Myeloma update

ASH 2014

Updates in Newly Diagnosed Multiple Myeloma

- FIRST: effect of age on lenalidomide/dexamethasone vs MPT in transplantation-ineligible pts
- Phase III: MPT-T vs MPR-R in transplantation-ineligible pts
- Weekly vs twice weekly carfilzomib in combination with cyclophosphamide/dexamethasone

Updates in Relapsed/ Refractory Multiple Myeloma

1st and second relapse

- ASPIRE: addition of carfilzomib to lenalidomide/dexamethasone
- Pomalidomide/bortezomib/dexamethasone

Double relapsed/refractory setting

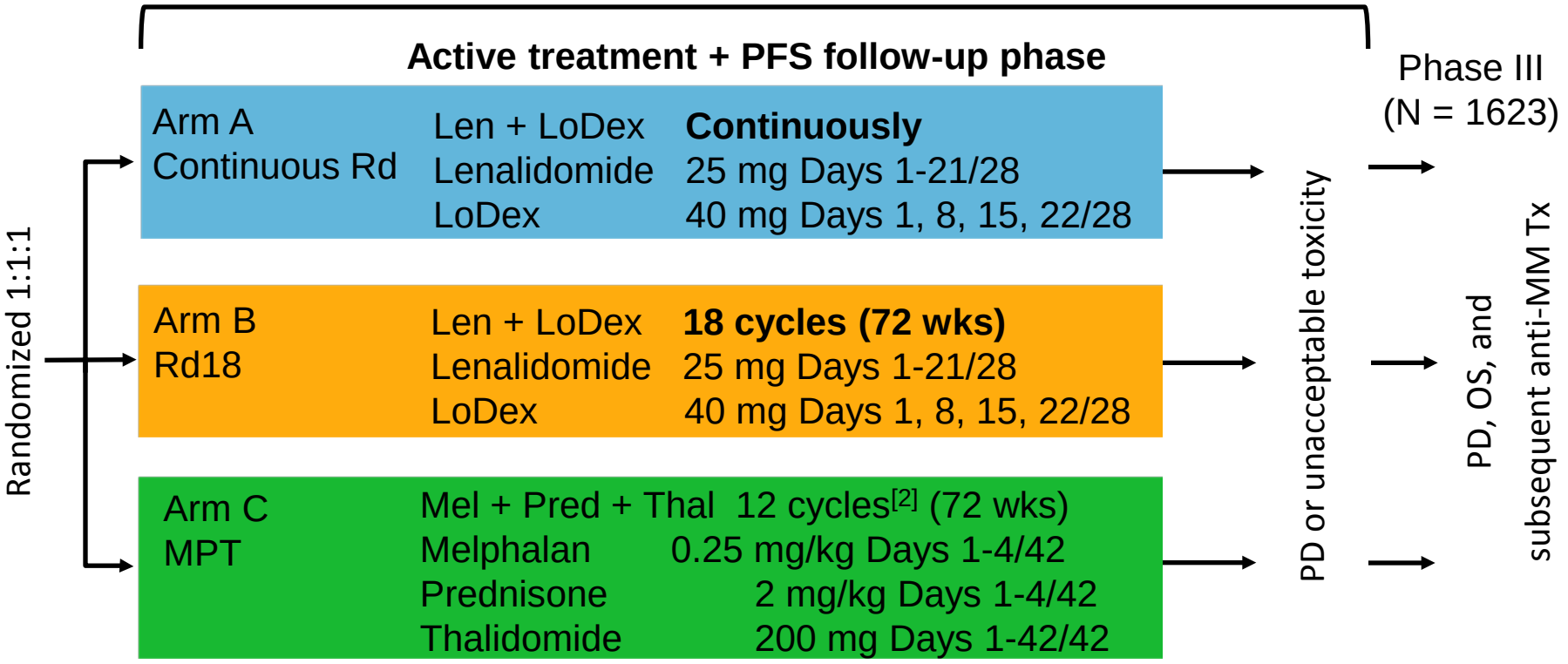
- Monoclonal antibodies in combination with lenalidomide/ dexamethasone
  - SAR650984 (anti–CD-38 mAb)
  - Daratumumab (anti–CD-38 mAb)
  - Elotuzumab (anti-SLAMF7/CS1 mAb)

Updates in Other Plasma Cell Disorders

- Phase III trial of melphalan/dexamethasone vs bortezomib/melphalan/dexamethasone for untreated AL amyloidosis

- Phase II trial of lenalidomide/dexamethasone in POEMS syndrome

FIRST Trial: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Pts

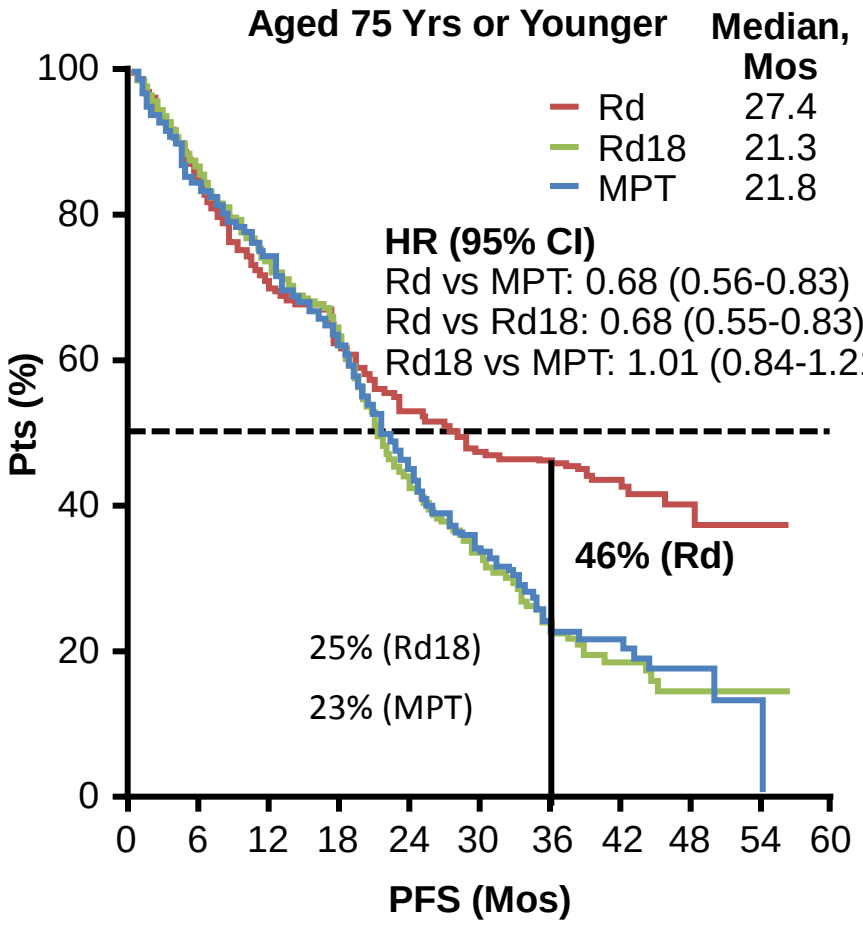


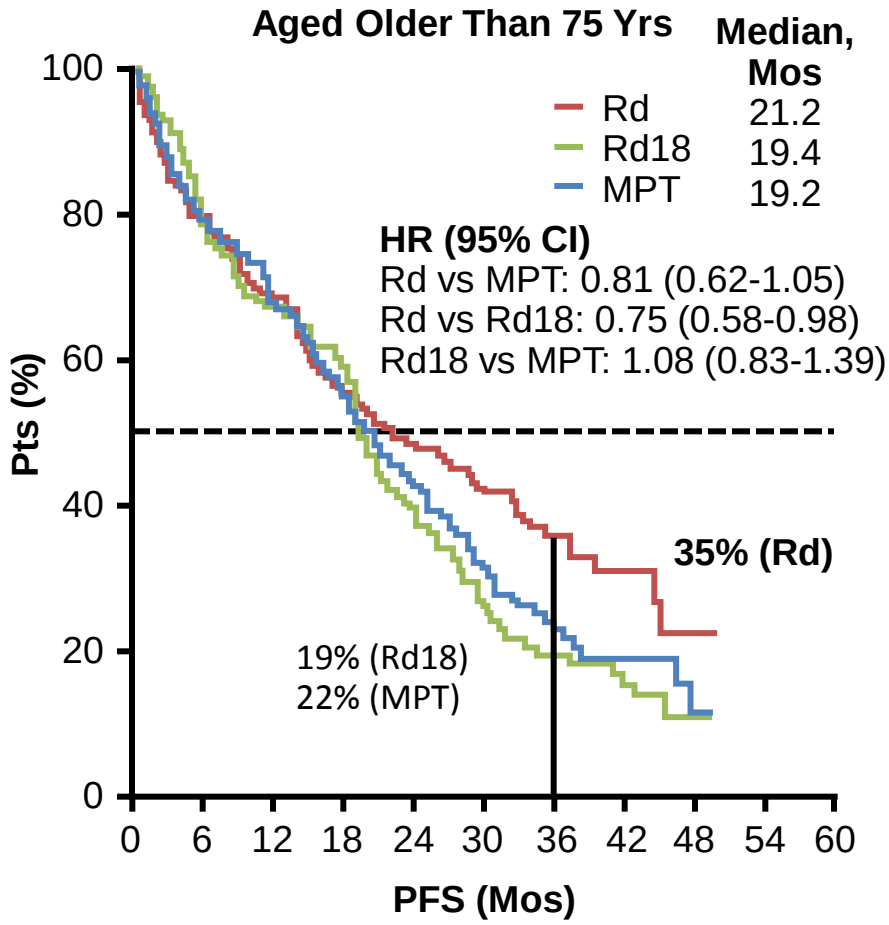
Pts > 75 yrs: LoDex 20 mg Days 1, 8, 15, 22/28; Thal 100 mg Days 1-42/42; Mel 0.2 mg/kg Days 1-4. Stratification: age, country, and ISS stage.

1. Hulin C, et al. ASH 2014. Abstract 81. 2. Facon T, et al. Lancet. 2007;370:1209-1218. 3. Hulin C, et al. J Clin Oncol. 2009;27:3664-3670. 4. Benboubker L, et al. N Engl J Med. 2014;371:906-917

FIRST Trial: PFS by Age Stratification

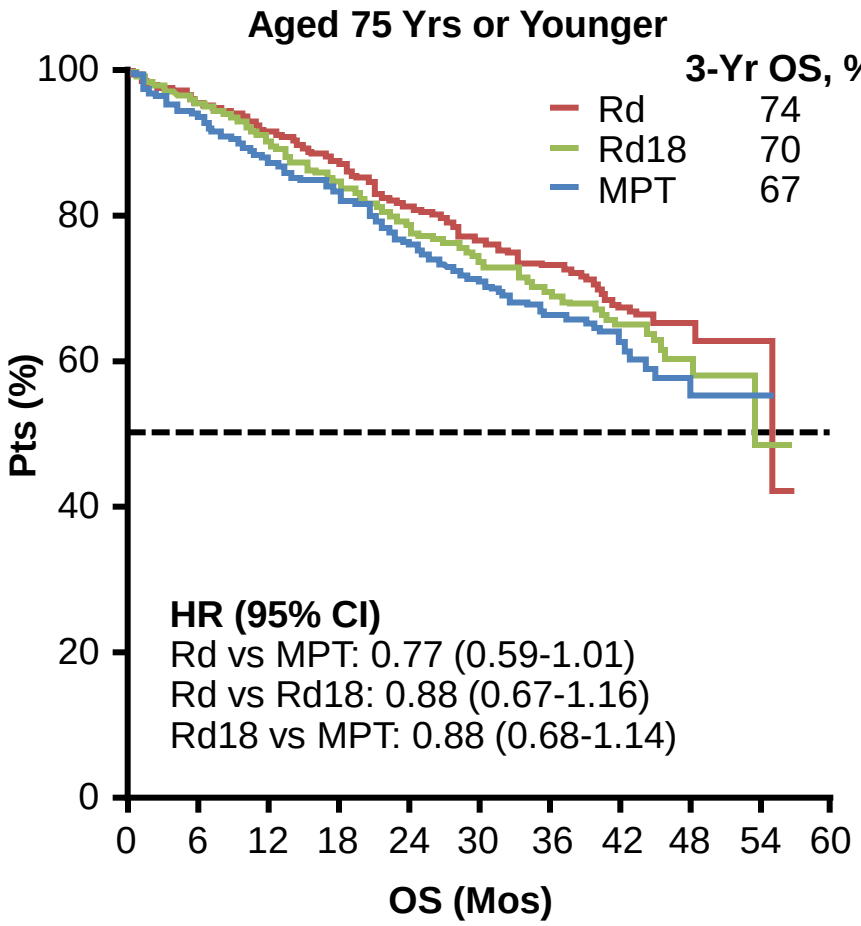
571 pts > 75 yrs

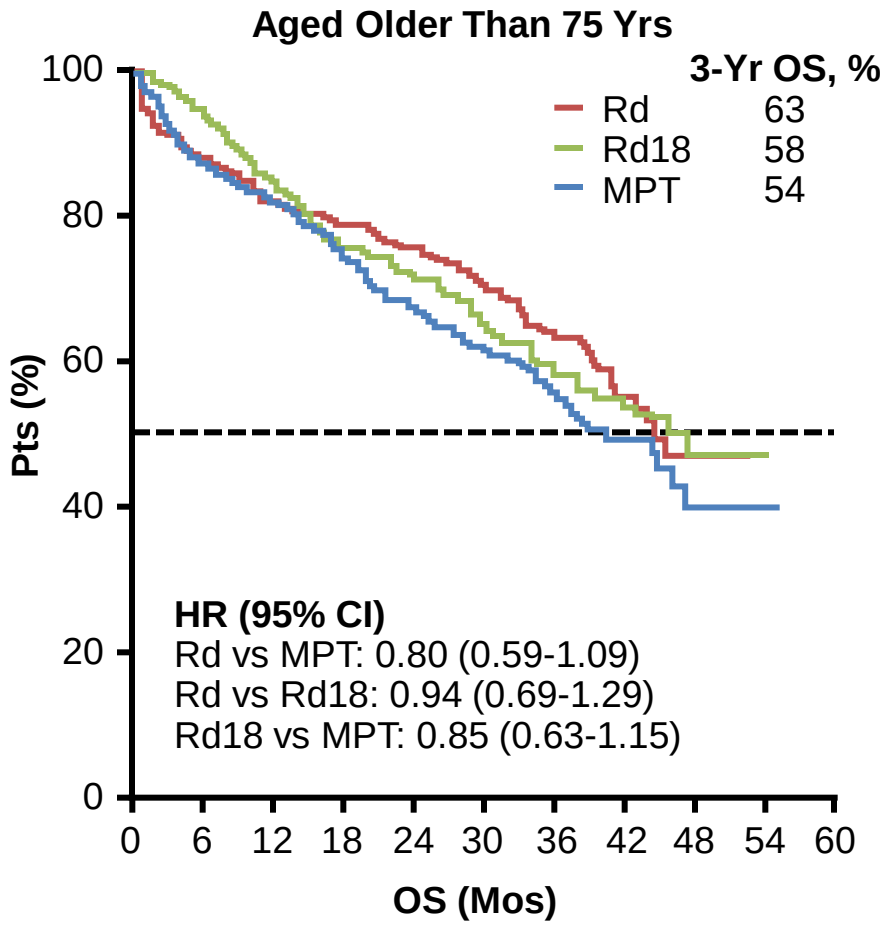




Hulin C, et al. ASH 2014. Abstract 81. Reproduced with permission.

FIRST Trial: OS by Age Stratification

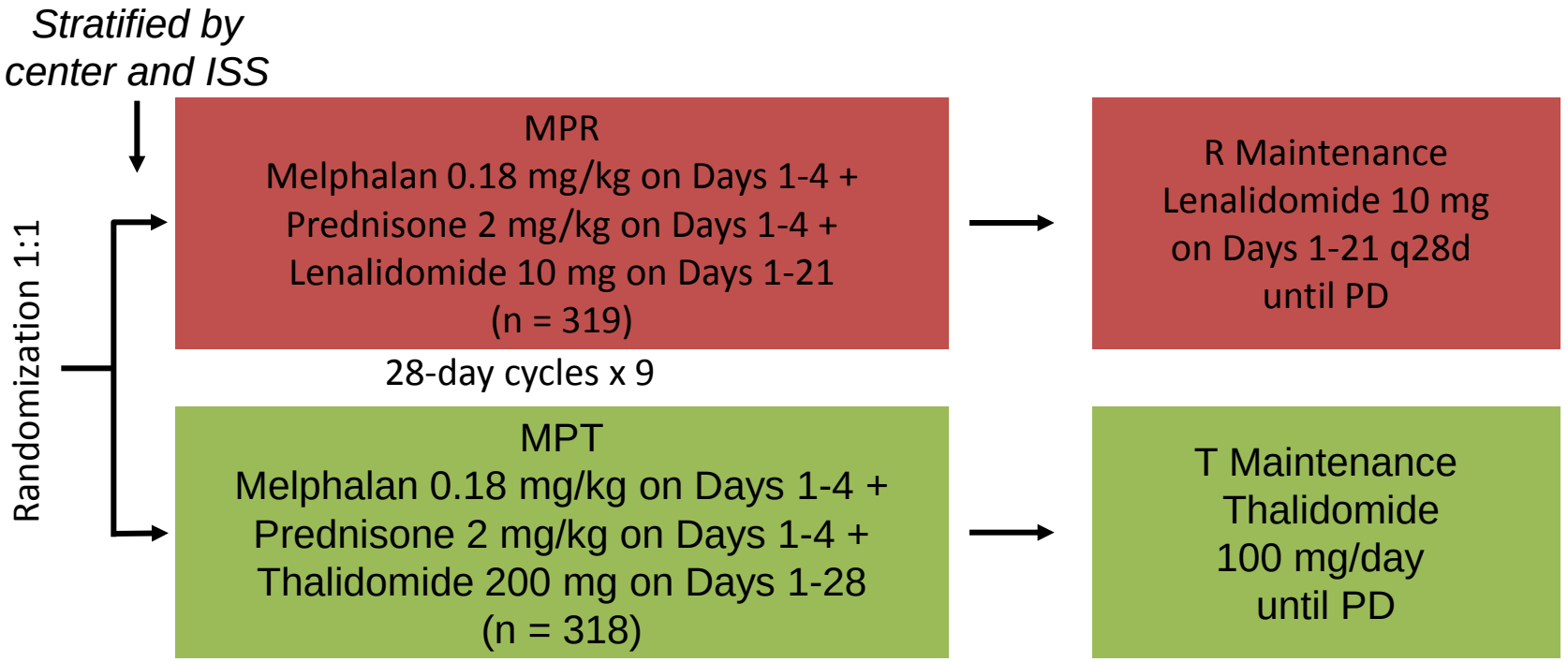




Hulin C, et al. ASH 2014. Abstract 81. Reproduced with permission.

Phase III Trial Comparing MPT-T vs MPR-R in SCT-Ineligible Pts with NDMM

- Joint study of the Dutch-Belgian Cooperative Trial Group for Hematology Oncology and the Nordic Myeloma Study Group



Granulocyte-colony stimulating factor administered if absolute neutrophil count < 0.5 x 10^9 cells/L or in event of febrile neutropenia during a cycle.

Zweegman S, et al. ASH 2014. Abstract 179.

Phase III Trial Comparing MPT-T vs MPR-R in SCT-Ineligible Pts with NDMM

	MPT - T	MPR - R
Total	280	280
Male/Female %	53/47	58/42
Median age [range]	72 [60-91]	73 [60-87]
< 75 years %	64	59
≥ 75 years %	36	41
ISS at randomization n (%)		
I	67 (24)	72 (26)
II	137 (49)	131 (47)
III	73 (26)	74 (26)
Unknown	3 (1)	3 (1)
LDH n (%)		
Normal	248 (89)	232 (83)
Elevated	20 (7)	29 (10)
Unknown	12 (4)	19 (7)
FISH analysis on isolated plasma cells , n (%)	210 (75)	222 (79)
1q amplification	52 (37)	50 (32)
t(4;14)	16 (11)	16 (9)
del(17p)	22 (12)	16 (8)

MPT-T vs MPR-R: Safety Analysis

Treatment Outcome, %	MPR-R		MPT-T	
	≤ 75 Yrs	> 75 Yrs	≤ 75 Yrs	> 75 Yrs
Completed 6 induction cycles	68	73	76	77
Initiated maintenance therapy	59	58	57	39
Discontinued maintenance	43		88	
▪ Due to AEs*	24	31	67	69
Median duration of maintenance, mos (range)	16 (0-53)	15 (1-52)	5 (0-49)	5 (0-44)

*Primarily due to peripheral neuropathy in thalidomide arm, hematologic toxicity in lenalidomide arm

- MPT-T associated with significantly higher rate of grade ≥ 2 neuropathy (45% vs 8%; *P* < .0001); higher rate of grade 3/4 hematologic AEs (including neutropenia [63% vs 27%], thrombocytopenia [28% vs 8%], and anemia [14% vs 5%]) vs MPR-R

Zweegman S, et al. ASH 2014. Abstract 179.

MPT-T vs MPR-R: Efficacy Analysis

- Median follow-up: 33.6 mos
- ORR similar between arms: 81% MPT-T vs 83% MPR-R
- No significant difference in PFS or OS

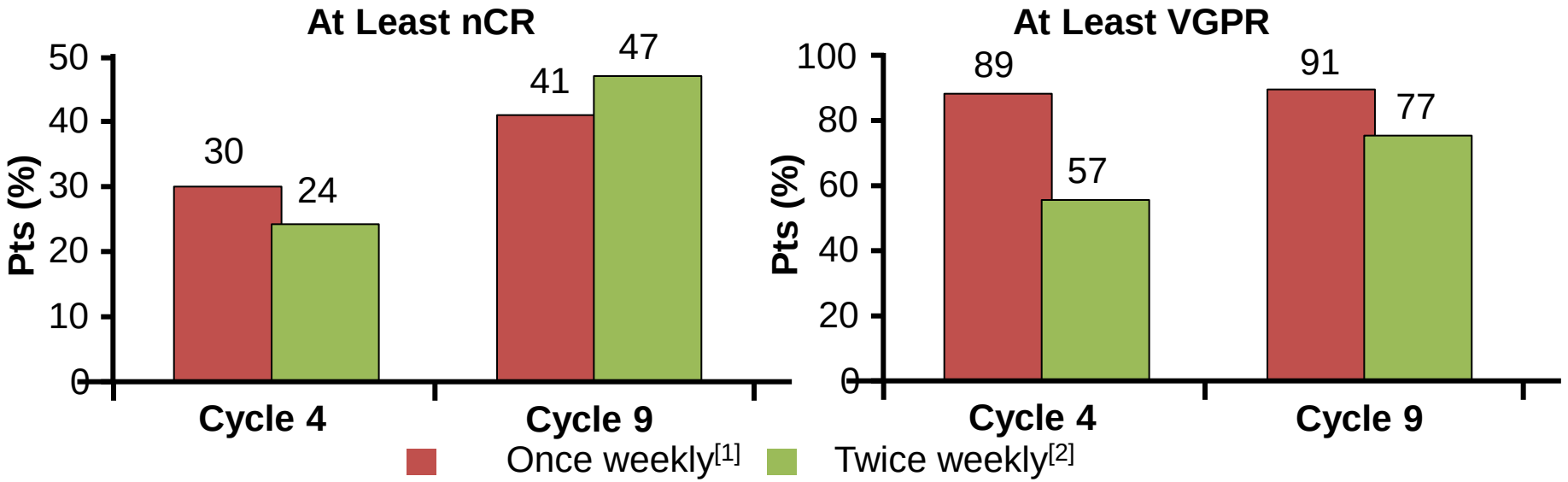
Outcome	MPR-R (n = 319)	MPT-T (n = 318)	HR (95% CI)	*P* Value
ORR (on protocol), %	83	81		
▪ CR	13	10		
▪ VGPR	32	38		
▪ PR	39	33		
Median PFS, mos	22	20	086 (0.72-1.04)	.12
Median OS, mos	NR	NR	0.79 (0.61-1.03)	.08
▪ 2-yr OS, %	84	73		
▪ 3-yr OS, %	69	64		
▪ 4-yr OS, %	55	52		

Zweegman S, et al. ASH 2014. Abstract 179.

Weekly Carfilzomib + Cyclophosphamide/ Dex: Preliminary Efficacy

MTD: 70mg/m2

Outcome	Phase I (n = 12)	MTD (n = 19)	Total (N = 28)
Median cycles received, n (range)	9 (1-9)	4 (1-9)	8 (1-9)
ORR (≥ PR), n (%)	11 (92)	15 (79)	24 (86)
▪ ≥ VGPR	9 (75)	11 (58)	18 (64)
▪ sCR + CR + nCR	4 (33)	4 (21)	7(25)



1. Palumbo A, et al. ASH 2014. Abstract 175. 2. Bringhen S, et al. Blood. 2014;124:63-69.
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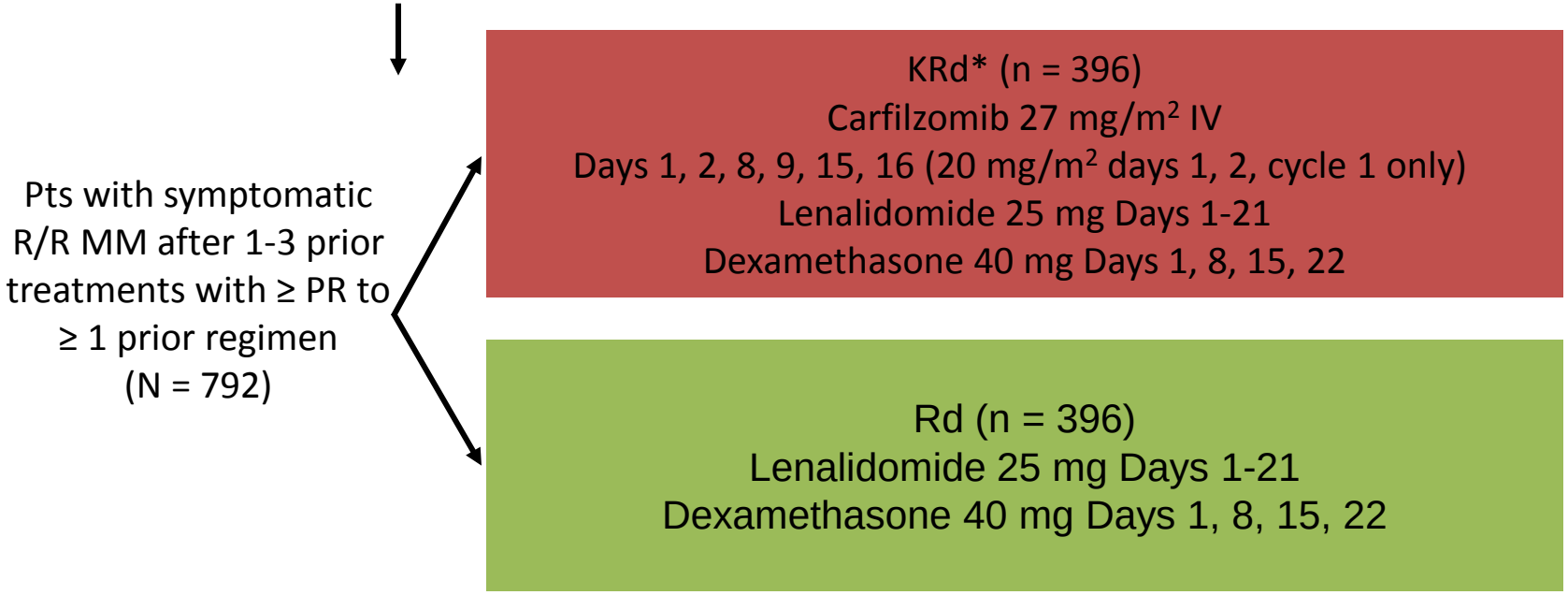
ASPIRE: Phase III Trial Comparing Len/ Dexamethasone ± Carfilzomib in R/R MM

- Randomized, open-label, multicenter phase III trial

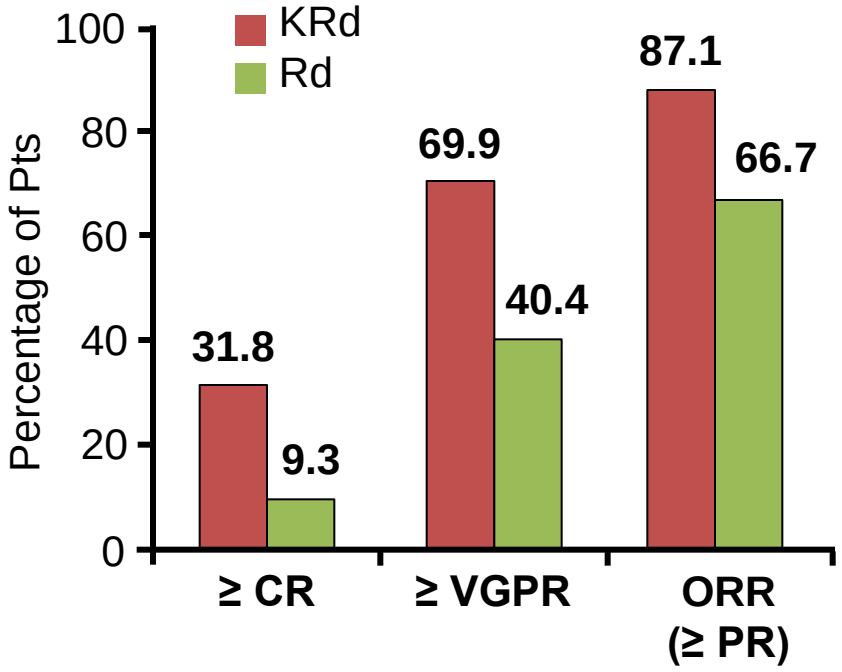
Stratified by β_2-microglobulin, prior bortezomib, and prior lenalidomide

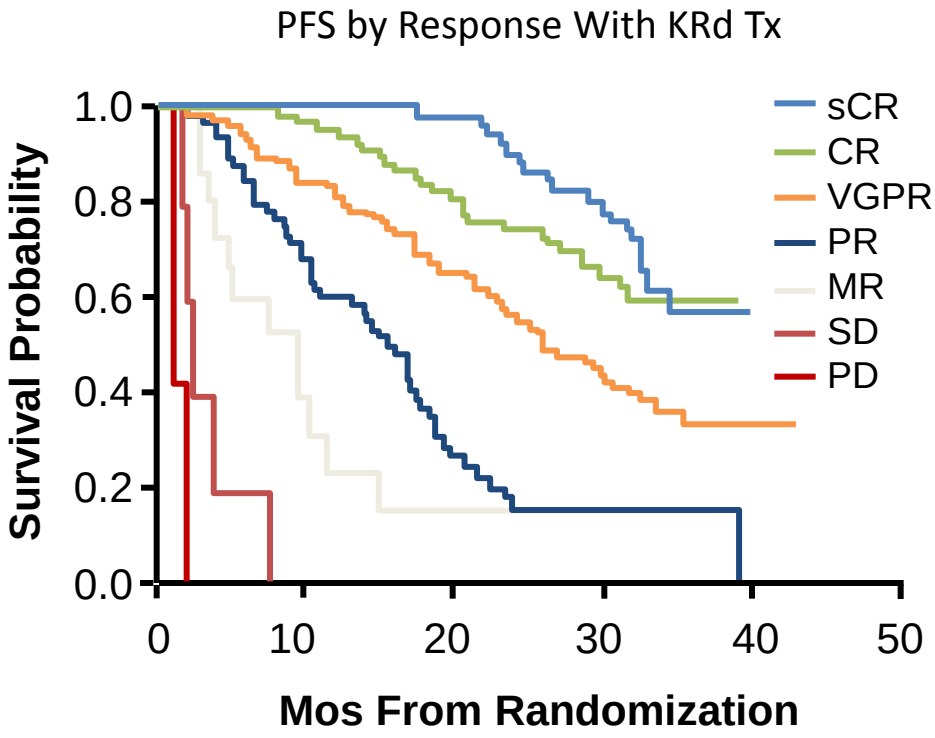


*After cycle 12, carfilzomib given on Days 1, 2, 15, 16. After cycle 18, carfilzomib discontinued.

Stewart AK, et al. ASH 2014. Abstract 79.

ASPIRE: Response Rates and PFS by Response

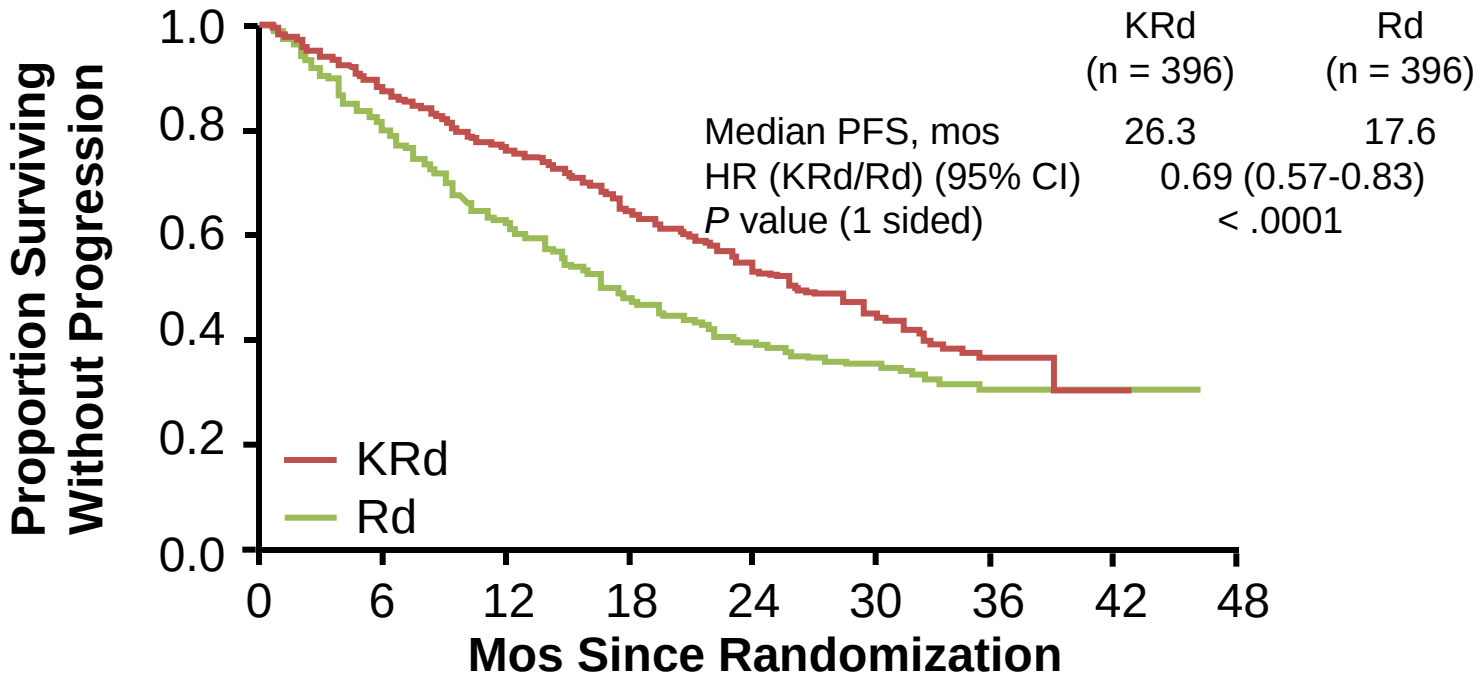




- AEs consistent with previous studies; no unexpected toxicities observed

Stewart AK, et al. ASH 2014. Abstract 79. Reproduced with permission.

ASPIRE: PFS in ITT Population (Primary Endpoint)

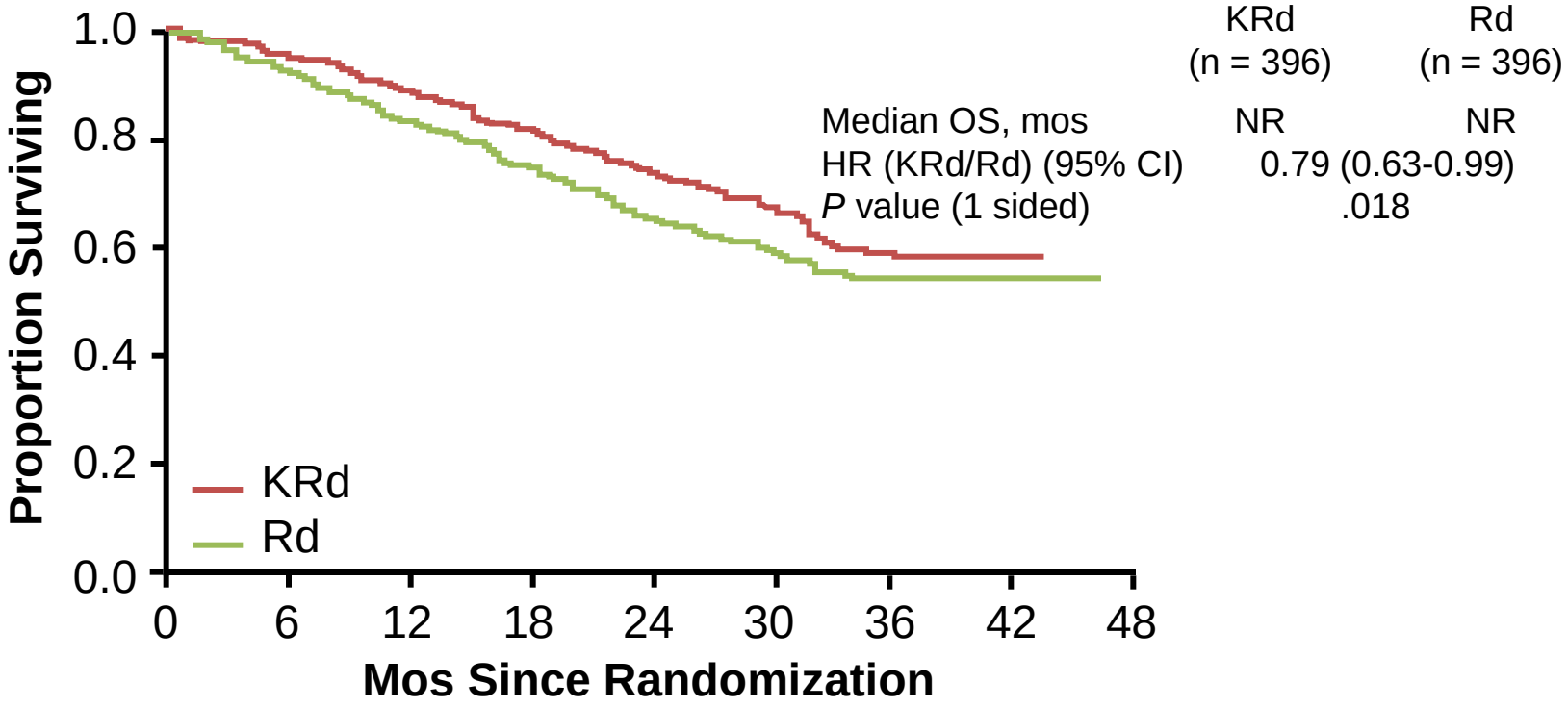


Risk Group by FISH	KRd (n = 396)		Rd (n = 396)		HR	*P* Value
	n	Median PFS, Mos	n	Median PFS, Mos		
High	48	23.1	52	13.9	0.70	.083
Standard	147	29.6	170	19.5	0.66	.004

Stewart AK, et al. ASH 2014. Abstract 79. Reproduced with permission.

ASPIRE: Interim OS Analysis

- Median follow-up: 32 mos
- Median OS was not reached; results did not meet prespecified statistical boundary (*P* = .005) at interim analysis



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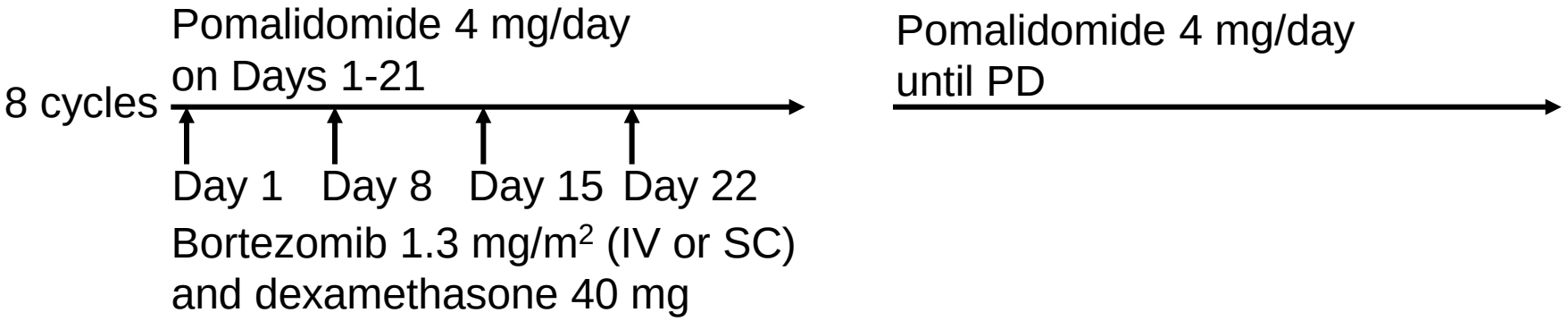
Pomalidomide/Bortezomib/Dexamethasone for Lenalidomide Refractory MM

- Phase I/II trial to determine MTD; assess safety and efficacy of pomalidomide/bortezomib/dexamethasone
  - Included pts with relapsed MM who had 1-4 previous lines of therapy and were resistant/refractory to lenalidomide. 57% had prior bortezomib
  - Accrual: 50 pts (phase I: 3 at dose level 1, 6 at dose level 2; phase II: 41)
- Current analysis: 47 pts treated at MTD (dose level 2 + phase II)



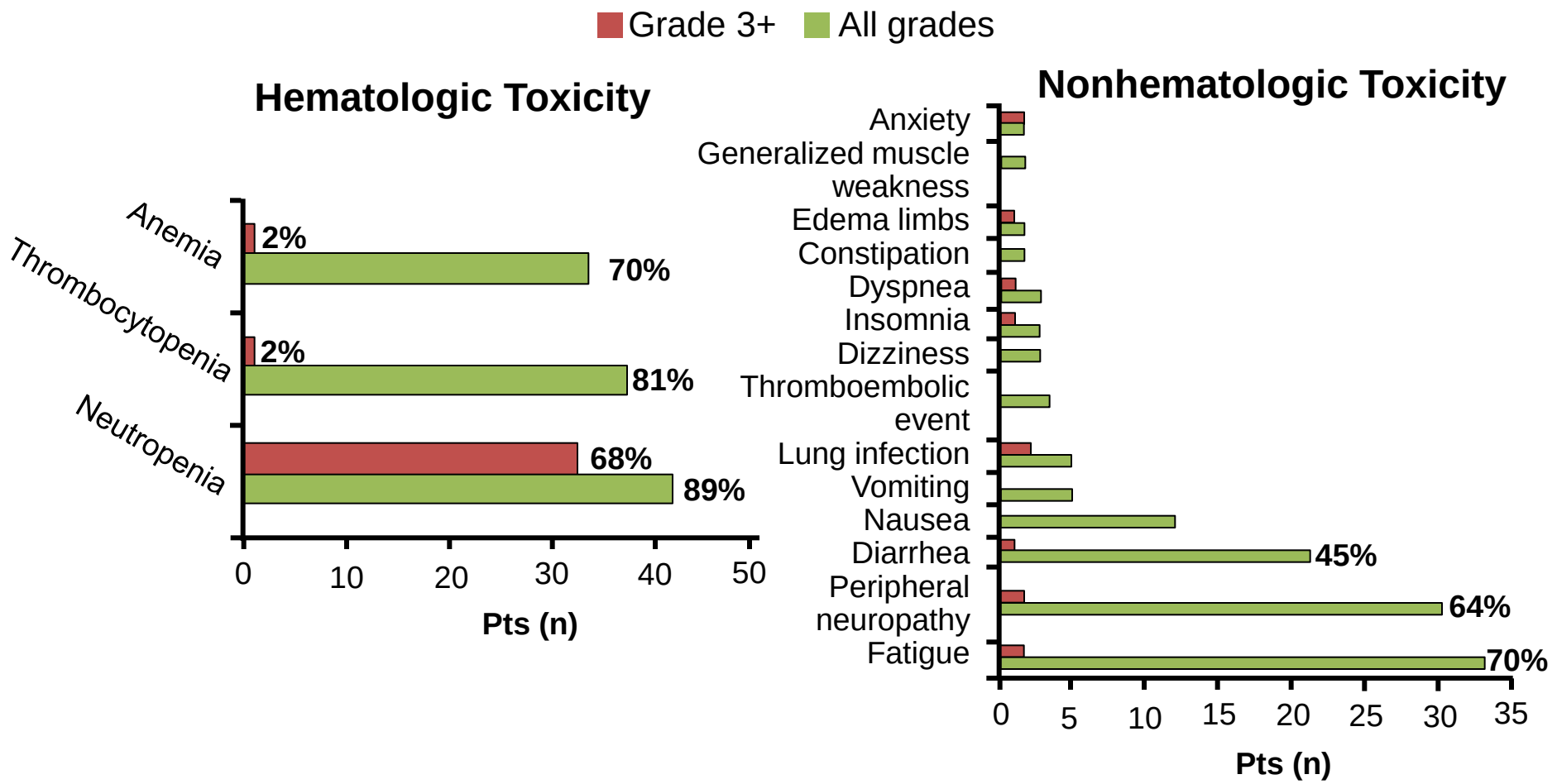
Lacy MQ, et al. ASH 2014. Abstract 304.

Pomalidomide/Bortezomib/Dexamethasone: Summary of Efficacy

Outcome	Pts Treated at MTD (N = 47)	Std-Risk Pts (n = 28)	Int-/High-Risk Pts (n = 19)
Response, n (%)			
▪ ORR	40 (85)	24 (86)	16 (84)
▪ sCR	3 (6)		
▪ CR	6 (13)		
▪ VGPR	12 (26)		
▪ PR	19 (40)		
Median OS, mos	NR	NR	NR
▪ Event free at 6 mos, %	100	100	100
▪ Event free at 12 mos, %	94	95	92
Median PFS, mos (95% CI)	10.7 (9.4-18.5)	16.3	9.5
Median DoR, mos (95% CI)	13.7 (8.5-16.8)		

Lacy MQ, et al. ASH 2014. Abstract 304.

Pomalidomide/Bortezomib/Dexamethasone: Summary of Adverse Events



Lacy MQ, et al. ASH 2014. Abstract 304. Reproduced with permission.

Phase I Trial: SAR650984 in Combination With Len/Dex in Relapsed/Refractory MM

- Phase Ib trial of SAR650984 + len/dex in relapsed/refractory MM
  - SAR650984 is a humanized IgG1 mAb to the CD38 receptor widely expressed in many heme malignancies
  - Dose escalation: SAR650984 3-10 mg/kg on Days 1 and 15 of each 28-day cycle + lenalidomide 25 mg on Days 1-21 of each 28-day cycle and dexamethasone 40 mg/wk during each 28-day cycle

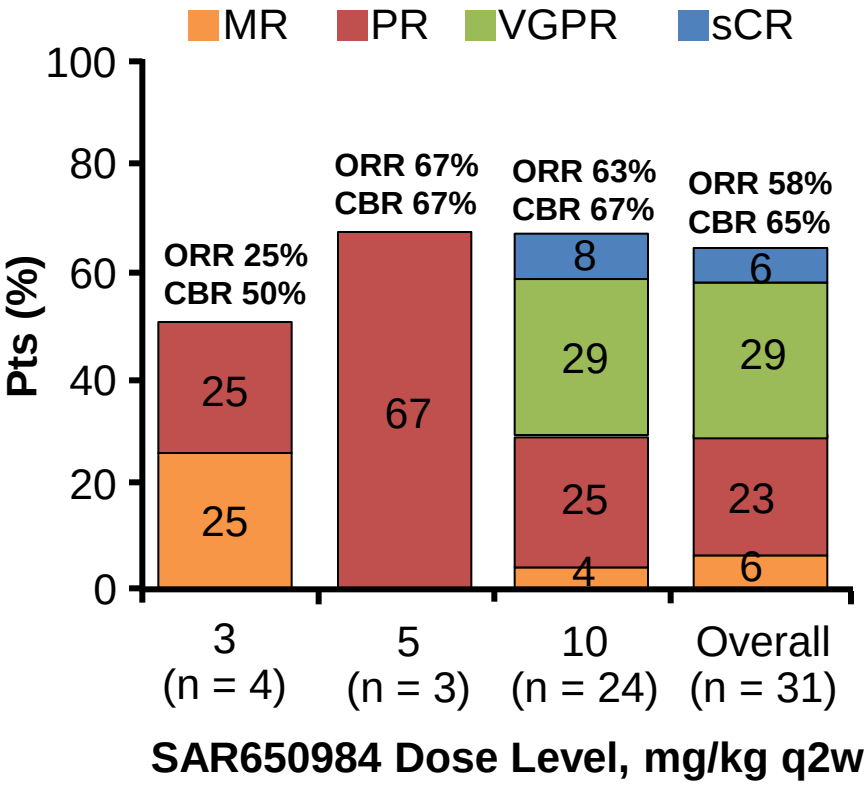
Previous MM Treatment	SAR650984 Dose, mg/kg q2w			Overall (N = 31)
	3 (n = 4)	5 (n = 3)	10 (n = 24)	
Median prior regimens, n (range)	10 (3-14)	7 (6-7)	6 (2-12)	7 (2-14)
Median prior lines, n (range)	6 (2-11)	6 (4-6)	4 (1-9)	4 (1-11)
Median time on last Len, mos (range)	7 (3-17)	3 (3-10)	10 (1-54)	9 (1-54)
Relapsed/refractory to IMiD	3 (75)	2 (67)	21 (88)	26 (84)

Martin TG, et al. ASH 2014. Abstract 83.

SAR650984 + Len/Dex: Efficacy Analysis

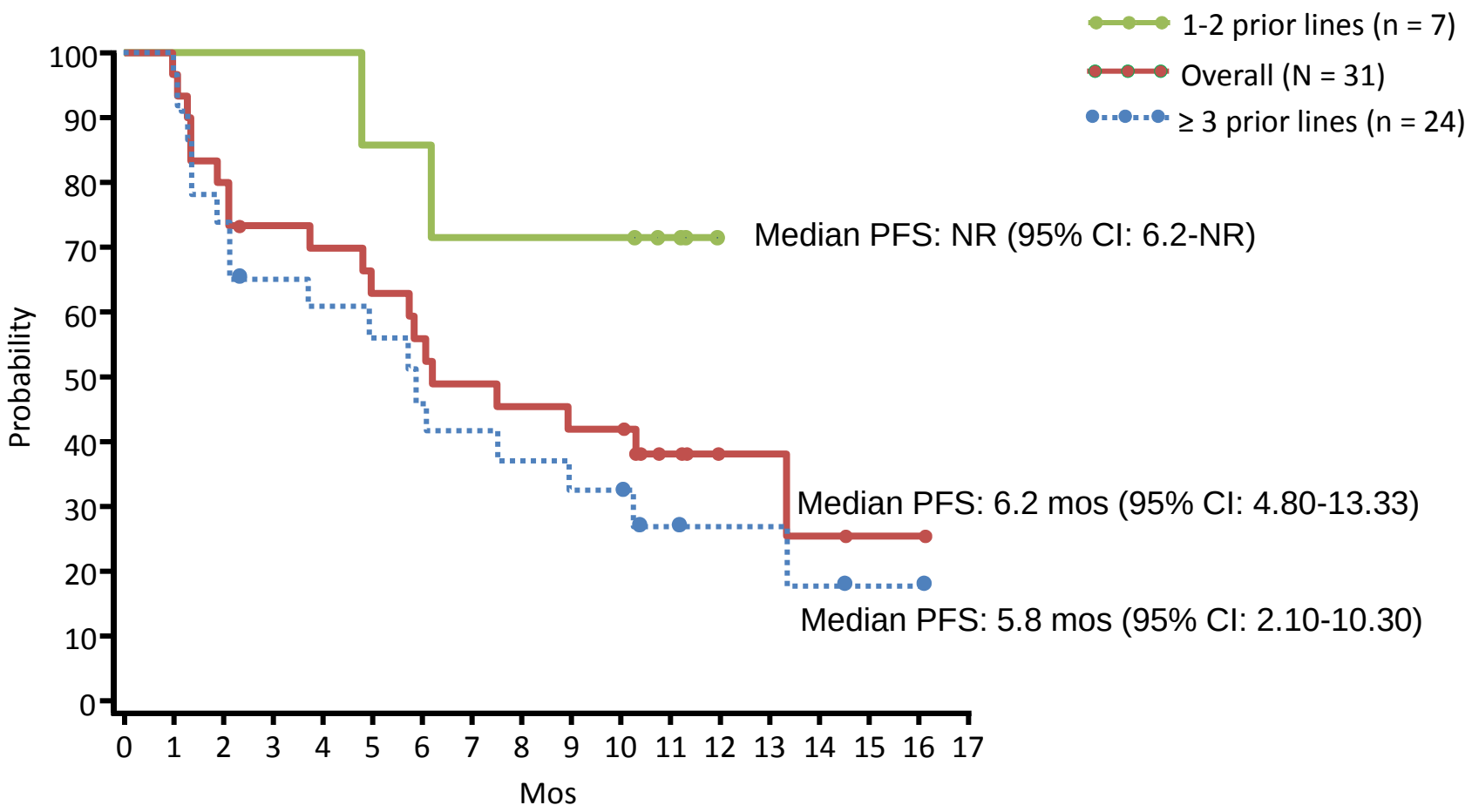
- DoR: 9.13 mo (range: 1.2-15.2)

Response, %	Total (N = 31)
ORR	58
▪ sCR	6
▪ VGPR	23
▪ PR	29
CBR	65
▪ MR	6
SD	19
PD	13
Not evaluable	3



Martin TG, et al. ASH 2014. Abstract 83. Reproduced with permission.

SAR650984 + Len/Dex: PFS by Previous Lines of Therapy



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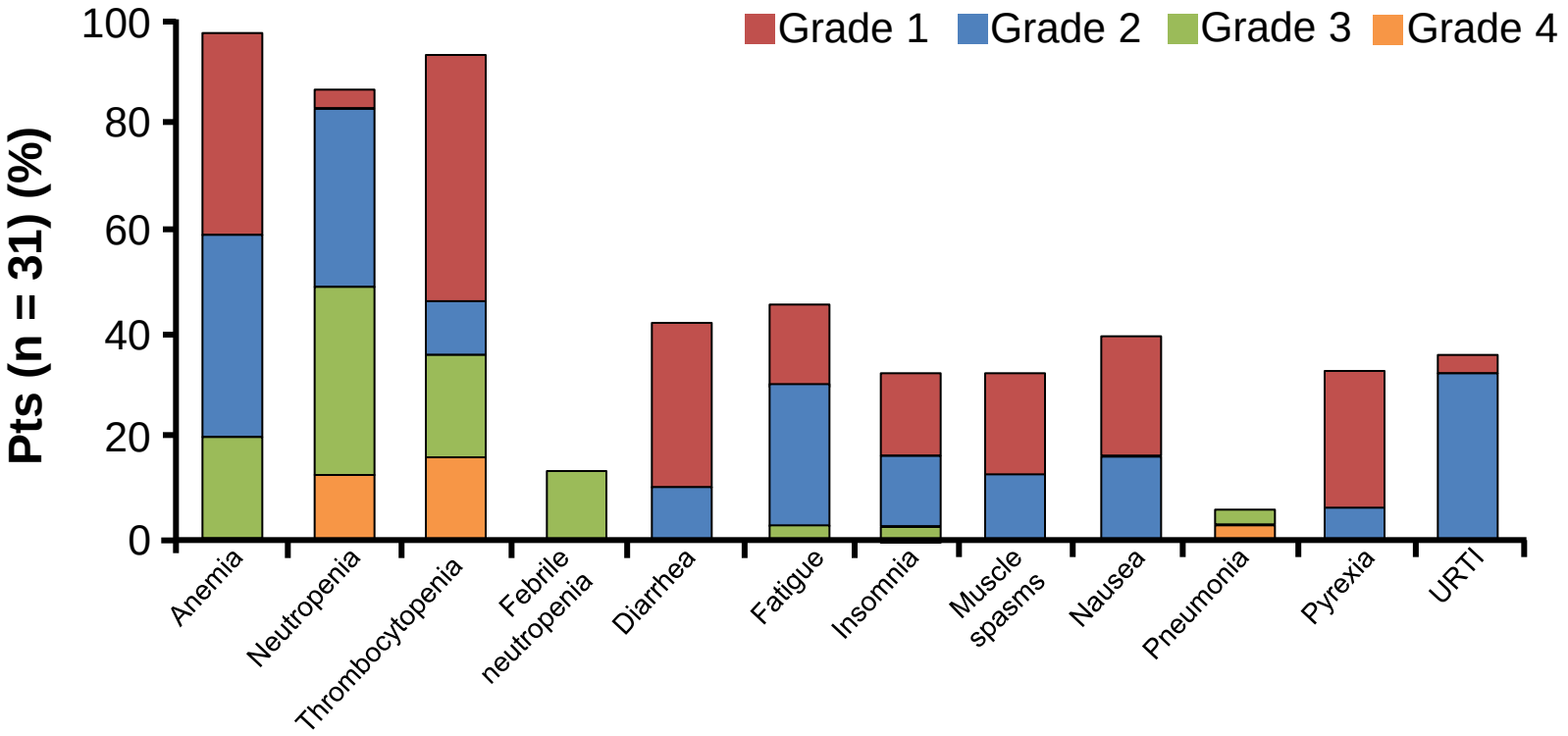
SAR650984 plus Len/Dex: Tx-Emergent AEs



- There were 15 incidences of infusion reaction, all occurring in the first 2 cycles
  - 2 pts discontinued treatment: 1 serious grade 3 anaphylactic reaction in cycle 1 and 1 nonserious grade 3 maculopapular rash in cycle 2 (AEs resolved in both pts)
  - Remaining incidents were grade 1/2 and did not lead to treatment discontinuation

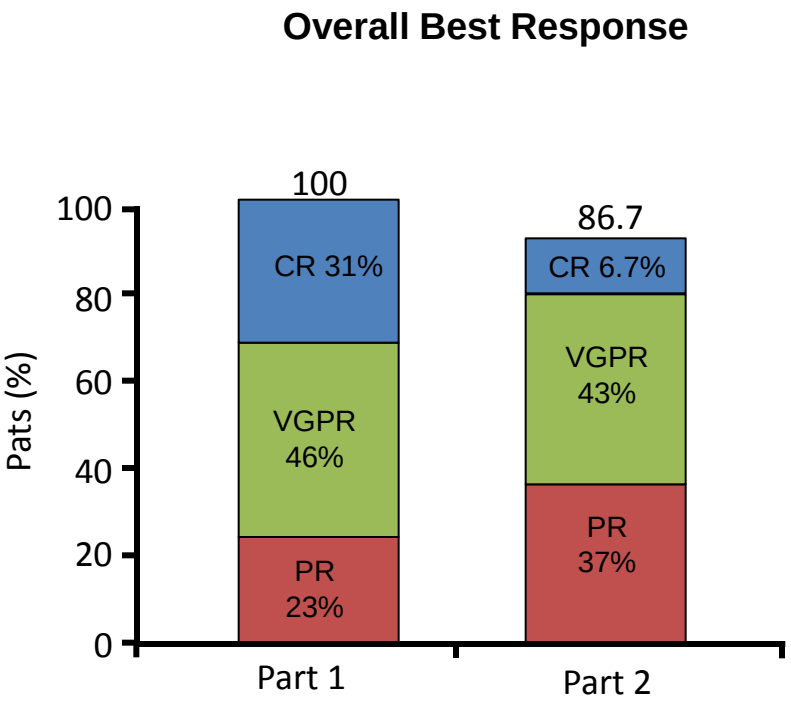
Martin TG, et al. ASH 2014. Abstract 83. Reproduced with permission.

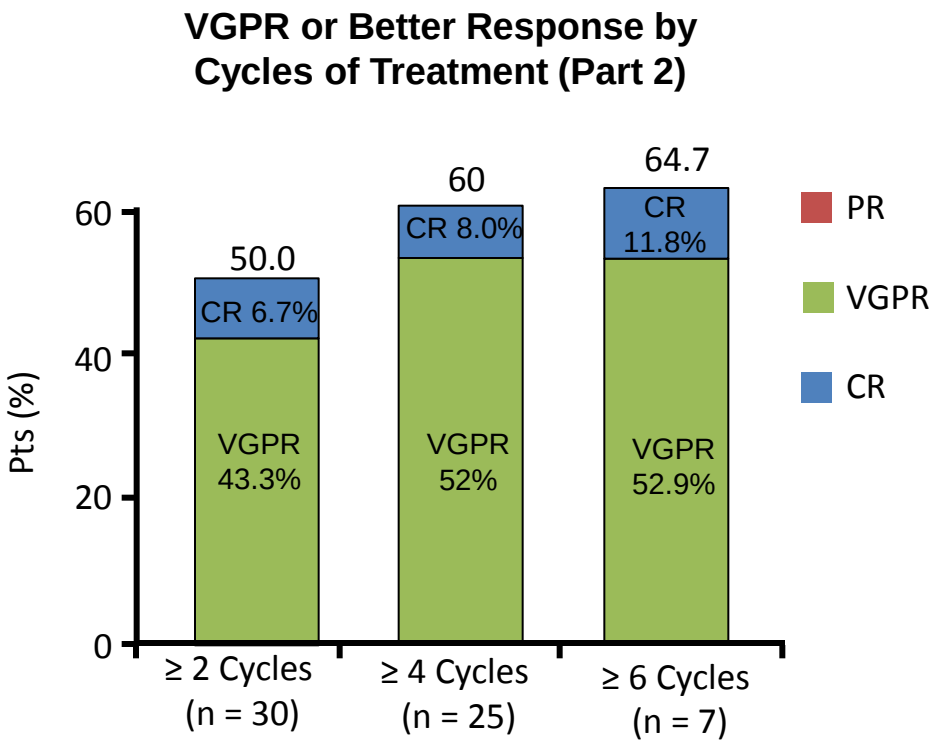
Phase I Trial: Daratumumab in Combination With Len/Dex in Rel/Ref MM

- Phase I/II dose-escalation trial of daratumumab in combination with len/dex in rel/ref MM (safety cohort: n =45; efficacy cohort: n = 43)
  - Daratumumab is a human mAb targeting CD38-expressing cells
  - Dose escalation: daratumumab 2-16 mg/kg/wk for 8 wks, twice monthly for 16 wks, then once monthly for 24 mos in total or until PD, unmanageable AE
  - Lenalidomide 25 mg on Days 1-21 of each 28-day cycle
  - Dexamethasone 40 mg/wk for of each 28-day cycle
- Median prior lines of therapy: 2 (range: 1-4); most with prior exposure to IMiDs and/or a proteasome inhibitor; 3 pts refractory to len
- MTD: daratumumab 16 mg/kg + len 25 mg and dex 40 mg/wk

Plesner T, et al. ASH 2014. Abstract 84.

Daratumumab in Combination With Len/Dex: Overall Best Response





- Mean follow-up: 12.9 mos (Part 1); 5.6 mos (Part 2)
- Median time to response: 1 mo for 16 mg/kg in Part 2; median time to CR: 4.9 mos in Part 2

Plesner T, et al. ASH 2014. Abstract 84. Reproduced with permission.

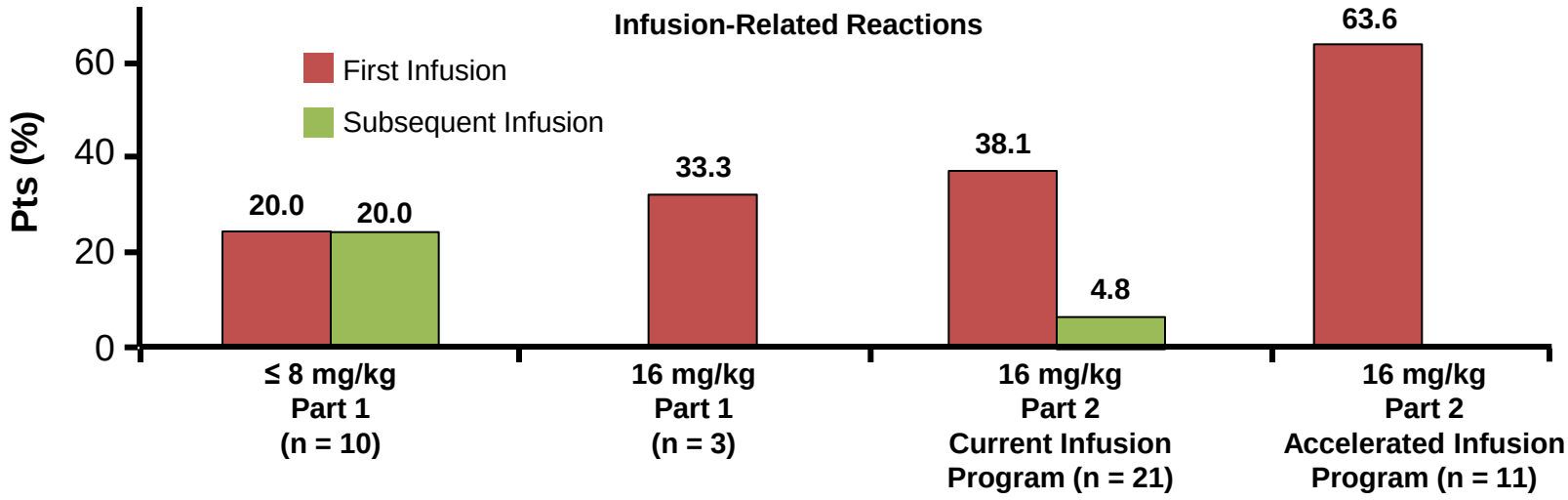
Daratumumab in Combination With Len/Dex: Adverse Events

Most Common (Incidence in > 10% Pts) AEs, %	Part 1 (n = 13)	Part 2 (n = 32)	Total (N = 45)
Total number of pts with AEs	100	100	100
Neutropenia	62	65	64
Muscle spasms	62	38	44
Diarrhea	54	18	31
Fatigue	62	16	29
Cough	31	28	29
Constipation	54	13	27
Nausea	38	19	24
Nasopharyngitis	62	3	20
Bone pain	31	13	18
Upper respiratory tract infection	46	3	16
Insomnia	31	6	16
Dyspnea	23	6	11
Anemia	31	19	11

Plesner T, et al. ASH 2014. Abstract 84.

Daratumumab in Combination With Len/Dex: Safety

- Daratumumab related serious AEs
  - Pneumonia, neutropenia, diarrhea (1 pt each receiving 16 mg/kg, early infusion program)
  - Laryngeal edema (1 pt receiving 16 mg/kg, accelerated infusion program)



- 19/45 pts reported infusion-related reactions; mostly grade 1-2

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Phase I Trial: Elotuzumab in Combination With Len/Dex in RR MM

- Phase Ib/II 1703 trial of elotuzumab + len/dex in relapsed/refractory MM
  - Elotuzumab is a humanized IgG1 mAb targeting SLAMF7, a glycoprotein highly expressed on myeloma and NK cells
  - Elotuzumab 10 or 20 mg/kg on Days 1, 8, 15, 22 for cycles 1-2; Days 1, 15 for subsequent cycles
  - Lenalidomide 25 mg on Days 1-21 of each 28-day cycle
  - Dexamethasone 28 mg + 8 mg IV on elotuzumab dosing days, or 40 mg/wk for of each 28-day cycle
- Current analysis on phase II data to assess efficacy and safety of combination
  - ~ 60% of pts received previous treatment with bortezomib and/or thalidomide and 20% to 30% were refractory to previous treatment

Richardson PG, et al. ASH 2014. Abstract 302.

Elotuzumab in Combination With Len/Dex: Final Efficacy Results

Response, %	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 36)	Total (N = 73)
ORR	92	76	84
▪ sCR	6	3	4
▪ CR	11	8	10
▪ VGPR	47	38	43
▪ PR	28	27	27
SD	8	19	14
Time to first response, mos	1.0	1.7	1.0
Median DoR, mos	23.0	18.0	20.8
Median PFS, mos	32.5	25.1	28.6

Richardson PG, et al. ASH 2014. Abstract 302.

Elotuzumab in Combination With Len/Dex: Final Safety Results

Preferred term, n (%)	Elo 10 mg/kg (n = 36)		Elo 20 mg/kg (n = 37)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	**24 (67)**	**5 (14)**	**25 (65)**	**2 (5)**
Muscle spasms	22 (61)	2 (6)	23 (62)	0
Fatigue	24 (67)	3 (8)	17 (46)	2 (5)
Constipation	18 (50)	0	19 (51)	0
Nausea	18 (50)	0	17 (46)	1 (3)
URI	19 (53)	1 (3)	15 (41)	1 (3)
Pyrexia	14 (39)	1 (3)	17 (46)	1 (3)
Back pain	17 (47)	3 (8)	13 (35)	1 (3)
Anemia	**17 (47)**	**6 (17)**	**12 (32)**	**5 (14)**
Insomnia	10 (28)	0	15 (41)	2 (5)
Cough	12 (33)	0	12 (32)	0
Hyperglycemia	**9 (25)**	**2 (6)**	**12 (32)**	**5 (14)**
Lymphopenia	**13 (36)**	**10 (28)**	**8 (22)**	**5 (14)**
Pain in extremity	9 (25)	0	12 (32)	0
Dyspnea	10 (28)	3 (8)	10 (27)	1 (3)
Peripheral edema	12 (33)	0	8 (22)	1 (3)
Thrombocytopenia	**13 (36)**	**7 (19)**	**7 (19)**	**6 (16)**
Asthenia	7 (19)	1 (3)	12 (32)	1 (3)
Nasopharyngitis	10 (28)	0	9 (24)	0
Neutropenia	**11 (31)**	**7 (19)**	**8 (22)**	**7 (19)**

Richardson PG, et al. ASH 2014. Abstract 302.

Infusion reactions: if pts tolerated 2 mL/min, flow rate increased to 5 mL/min

- 33% of infusions were at rate of 5 mL/min
- 11% experienced infusion reactions
  - 7 at 2 mL/min rate
  - 1 at ≥ 2 mL/min rate
- Most common events included pyrexia (3), nausea (1), rash (3)

Phase III Trial: Melphalan/Dexamethasone ± Bortezomib for Untreated AL Amyloidosis

- EMN-03: multicenter, randomized phase III trial comparing MDex and BMDex in newly diagnosed AL amyloidosis in Europe and Australia

Continued until any of following:

- End of planned treatment (9 or 8 cycles)
- CR after cycle 6
- PR + organ response after cycle 6
- < PR after cycle 3
- Progression of clonal plasma cell disease

Dosing in BMDex arm

- Cycles 1, 2 (28 days): bortezomib 1.3 mg/m^2 on Days 1, 4, 8, 11; melphalan 0.22 mg/kg on Days 1-4; dexamethasone 40 mg on Days 1-4
- Cycles 3-8 (35 days): bortezomib 1.3 mg/m^2 on Days 1, 8, 15, 22; melphalan 0.22 mg/kg on Days 1-4; dexamethasone 40 mg on Days 1-4

Dosing in MDex arm

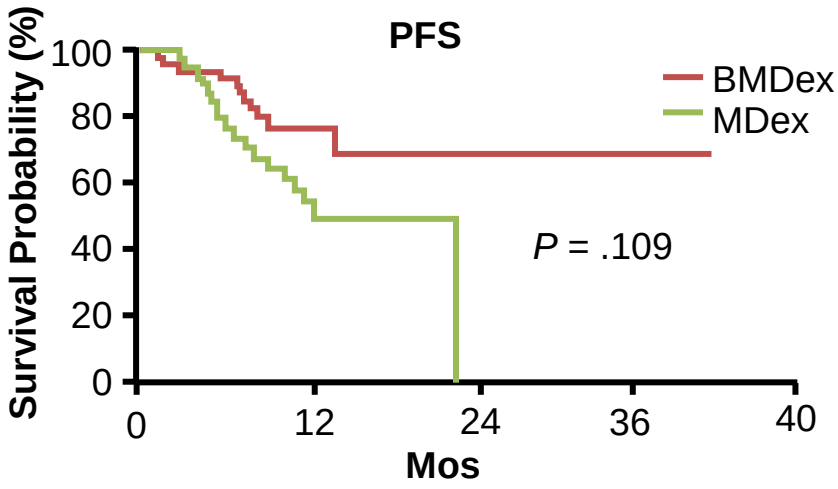
- Cycles 1-9 (28 days): melphalan 0.22 mg/kg on Days 1-4; dexamethasone 40 mg on Days 1-4

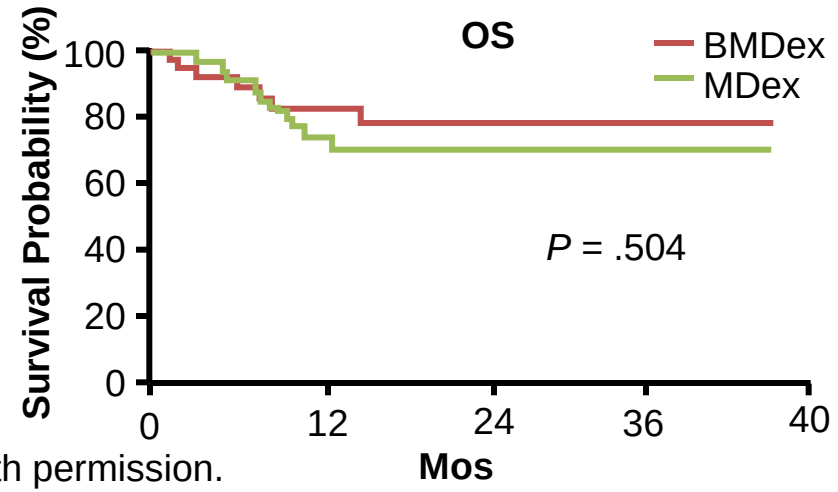
Kastritis E, et al. ASH 2014. Abstract 35.

Melphalan/Dexamethasone ± Bortezomib in AL Amyloidosis: Efficacy Summary

Response After Cycle 3, n (%)			
Response	**MDex (29 pts)**	**BMDex (30 pts)**	***P***
Overall Hem	**15 (52)**	**22 (73)**	**.086**
CR	1 (3)	4 (13)	.173
VGPR	9 (31)	11 (37)	.648
PR	4 (14)	7 (23)	.347
Cardiac	5/23 (22)	4/17 (23)	.893
Renal	6/15 (40)	3/16 (19)	.193

Best Response (Median 5 Cycles), n (%)			
Response	**MDex (29 pts)**	**BMDex (30 pts)**	***P***
Overall Hem	**15 (52)**	**23 (77)**	**.045**
CR	6 (21)	7 (23)	.807
VGPR	6 (21)	11 (37)	.176
PR	3 (10)	5 (17)	.478
Cardiac	5/23 (22)	4/17 (23)	.893
Renal	7/15 (47)	5/16 (31)	.378





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Melphalan/Dexamethasone ± Bortezomib in AL Amyloidosis: Safety

Grade ≥ 3 AE, n (%)	MDex (n = 40, 163 cycles)	BMDex (n = 40, 144 cycles)	*P* Value
Overall	**19 (12)**	**39 (27)**	**< .001**
Cytopenia	9 (5)	15 (10)	.111
Fluid retention	4 (2)	3 (2)	.828
Fatigue	2 (1)	1 (0.5)	--
cTn increase	1 (0.5)	1 (0.5)	--
Diarrhea	1 (0.5)	0	--
Renal failure	1 (0.5)	3 (2)	--
Insomnia	0	2 (1)	--
Peripheral neuropathy	0	3 (2)	--
Injection-site reaction	0	1 (0.5)	--

- 14 pts(35%) experienced at least 1 grade ≥ 3 AE in each group
- There were 4 (cardiac) deaths in the first 100 days, 1 in the MDex arm and 3 in the BMDex arm (*P* = .307)

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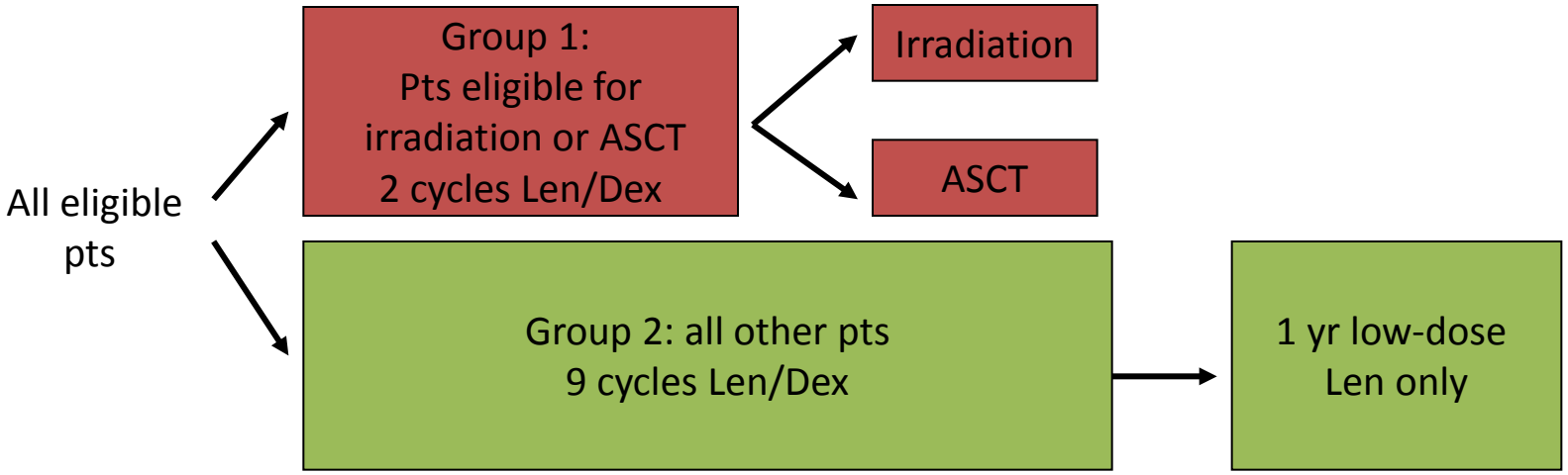
Phase II: Lenalidomide/Dexamethasone in POEMS Syndrome

- Prospective phase II trial of lenalidomide/dexamethasone in pts with newly diagnosed or relapsing POEMS syndrome



Lenalidomide: 25 mg 21 days/28 (10 mg if creatinine clearance < 50 ml/min)
Dexamethasone: 40 mg/wk (20 mg if older than 75 yrs of age or frail)
Low-dose Lenalidomide: 10 mg 28 days/28 for 12 cycles
Aspirin or low molecular weight heparin given as venous thromboembolic event prophylaxis

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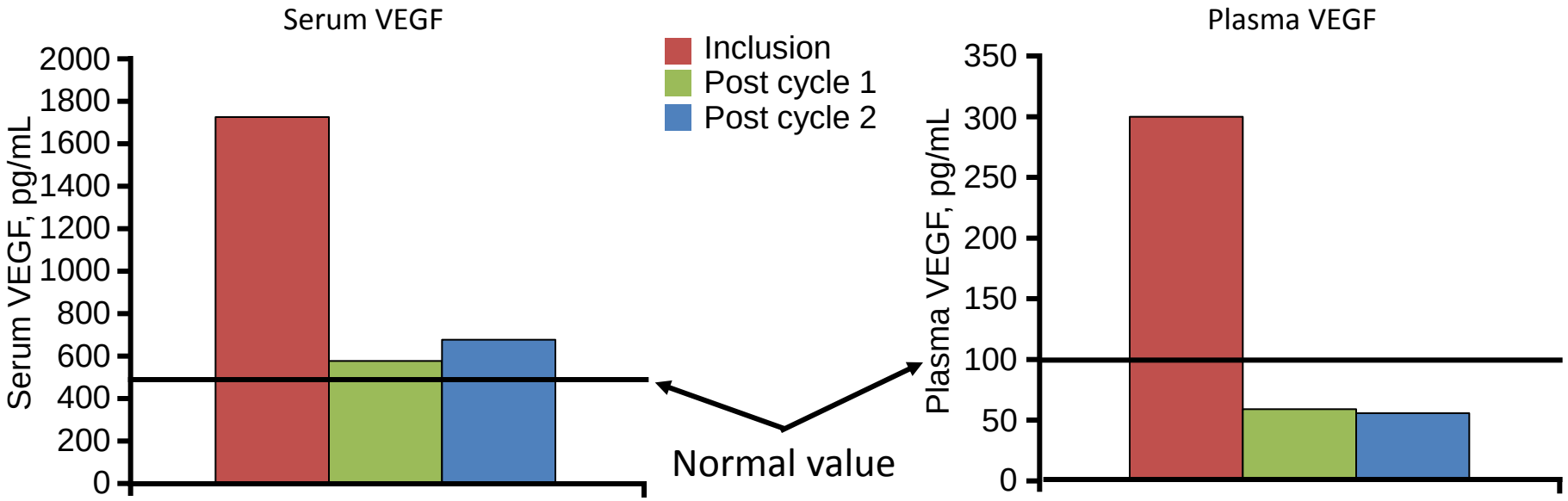
Lenalidomide/Dexamethasone in POEMS Syndrome: Efficacy Summary



- VEGF normal at inclusion: serum 1 pt, plasma 7 pts
- After 2 cycles, VEGF normal: serum 10 pts, plasma 20 pts
  - VEGF level with > 50% drop: serum 17 pts, plasma 20 pts

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Lenalidomide/Dexamethasone in POEMS Syndrome: Efficacy Summary

- Hematologic responses in assessable pts after 2 cycles
  - Measurable IgG M-spike (n = 9): VGPR (n = 5); PR (n = 1); stable (n = 3)
  - IgA (n = 12): CR (n = 1); PR (n = 3); stable (n = 9)
  - FLC λ (n = 21): normalized (n = 9); > 50% reduction (n = 3)
- Neurologic responses after 2 cycles
  - Improvement with ONLS: n = 11
  - Improvement with NIS score: n = 10
  - Improvement based on clinical judgment of investigator: n = 16
  - 10-meter walking test improved in 5 of 8 evaluable pts

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Lenalidomide/Dexamethasone in POEMS Syndrome: Efficacy Last Follow-up

Parameter	Group 1: ASCT (n = 8)	Group 1: Radiation (n = 9)	Group 2 (n = 9)
Clinical status	No relapses	1 relapse at 6 mos (in pt with BM involvement)	▪ 1 PD after 9 cycles ▪ 3 pts on therapy ▪ 3 pts on maintenance ▪ 2 pts off tx
Median VEGF level at baseline, pg/mL (range)			
Serum	5237 (1544-8640)	1423 (705-3560)	1606 (162-12,000)
Plasma	384 (17-924)	232 (48-1025)	254 (33-1794)
Median VEGF level at last follow-up, pg/mL (range)			
Serum	530 (294-1951)	457 (170-472)	870 (115-6980)
Plasma	75 (19-91)	66 (12-145)	42 (19-844)

- In group 1, ASCT feasible after 2 cycles (8 of 9 pts received ASCT, median follow-up: 10.5 mos)
  - No collection failures, engraftment syndrome; 1 death following ASCT (cerebral bleeding after falling)

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