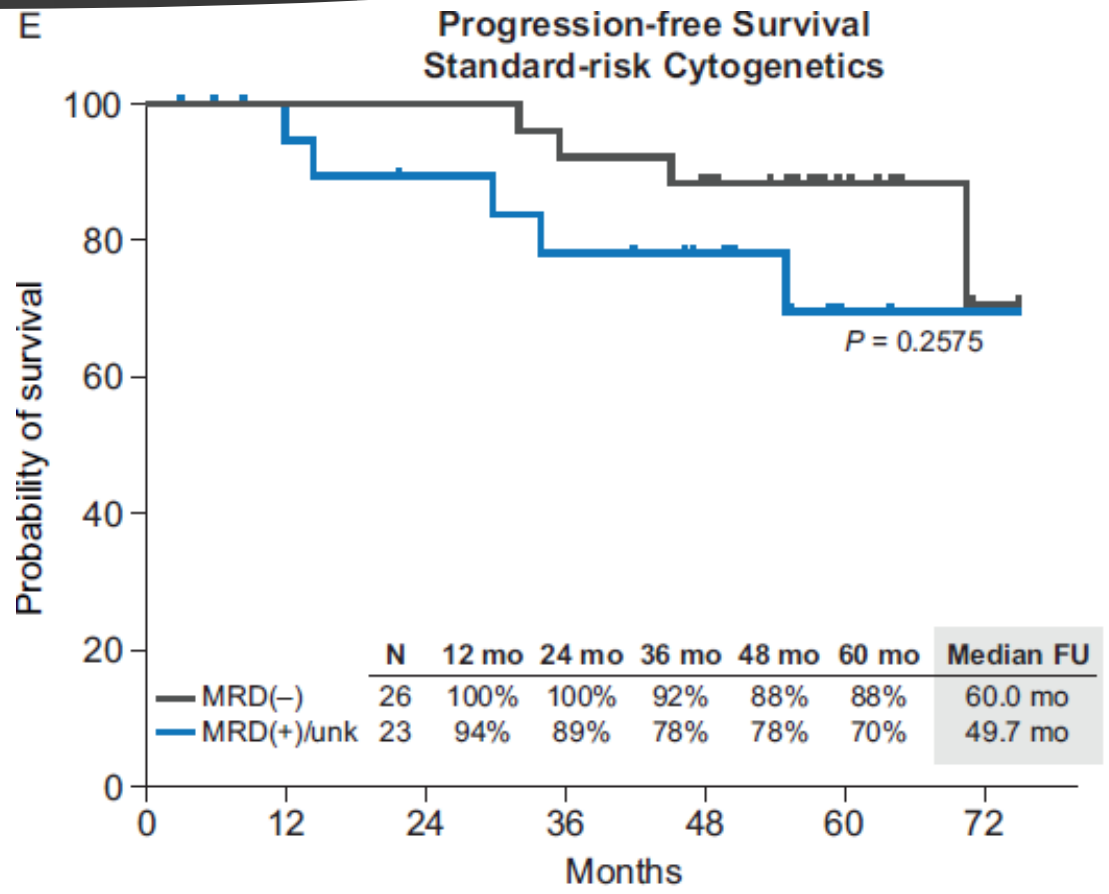




Jasielec Blood

MMRC: Extended KRd: PFS by High Risk and Standard Risk Cytogenetics





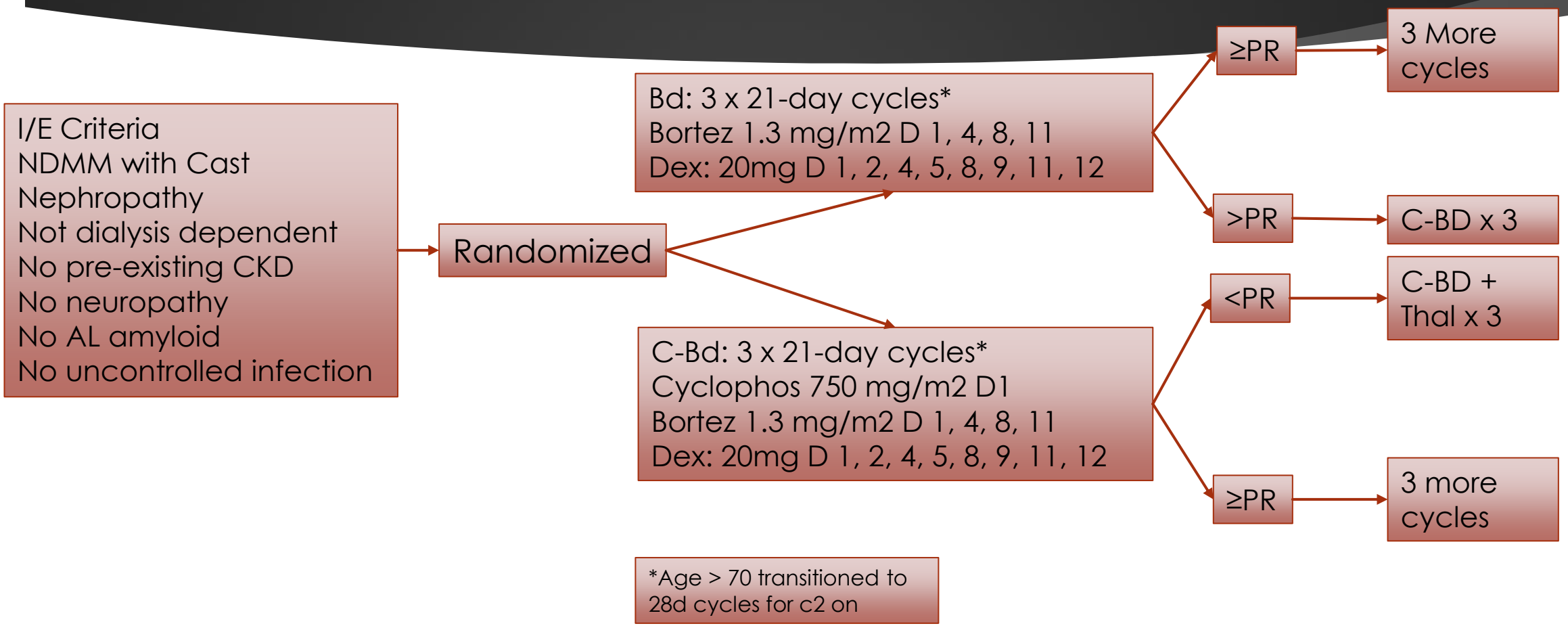
Jasielec Blood 2020

NDMM with Acute Kidney Injury

Randomized Trial Comparing Double Versus Triple Bortezomib-Based Regimen in Patients With Multiple Myeloma and Acute Kidney Injury Due to Cast Nephropathy

Frank Bridoux, MD, PhD[1,2,3]; Bertrand Arnulf, MD, PhD[4]; Lionel Karlin, MD[5]; Nicolas Blin, MD[6]; Nolwenn Rabot, MD[7]; Margaret Macro, MD[8]; Vincent Audard, MD, PhD[9]; Karim Belhadj, MD[10]; Brigitte Pegourie, MD[11]; Pierre Gobert, MD[12]; Emilie Cornec Le Gall, MD, PhD[13]; Bertrand Joly, MD[14]; Alexandre Karras, MD, PhD[15]; Arnaud Jaccard, MD, PhD[2,3,16]; Karine Augeul-Meunier, MD[17]; Salomon Manier, MD, PhD[18]; Bruno Royer, MD[19]; Denis Caillot, MD, PhD[20]; Mourad Tiab, MD[21]; Sébastien Delbes, MD[22]; Felipe Suarez, MD, PhD[23]; Cécile Vigneau, MD, PhD[24]; Sophie Caillard, MD, PhD[25]; Nina Arakelyan-Laboure, MD[26]; Damien Roos-Weil, MD, PhD[27]; Sylvie Chevret, MD, PhD[28]; and Jean Paul Fermand, MD[4]; for the MYRE study group

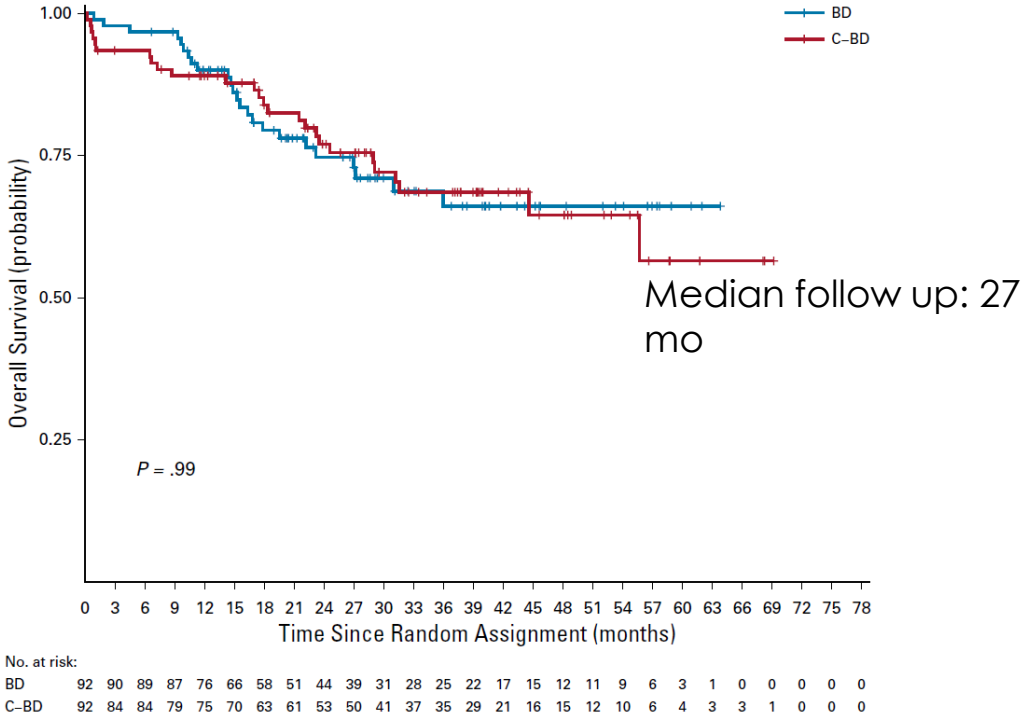
MYRE: Design



Bridoux et al JCO

MYRE: Responses and OS

- Renal response at 3 months
  - BD: 44.6%
  - C-BD: 51.1%
  - Risk ratio 0.87 (0.64 – 1.18)
- Overall Response at 3 months
  - BD: 78.3%
  - C-BD: 77.2%
- ≥VGPR at 6 months
  - BD: 46.8%
  - C-BD51.1%
  - RR 0.88 (0.66 – 1.17)



Median follow up: 27 mo

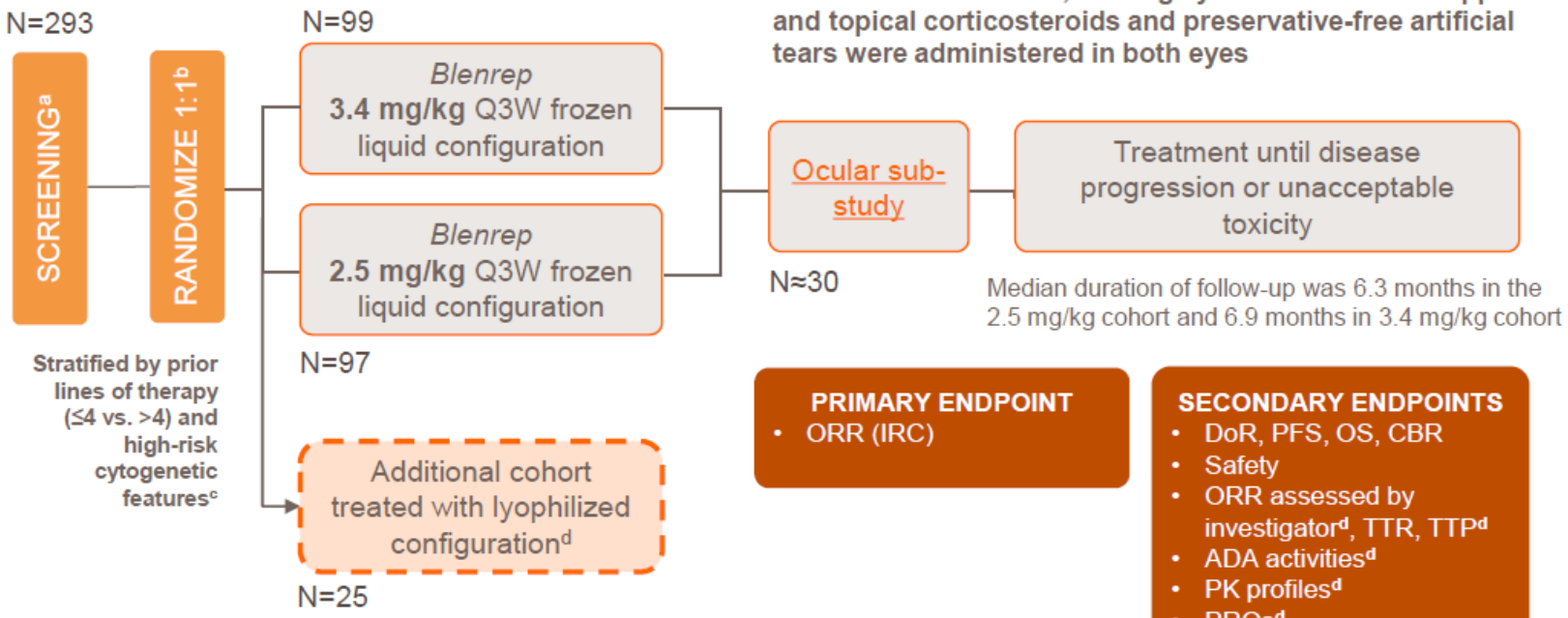
Bridoux et al JCO

Newly Diagnosed Multiple Myeloma: Summary

- The standard of care of NDMM should be RVd based on S0777 and E1A11: ENDURANCE
  - BUT…. E1A11 excluded t(14;16), t(14;20) and del(17p)
- The CR and MRD- rates with extended KRd in the high risk population are provocative
  - I may still consider this, since these patients were excluded from E1A11
- What about D-RVd?
  - If you're an "early adopter," or if you think MRD- rates are an adequate surrogate, GRIFFIN probably gives you enough push to adopt now
  - While I personally would like to see some data on PFS, we're beginning to incorporate into our treatment plans
  - It will be hard to assess survival outcomes in GRIFFIN because of the difference in post-BMT maintenance
  - Interestingly, D-RVd did not seem to affect outcomes in high-risk populations. More to come with this, I'm sure (along with all the caveats that come with sub-group analyses)
- For NDMM with AKI:
  - Bolus dosing of cyclophosphamide is not effective
  - However, hyper-fractionated cyclophosphamide, or lower dose oral cyclophos may provide improved outcomes by providing more consistent cytotoxic therapy
  - Randomized trials are clearly needed in this population

DREAMM-2: Study Design

A phase II, open label, randomized 2-dose study in RRMM who were refractory to an immunomodulatory drug, proteasome inhibitor and refractory/intolerant to an anti-CD38 monoclonal antibody.



[a]Screening occurred between June 18, 2018, and Jan 2, 2019

[b]DREAMM-2 was not designed to compare between the 2 doses

[c]Presence or absence of t(4;14), t(14;16) or 17p13del

[d]To be reported separately

ADA = anti-drug antibody; CBR = clinical benefit rate; DoR = duration of response; HR-QoL = health-related quality-of-life; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetics; PRO = patient reported outcome; Q3W = every 3 weeks; TTP = time to progression; TTR = time to (best) response.

Lonial et al, Lancet Onc 2020

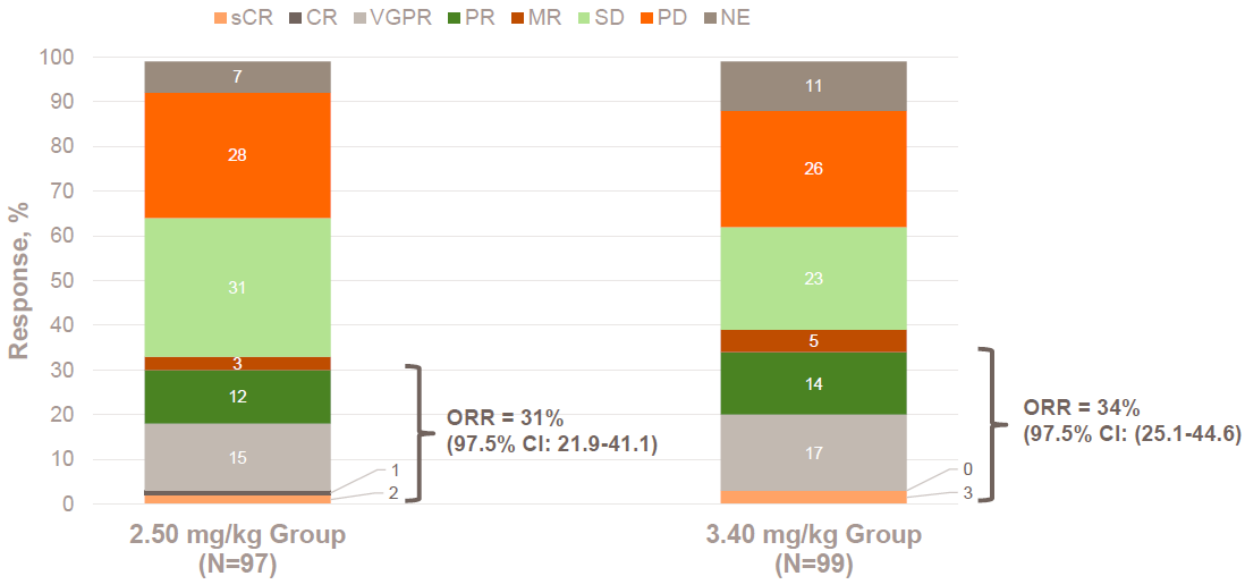
DREAMM-2: Demographics

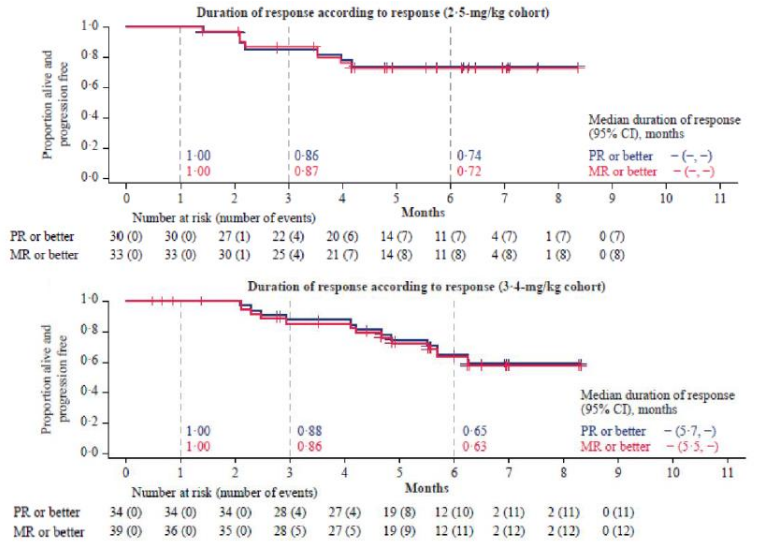
Characteristic	2.5-mg/kg Cohort (N=97)	3.4-mg/kg Cohort (N=99)
Age, median (IQR), years	65 (39–85)	67 (34–84)
18 to <65 years	45 (46)	36 (36)
65 to <75 years	39 (40)	46 (46)
≥75 years	13 (13)	17 (17)
Sex		
Male	51 (53)	56 (57)
Female	46 (47)	43 (43)
Race		
White	72 (74)	83 (84)
Black or African American	16 (16)	11 (11)
Renal impairment per eGFR (mL/min/1.73m²)		
Normal (≥90)	19 (20)	17 (17)
Mild (≥60 to <90)	48 (49)	52 (52)
Moderate (≥30 to <60)	24 (25)	22 (22)
Severe (≥15 to <30)	2 (2)	5 (5)
Time from initial diagnosis, median (IQR), years[a]	5.49 (4.01-7.02)	5.08 (4.16-7.48)
ISS Disease stage at screening		
Stage I	21 (22)	18 (18)
Stage II	33 (34)	51 (52)
Stage III	42 (43)	30 (30)
Unknown	1 (1)	0
Cytogenetic abnormalities		
t(11;14)	16 (16)	9 (9)
t(14;20)	3 (3)	0
Del 13	18 (19)	17 (17)
Hyperdiploidy	7 (7)	4 (4)
Other	28 (29)	23 (23)
High-risk cytogenetics	41 (42)	47 (47)
17p13del	16 (16)	22 (22)
t(4;14)	11 (11)	11 (11)
t(14;16)	7 (7)	2 (2)
1q21+	25 (26)	30 (30)

Characteristic	2.5-mg/kg Cohort (N=97)	3.4-mg/kg Cohort (N=99)
Type of myeloma		
IgG	65 (67)	73 (74)
Non-IgG	33 (33)	26 (26)
Extramedullary disease	22 (23)	18 (18)
Prior lines of therapy[b]		
Median (IQR)	7 (3–21)	6 (3–21)
≤4 lines	16 (16)	17 (17)
>4 lines	81 (84)	82 (83)
Prior therapies received		
Proteasome inhibitor	95 (98)	97 (98)
Bortezomib	74 (76)	64 (65)
Carfilzomib		
Immunomodulatory drug		
Lenalidomide	97 (100)	99 (100)
Pomalidomide	89 (92)	84 (85)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100)	96 (97)
Isatuximab	3 (3)	2 (2)
Refractory to prior therapies[c]		
Proteasome inhibitor		
Bortezomib	74 (76)	74 (75)
Carfilzomib	63 (65)	57 (58)
Immunomodulatory drug		
Lenalidomide	87 (90)	88 (89)
Pomalidomide	84 (87)	77 (78)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100)	91 (92)
Isatuximab	3 (3)	1 (1)

Lonial et al, Lancet Onc

DREAMM-2: ORR and DOR





At a median duration of follow-up of 6.3 (IQR: 3.7–7.7) and 6.9 (IQR: 4.8–7.9) months, respectively, the median duration of response was not reached

Lonial et al, Lancet Onc

DREAMM-2: Special Attention to Occular Toxicity

Adverse Event of Special Interest	*Blenrep* 2.5-mg/kg Cohort (N=95)	*Blenrep* 3.4-mg/kg Cohort (N=99)
	Percentage of patients	
Thrombocytopenia[a]	35	59
Infusion-related reactions[b]	21	16
Keratopathy	71	75

Events reported based on Common Terminology Criteria for Adverse Events criteria v4.03[14] in the safety population (including all patients who received at least one dose of trial treatment)

[a]Thrombocytopenia includes the preferred terms thrombocytopenia, decreased platelet count, and cerebral hemorrhage. [b]Infusion-related reactions includes preferred terms infusion-related reaction, pyrexia, chills, diarrhea, nausea, vomiting if occurring within 24 hours.

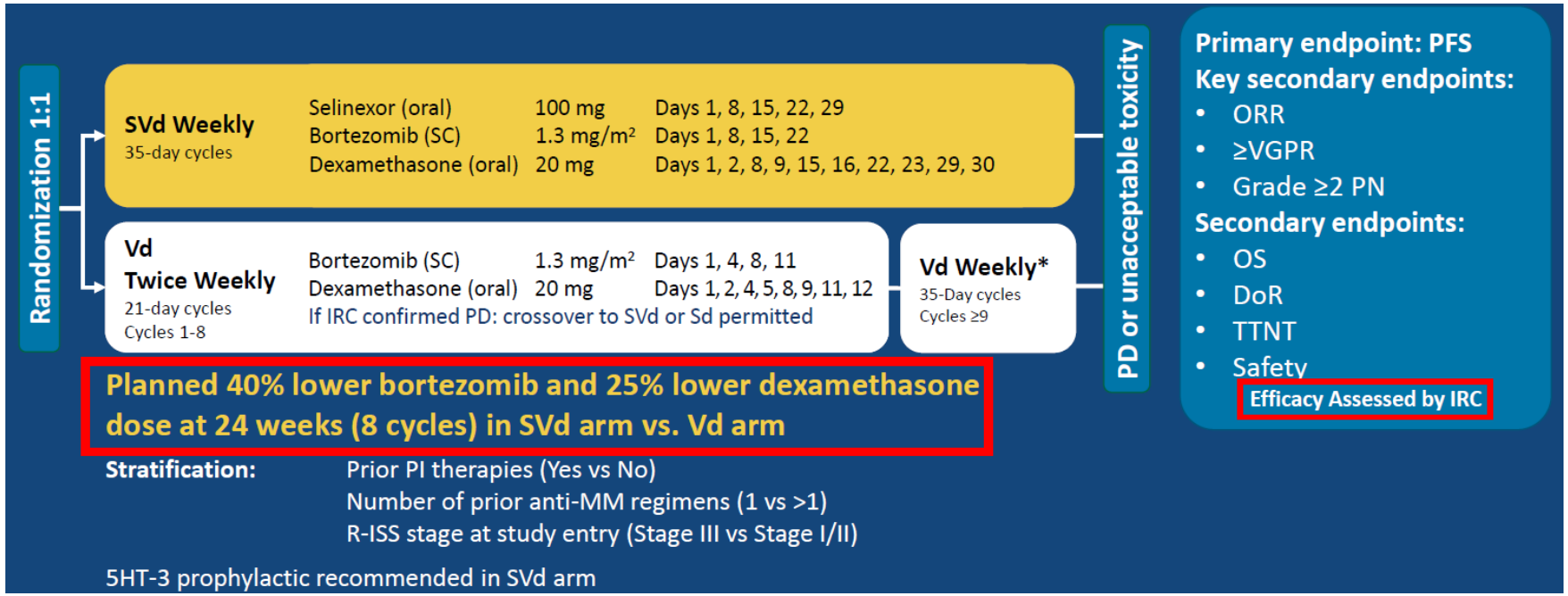
	Blenrep 2.5-mg/kg Cohort (N = 17)		*Blenrep* 3.4-mg/kg Cohort (N = 12)	
	With corticosteroid eye drops	Without corticosteroid eye drops	With corticosteroid eye drops	Without corticosteroid eye drops
Median (IQR) days to initiation of drug-related change in corneal epithelium (based on exam findings)	24 (21-30)	27 (21-42)	25 (9-40)	25 (21-40)
Percentage of Patients with Grade 3 Events, %	29	18	42	50

Lonial et al, Lancet Onc

Thoughts:

- BelMaf is a promising agent
- Ocular toxicity is common, frequently requires dose reductions/holds
- Evaluation by an ophthalmologist or optometrist are required every cycle
  - Unique and potentially challenging collaborative practice
  - May prove to be a barrier

Selinexor Bortez Dex (SVd): BOSTON study



Dimopoulos et al ASCO

BOSTON: Key I/E criteria

Key Inclusion Criteria

- Progressive measurable MM per IMWG criteria[1]
- 1–3 prior anti-MM regimens (at least a PR to a prior PI, if received)
- Patients with moderate or severe renal impairment (CrCl ≥ 20mL/min) allowed, patients requiring dialysis excluded
- ECOG status score 0–2
- Adequate hepatic and hematopoietic function
  - ANC > 1,000/µL
  - Platelets > 75,000/µL

Key Exclusion Criteria

- > Grade 2 neuropathy or ≥ Grade 2 neuropathy with pain at baseline
- Prior exposure to a SINE, including selinexor
- Prior malignancy that required treatment/had evidence of recurrence
- Concurrent medical condition/disease/active infection
- Active plasma cell leukemia
- MM involving the CNS

Dimopoulos et al ASCO

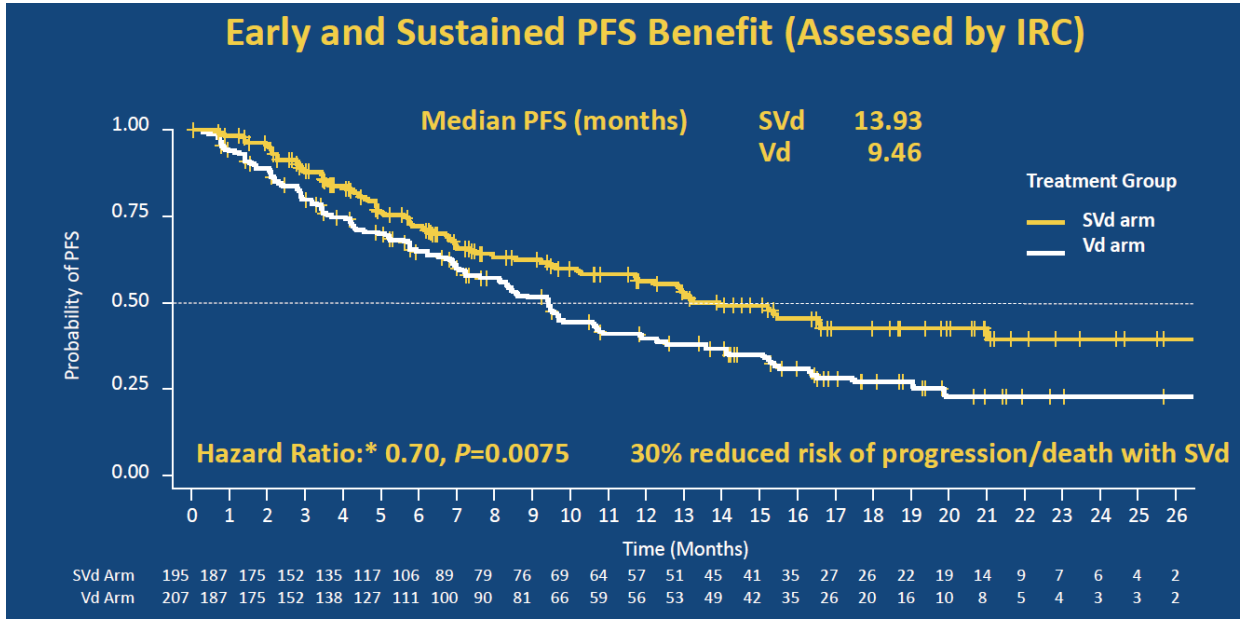
BOSTON study: Demographics

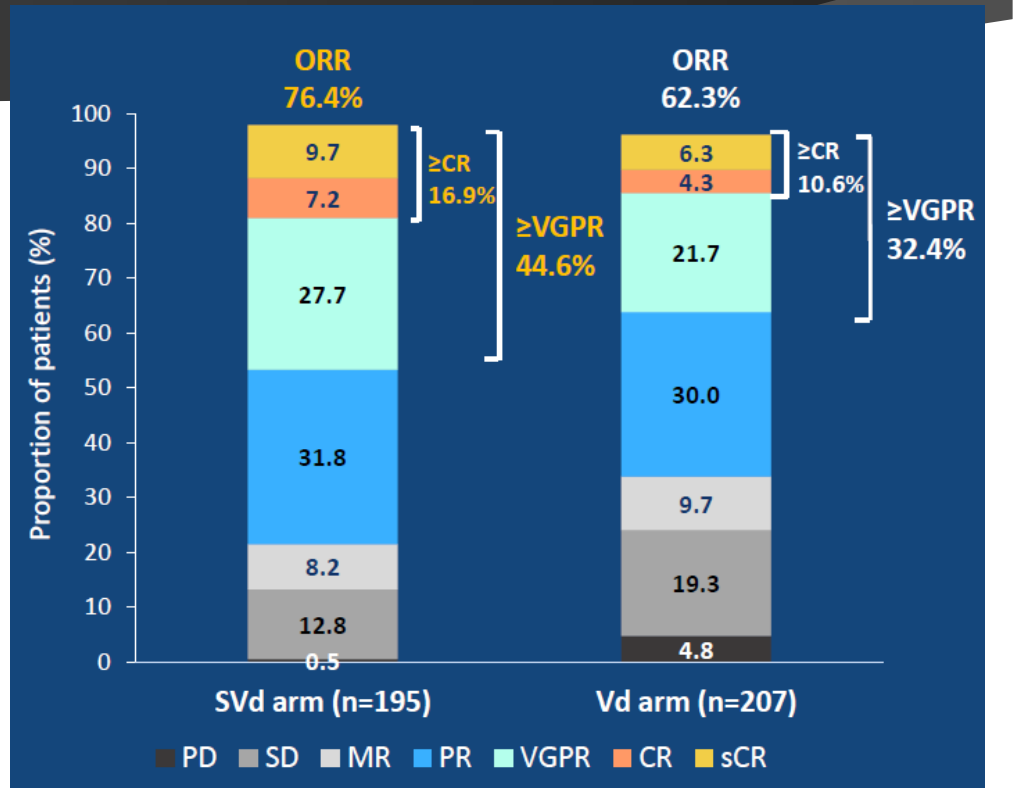
Patient and Disease Characteristics Well Balanced Between Treatment Arms

Characteristic	SVd arm (n=195)	Vd arm (n=207)	
Media Age, years (range)	66 (40, 87)	67 (38, 90)	
≥75 years, n (%)	34 (17)	47 (23)	
Male, n (%)	115 (59)	115 (56)	
Creatinine Clearance, mL/min, n (%)			
<30	3 (2)	10 (5)	
30-60	53 (27)	60 (29)	
Time since initial diagnosis, years, (range)	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)	
High Risk Cytogenetic, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)*	97 (50)	95 (46)	
R-ISS disease stage at screening, n (%)			
I or II	173 (89)	177 (86)	
III	12 (6)	16 (8)	
Unknown	10 (5)	14 (7)	
Number of prior lines of therapy, n (%)			
1	99 (51)	99 (48)	
2	65 (33)	64 (31)	
3	31 (16)	44 (21)	
Prior Therapies, n (%)			
Bortezomib	134 (68.7)	145 (70.0)	
Carfilzomib	20 (10.3)	21 (10.1)	
	79.0%		80.1%
Daratumumab	11 (5.6)	6 (2.9)	
Lenalidomide	77 (39.5)	77 (37.2)	

Dimopoulos et al ASCO

BOSTON study: PFS and ORR





Dimopoulos et al ASCO

BOSTON study: PFS and ORR

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight decreased	26.2	2.1	12.3	1.0
Asthenia	24.6	8.2	13.2	4.4
Cataract§	21.5	8.7	6.4	1.5
Vomiting	20.5	4.1	4.4	0

Dimopoulos et al ASCO 2020

Thoughts

- Selinexor remains challenging to give
- Prophylactic olanzapine may help with anorexia and nausea
- Combinatorial therapy is rationale, since the mechanism of action is inhibiting nuclear export
- Hopefully we'll see additional data from STORM coming out soon with carfilzomib, daratumumab and pomalidomide dosing

Current Clinical Trial Portfolio

Treatment Line	Newly Diagnosed	BMT	Maintenance	Relapse: 1-3 prior lines	Relapse: Multiply R/R	Phase 1	CAR-T	Open?
SWOG 1803			Post-BMT maintenance,					Yes
PHI-100: KRD+AMG232				Not refractory to KRd, prior carfilzomib allowed				Yes
UCHMC 1915: Elo/Ipi								Awaiting SRC
UCHMC 1809: DIPd				No prior progression on Pom, no prior Dara or Ix				Yes
KITE-718-301							HLA restricted; must express MAGE A3/A6	Yes
POSIEDA							Prior Dara, PI, imid, no cardiovascular dz	Yes
SUTRO BCM-1						NHL+MM		Yes
UCHMC 20XX: BelMaf/Pom				2-4 prior lines of therapy	2-4 prior lines			Protocol Development
DREAMM				Patients with eGFR<30				Awaiting SRC
KPG 818						NHL+MM		Awaiting SRC
AEVI-007								Awaiting SRC