What's New in Newly Diagnosed Multiple Myeloma

- ***Current Concepts, Emerging Approaches***

IMWG Criteria for Diagnosis of MM

MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein <3 g/dL ▪ Clonal plasma cells in BM <10% ▪ No myeloma-defining events	▪ M-protein ≥3 g/dL (serum) or ≥500 mg/24 hr (urine) ▪ Clonal plasma cells in BM ≥10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥1 SLiM-CRAB* features

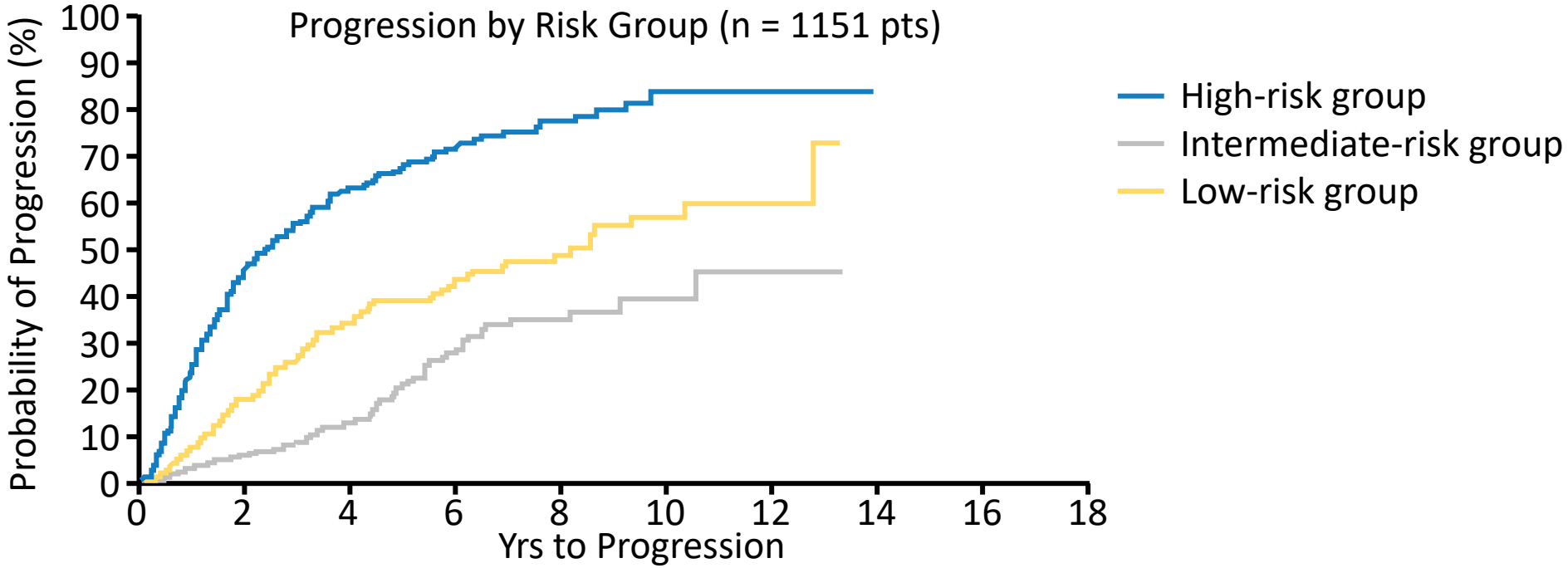
*S: ≥60% clonal bone marrow plasma cells
Li: Serum free light chain ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)
M: MRI studies with >1 focal lesion (>5 mm in size)

C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hgb <10 g/dL or 2 g/dL < normal)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar. Lancet Oncol. 2014;15:e538.

IMWG Risk Stratification for Smoldering Myeloma: 2/20/20 Model

- Risk factors include serum M-spike > 2 g/dL; FLC ratio > 20; BMPC > 20%



Risk Stratification	Number of Risk Factors	HR (95% CI) vs Low Risk	2-Yr Risk of Progression, %	Patients, n (%)
Low risk	0	Reference	5	424 (37)
Intermediate risk	1	2.25 (1.68-3.01)	17	312 (27)
High risk	2-3	5.63 (4.34-7.29)	46	415 (36)

San Miguel. ASCO 2019. Abstr 8000.

E3A06: Single-Agent Lenalidomide vs Observation in Intermediate- or High-Risk Smoldering Myeloma

Patients with high-risk smoldering MM within 5 yrs,* BM plasmacytosis ≥ 10%, abnormal FLC ratio < 0.26 or > 1.65,† measurable M-protein in serum and/or urine, no lytic lesions by skeletal survey, no baseline bone lesions or plasmacytoma by MRI
(phase II: N = 44)
(phase III: N = 182)

Stratified by time since smoldering MM diagnosis (≤ 1 vs > 1 yr)

Lenalidomide
25 mg Days 1-21 Q28D
Aspirin 325 mg Days 1-28
until PD or toxicity§
(n = 44)

- Primary endpoint: safety and success of stem cell mobilization

Lenalidomide
25 mg Days 1-21 Q28D
Aspirin 325 mg Days 1-28
until PD or toxicity†
(n = 90)

Observation
until PD†
(n = 92)

Phase III

- Primary endpoint: PFS‡
  Secondary endpoints: OS, ORR, QoL, safety
- Correlative endpoints: GEP, immune function, MRI

*Updated from 1 yr after enrolled 10 patients. †Updated from < 0.125 or > 8.0 after enrolled 10 patients. ‡Stem cell mobilization after 4-6 cycles of therapy; optional stem cell collection, but strongly recommended. §PFS defined as death or symptomatic disease indicating treatment (by both biochemical and CRAB criteria).

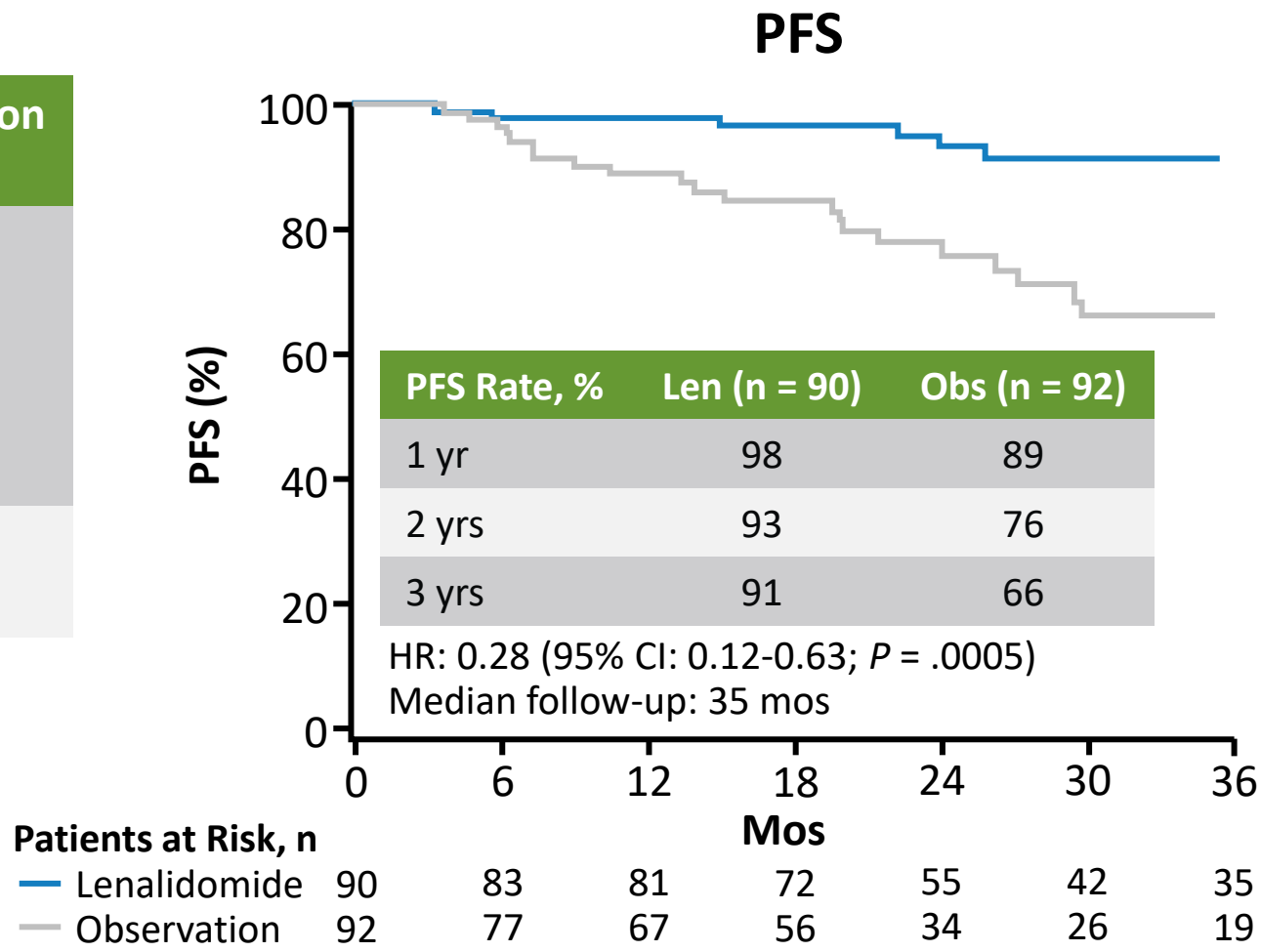
Lonial. J Clin Oncol. 2020;38:1126-1137.

E3A06: Lenalidomide Monotherapy Improves PFS in SMM

Response, n (%)	Lenalidomide (n = 88)	Observation (n = 92)
ORR	54.5	0
▪ ≥ CR	0	0
▪ VGPR	4.5	0
▪ PR	50	0
Median TTR, mos (range)	5 (1-23)	NA

- In phase II, PFS rates at 1 yr, 2 yrs, and 3 yrs were 98%, 87%, and 78%, respectively (median follow-up: 82 mos)

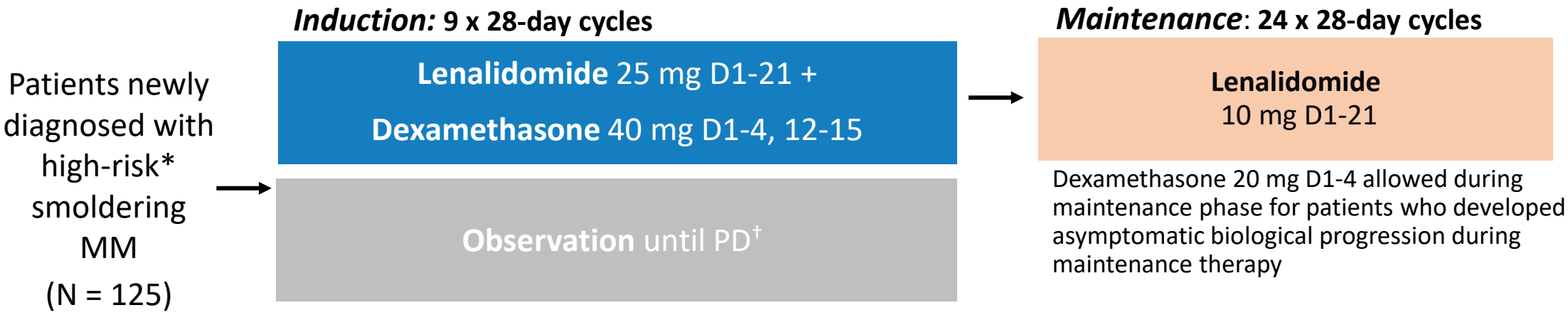
5-yr PFS in the phase II run-in: 78%



Lonial. J Clin Oncol. 2020;38:1126.

Phase III QuiRedex Trial: Rd vs Observation in High-Risk Smoldering MM

- Open-label, randomized, controlled phase III trial



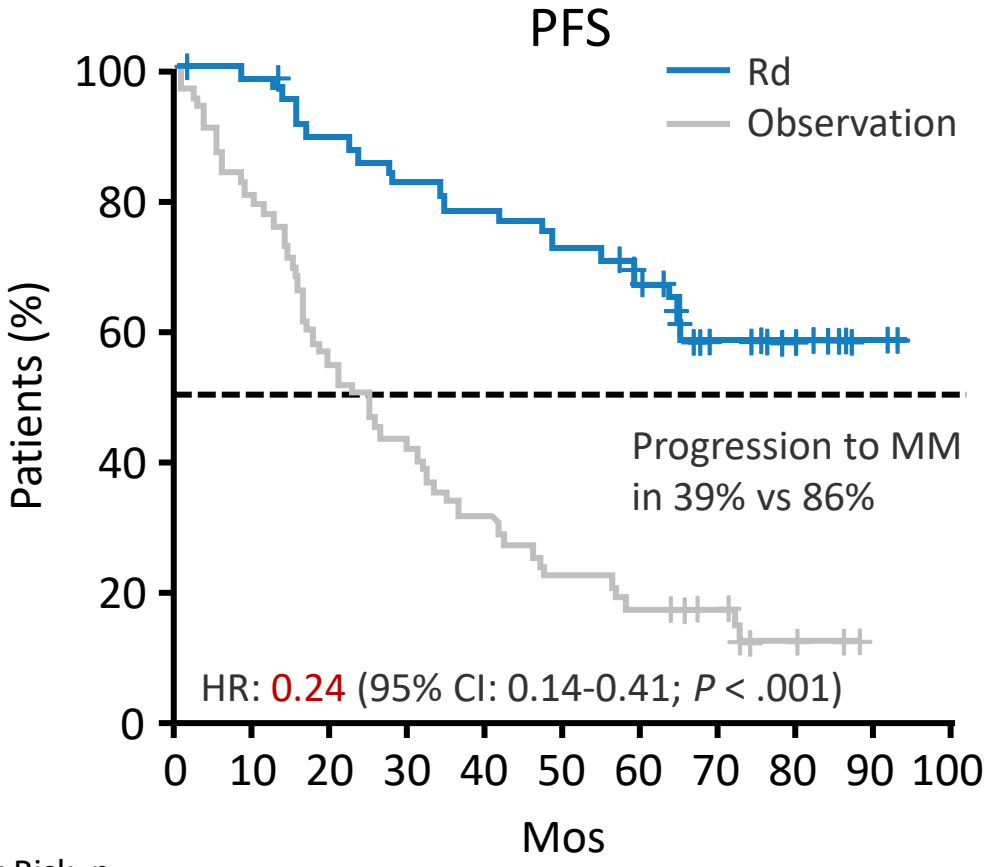
*Defined as either ≥ 10% BMPC or presence of M-spike (IgG ≥ 3 g/dL or IgA ≥ 2 g/dL, or Bence Jones proteinuria > 1 g/24 h), or both, AND ≥ 95% phenotypically aberrant PC in BMPC compartment with immunoparesis (reductions in one or two uninvolved immunoglobulins of >25% compared with normal values).

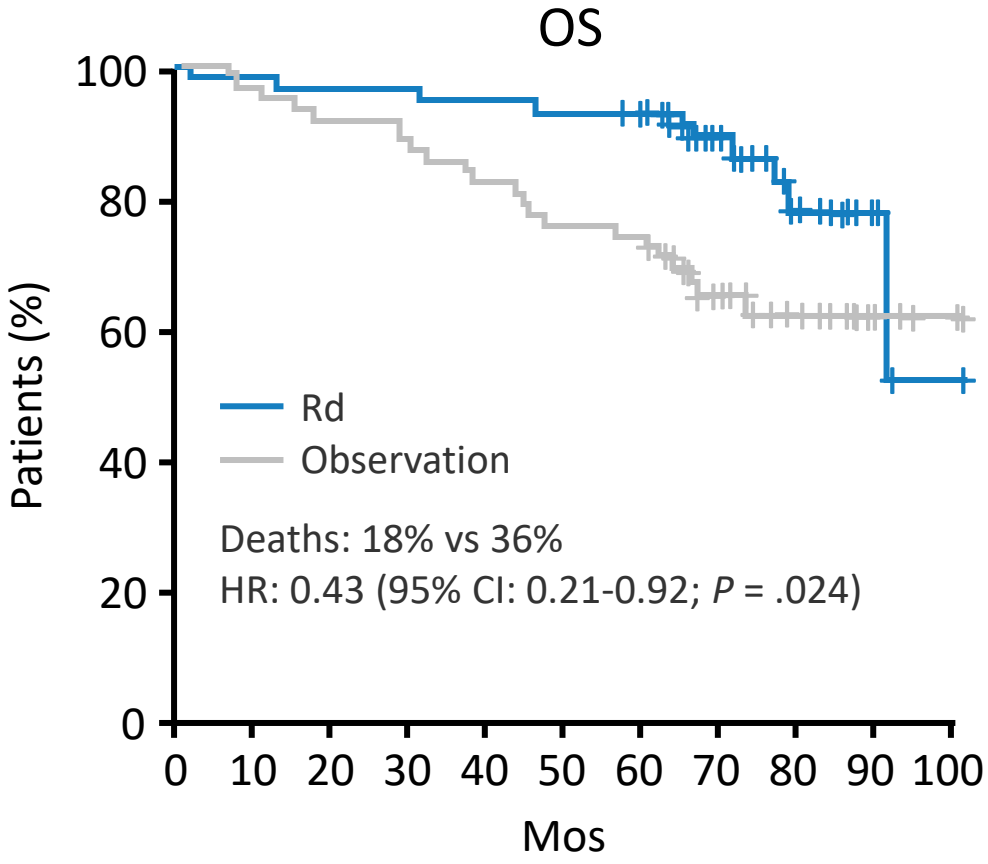
- Patients with hypercalcemia, bone lesions, renal failure, or anemia were excluded

- Primary endpoint: time to progression to symptomatic disease
- Secondary endpoints: OS, response, safety

Mateos. Lancet Oncol. 2016;17:1127.

Phase III QuiRedex Study of Rd vs Observation in High-Risk Smoldering MM: Survival Results





Patients at Risk, n											
Treatment group	57	55	49	45	43	40	35	20	11	1	..
Observation group	62	49	33	26	19	14	11	7	2	0	..

57	55	55	54	54	53	50	31	15	2	0
62	59	57	54	50	47	44	25	15	4	0

Mateos. Lancet Oncol. 2016;17:1127.

Summary

- Based on current diagnostic criteria, smoldering MM is defined as having M-protein ≥ 3 g/dL (serum) and ≥ 10% to 60% clonal plasma cells in BM
- Identify patients with high-risk smoldering myeloma using IMWG 2/20/20 criteria, with ≥ 2 of the following risk features:
  1. M-spike > 2 g/dL
  2. FLC ratio > 20
  3. BMPC > 20%
  - Consider treatment with lenalidomide with or without dexamethasone for patients with high-risk smoldering MM
  - Reduces the risk of clinical progression by 72% to 76%
  - E3A06: PFS 91% in 3y for those with high-risk disease per 2018 Mayo Clinic criteria

Active Myeloma

Defining High Risk

- Cytogenetic abnormalities
  - t(4;14), t(14;16), t(14;20), del(17p), gain/amp(1q)
  - High-risk GEP
- Laboratory factors
  - ISS III (↓ albumin/↑ β2-microglobulin)
  - ↑ LDH
- Clinical features
  - Plasma cell leukemia
  - Extramedullary involvement
  - Age
- Functional high risk (determined after initiation of therapy)
  - Primary refractory
  - Rapid progression within 18 mo from diagnosis

Bannerjee. Front Oncol. 2023;13:124966. Palumbo. JCO. 2015;33:2863. Soekojo. Blood Cancer J. 2022;12:24. Usmani. Leukemia. 2015;29:2119.

ISS Staging Systems

ISS Definition	
I	▪ Serum albumin ≥3.5 g/dL *AND* ▪ β_2-M <3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥5.5 mg/L

R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)

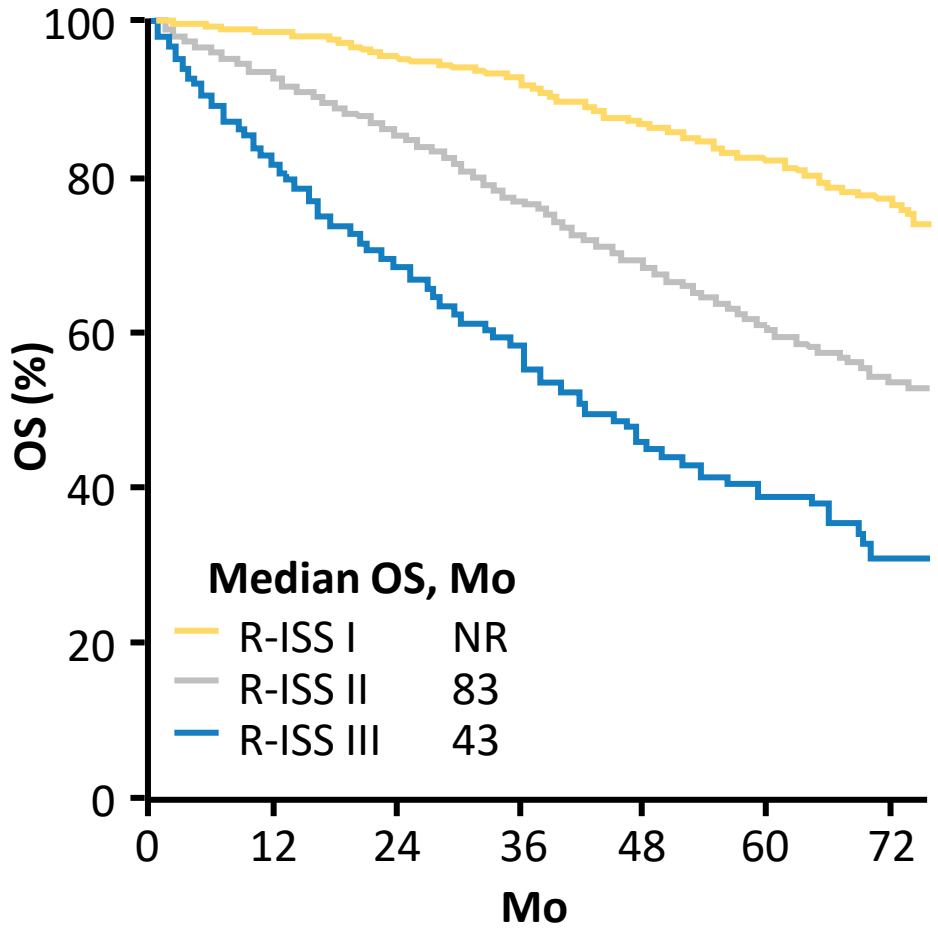
R2-ISS* Definition	
I	**Low risk: 0 points**† ▪ Not ISS stage II or III ▪ Serum LDH ≤ ULN ▪ With t(4;14) or del(17p); 1q+ not detected
II	**Low-intermediate risk: 0.5-1 points**† ▪ ISS stage II *OR* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), del(17p), or 1q
III	**Intermediate-high risk: 1.5-2 points**† ▪ Any combination of high-risk features equaling score of 1.5-2
IV	**High risk: 3-5 points**† ▪ Any combination of high-risk features equaling score of 3-5

*Validated only for NDMM. †Based on influence on OS. ISS-III = 1.5 points, ISS-II = 1 point; del(17p) = 1 point; t(14;4) = 1 point; 1q+ = 0.5 points; serum LDH > ULN = 1 point.

Palumbo. J Clin Oncol. 2015;33:2863. D'Agostino. J Clin Oncol 2022;40:3406. NCCN Myeloma v3.2024.

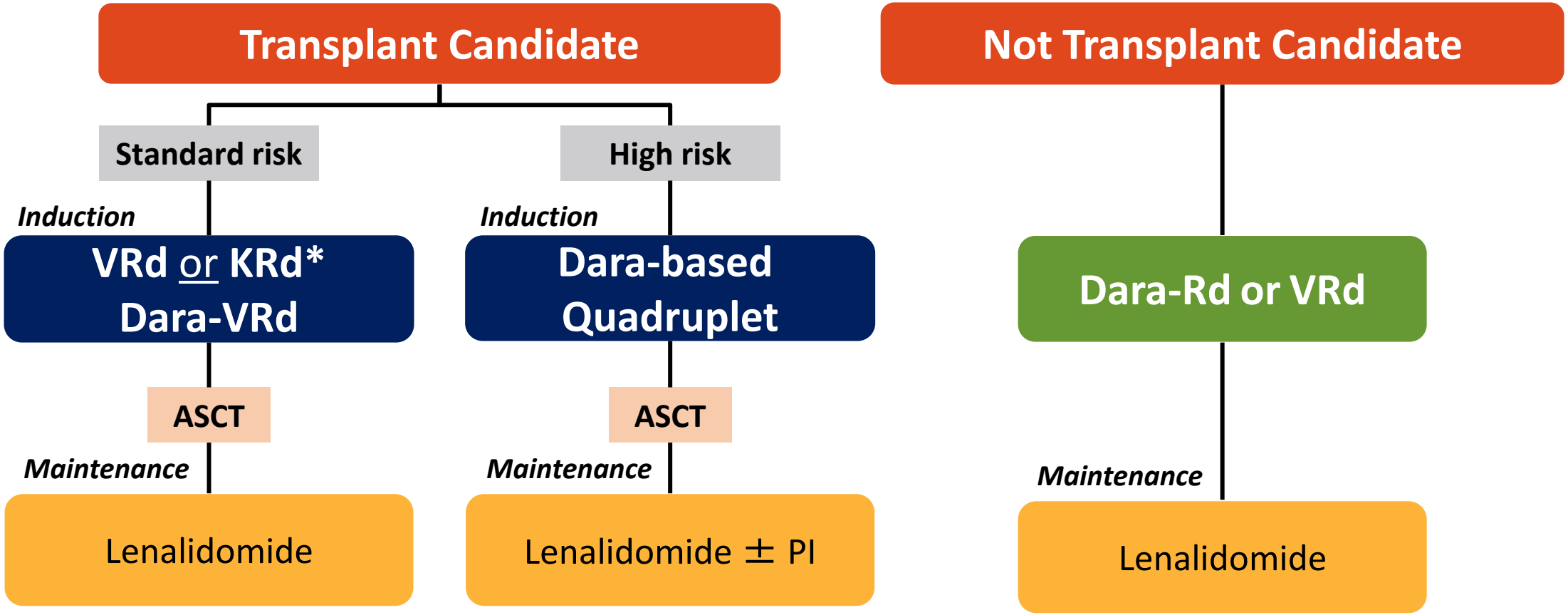
Revised ISS Staging System and Overall Survival

	R-ISS Definition
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not ISS stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo. JCO. 2015;33:2863.

Proposed Treatment Algorithm for Newly Diagnosed Multiple Myeloma



*Ixazomib may be substituted for carfilzomib in select patients.

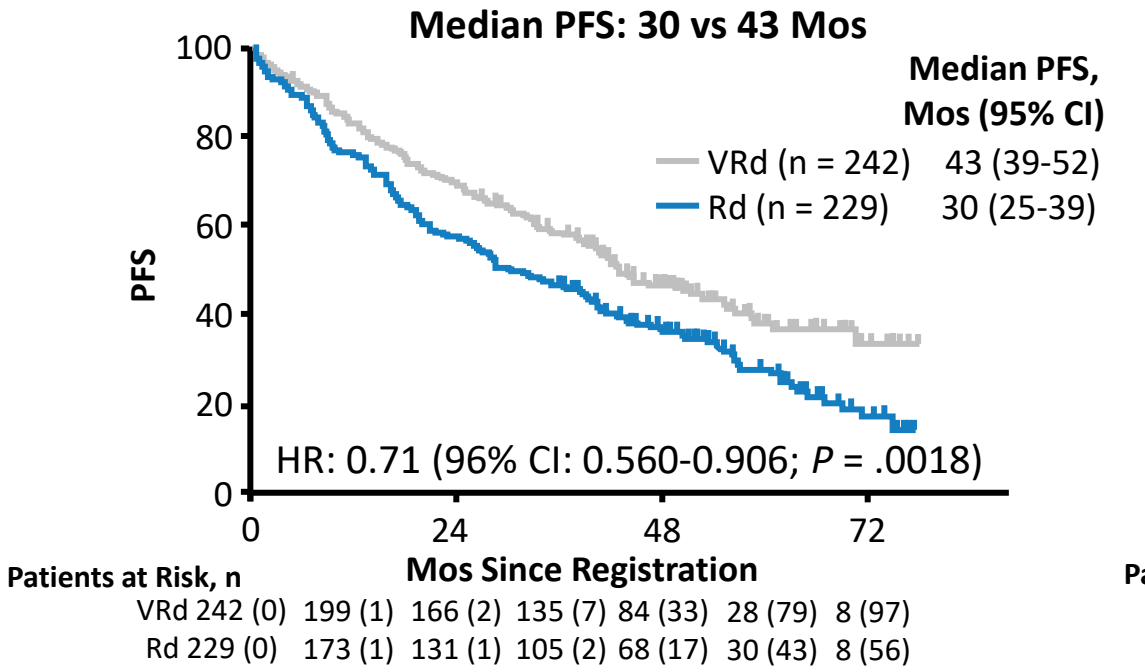
Adapted from NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. v.2.2024. nccn.org.

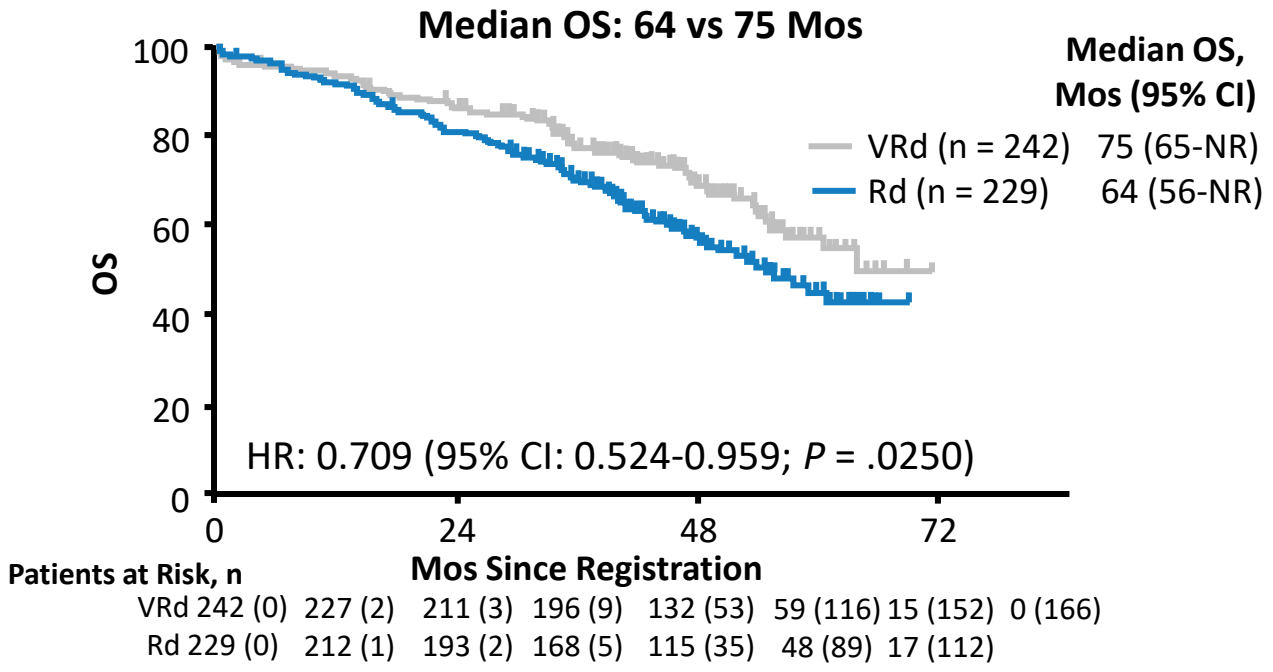
Triplets vs Doublets

Phase III SWOG S0777: VRd vs Rd for ASCT-Ineligible Patients With MM (N = 525)

VRd Arm
Eight, 21-day induction cycles. Len 25 mg D1-14; Bort 1.3 mg/m^2 IV D1, 4, 8, 11; Dex 20 mg D1, 2, 4, 5, 8, 9, 11, 12
Rd Arm
Six, 28-day cycles. Len 25 mg D1-21; Dex 40 mg D1, 8, 15, 22
Maintenance (both arms)
28-day cycles. Len 25 mg D1-21; Dex 40 mg D1, 8, 15, 22

Response, %	VRd	Rd
ORR	81.5	71.5
▪ PR	38.0	39.7
▪ VGPR	27.8	23.4
▪ CR	15.7	8.4
▪ ≥ VGPR	43.5	31.8





Durie. Lancet. 2017;389:519.

IMiDs or Cyclophosphamide in Combination With a Proteasome Inhibitor and Dexamethasone?

IFM2013-04: VTD vs VCD Induction Before HDT/ASCT in Newly Diagnosed MM

- Prospective, randomized, open-label phase III trial in patients younger than 65 yrs of age with untreated, symptomatic MM with measurable paraprotein in serum or urine

Outcome After 3 Cycles	VTD (n = 169)	VCD (n = 169)	*P* Value
ORR (ITT), %	92.3	83.4	.01
▪ ≥ VGPR	66.3	56.2	.05
▪ ≥ CR	13.0	8.9	.22

Moreau. Blood. 2016;127:2569.

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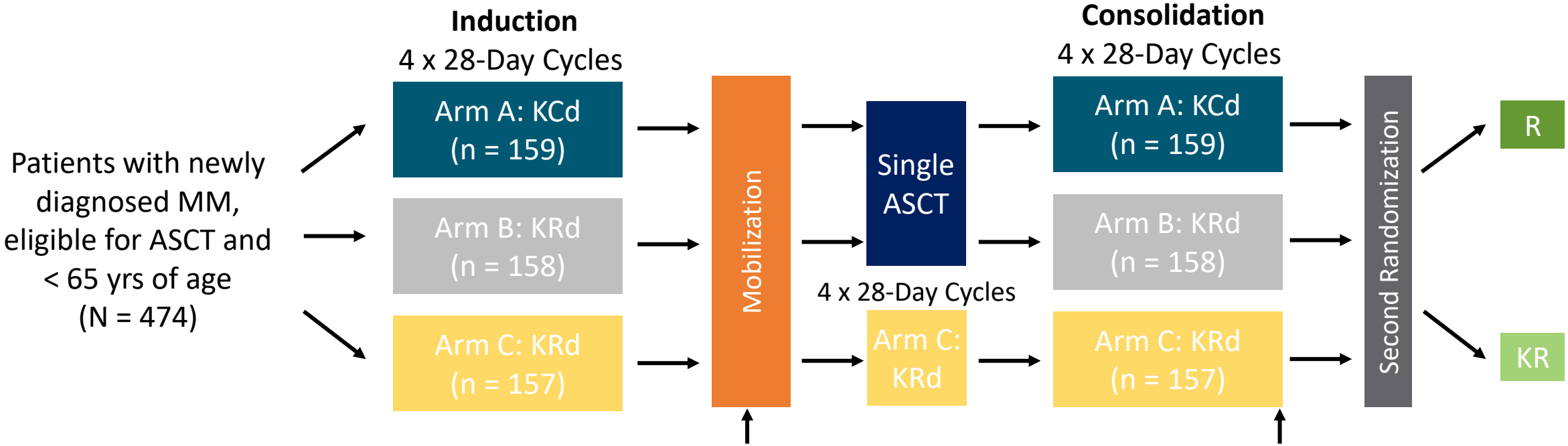
Outcome After 3 Cycles	VTD (n = 169)	VCD (n = 169)	*P* Value
ORR (ITT), %	92.3	83.4	.01
▪ ≥ VGPR	66.3	56.2	.05
▪ ≥ CR	13.0	8.9	.22
Grade 3/4 AEs, %			
▪ Anemia	4.1	9.5	.05
▪ Thrombocytopenia	4.7	10.6	.04
▪ Neutropenia	18.9	33.1	003
▪ Peripheral neuropathy	7.7	2.9	.05
Stem cell mobilization			
▪ Median stem cell yield, 10^6 CD34+ cells/kg	10.7	9.2	.05

Moreau. Blood. 2016;127:2569.

FORTE Study: KCd vs KRd in Newly Diagnosed MM

- Multicenter, randomized, open-label phase II study

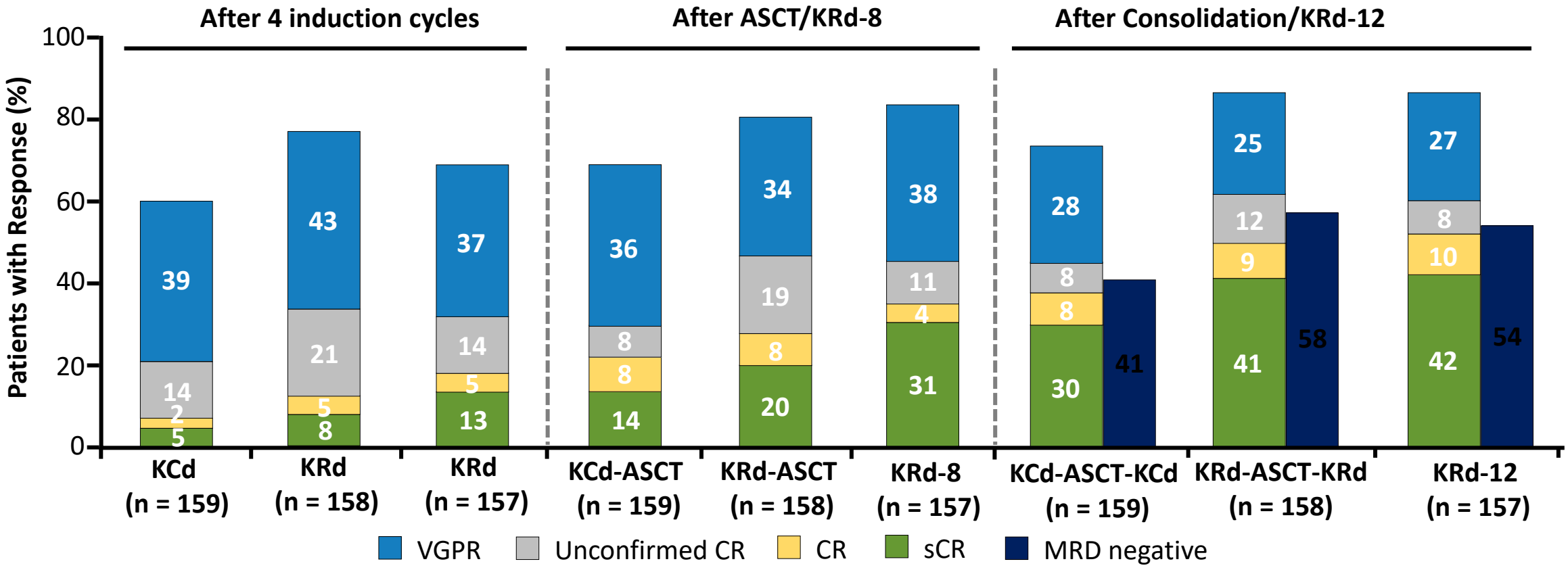


Dosing:

- KRd-ASCT-KRd: 4 28-day cycles with KRd induction (carfilzomib 20/36 mg/m^2 IV Days 1,2,8,9,15,16; lenalidomide 25 mg days 1-21; dexamethasone 20 mg Days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KRd consolidation cycles
- KRd12: 12 KRd cycles
- KCd-ASCT-KCd: 4 28-day induction cycles with KCd (carfilzomib 20/36 mg/m^2 IV Days 1,2,8,9,15,16; cyclophosphamide 300 mg/m^2 Days 1,8,15; dexamethasone 20 mg Days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KCd consolidation cycles

Gay. ASH 2018. Abstr 121.

FORTE: Responses With KCd vs KRd Induction and Consolidation in Newly Diagnosed MM



Lenalidomide improved depth of response compared with cyclophosphamide in combination with carfilzomib and dexamethasone

Gay. EHA 2019. Abstr S872.

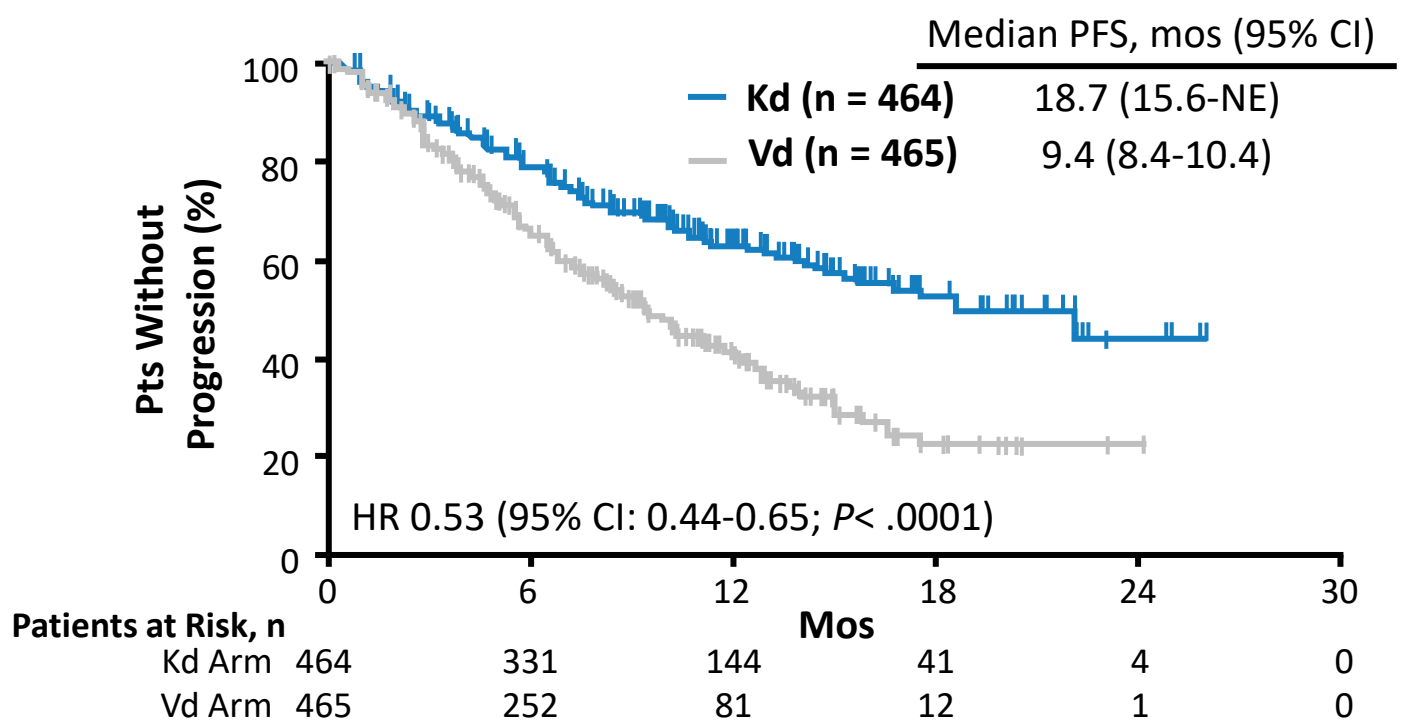
Bortezomib or Carfilzomib?

What Is the Best Proteasome Inhibitor?

- ENDEAVOR: open-label, randomized phase III trial of Vd vs Kd in R/R MM (N = 1096)
  - Treatment given until PD or unacceptable AE
  - Eligibility: 1-3 prior lines of therapy

Response, %	Vd (n = 465)	Kd (n = 464)
ORR	63	77
sCR	2	2
CR	4	11
≥ VGPR	29	54

PFS



Median OS (interim analysis): 40.0 mos with Vd vs 47.6 mos with Kd

Dimopoulos. Lancet Oncol. 2016;17:27. Dimopoulos. Lancet Oncol. 2017;18:1327.

Neuropathy With Bortezomib- vs Carfilzomib-Based Therapy in Myeloma

- Phase III ENDEAVOR trial in patients with R/R MM after 1-3 previous treatments[1]
- Phase III CLARION trial in ASCT-ineligible patients with ND MM[2]

Neuropathy, %	ENDEAVOR (N = 929)[1]	
	Vd	Kd
All grades	43	17
Grade ≥ 3 PN	9	2

Neuropathy, %	CLARION (N = 955)[2]	
	VMP	KMP
All grades	33.0	6.1
Grade ≥ 3 PN	7.9	0.2

Grade ≥ 3 neurologic toxicity in S0777[3]: VRd 33% vs Rd 11%

1. Dimopoulos. Lancet Oncol. 2016;17:27. 2. Facon. Blood. 2019;133:1953. 3. Durie. Lancet. 2017;389:519.

Cardiovascular Toxicity of PIs: The PROTECT Study

Prospective study of cardiovascular toxicity of PI-based therapy

- N = 95 patients with relapsed MM following at least 1 line of bortezomib- or carfilzomib-based therapy
- No symptomatic arrhythmia or ≥ NYHA class 3 heart failure within 3 mos of treatment start
- No light-chain amyloidosis
- Cardiac assessment over first 6 cycles: ECG with each cycle, TTE every 2 cycles, cardiac biomarkers twice per cycle
  - Cardiac toxicity assessed using CTCAE version 4.03
- **Primary endpoint**: incidence of and risk factors for cardiovascular events over 18 mos
- Secondary endpoints: PFS, OS

Cornell. J Clin Oncol. 2019;37:1946.

PROTECT Study: Cardiovascular AEs With PIs in MM

- Median lines of therapy (carfilzomib vs bortezomib): 2 vs 1
- Median time from diagnosis: 37.4 vs 18.6 mos
- Male: 74% vs 50%
- Smoking history: 43% vs 14%

Cardiovascular AE, %	Carfilzomib-Based Therapy (n = 65)		Bortezomib-Based Therapy (n = 30)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Heart failure	18.5	16.9	6.7	3.3
Chest pain	12.3	1.5	3.3	0
Hypertension	NR	20.0	NR	6.7
Arrhythmia	3.1	3.1	3.3	0
Acute coronary syndrome	1.5	3.0 (1 grade 5 event)	0	0
Pulmonary hypertension	3.1	3.1	0	0
Venous thromboembolic event	0	0	0	3.3
Patients with any CVAE	51		17	

Median time to first CVAE: 31 days (range: 0-151), 86% within 3 mos

Cornell. J Clin Oncol. 2019;37:1946.

Monoclonal Antibodies in Newly Diagnosed Multiple Myeloma

MAIA: Daratumumab Plus Rd vs Rd Alone in Newly Diagnosed MM

- Randomized phase III trial

Stratified by ISS (I vs II vs III), region (N America vs other), age (< 75 vs ≥ 75 yrs)

Patients with ASCT-ineligible newly diagnosed MM, ECOG PS 0-2, CrCl ≥ 30 mL/min (N = 737)

Daratumumab 16 mg/kg IV (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7+) + **Lenalidomide** 25 mg/day PO D1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 368)

Lenalidomide 25 mg/day PO D1-21 + **Dexamethasone** 40 mg/wk* PO or IV (n = 369)

28-day cycles until progression

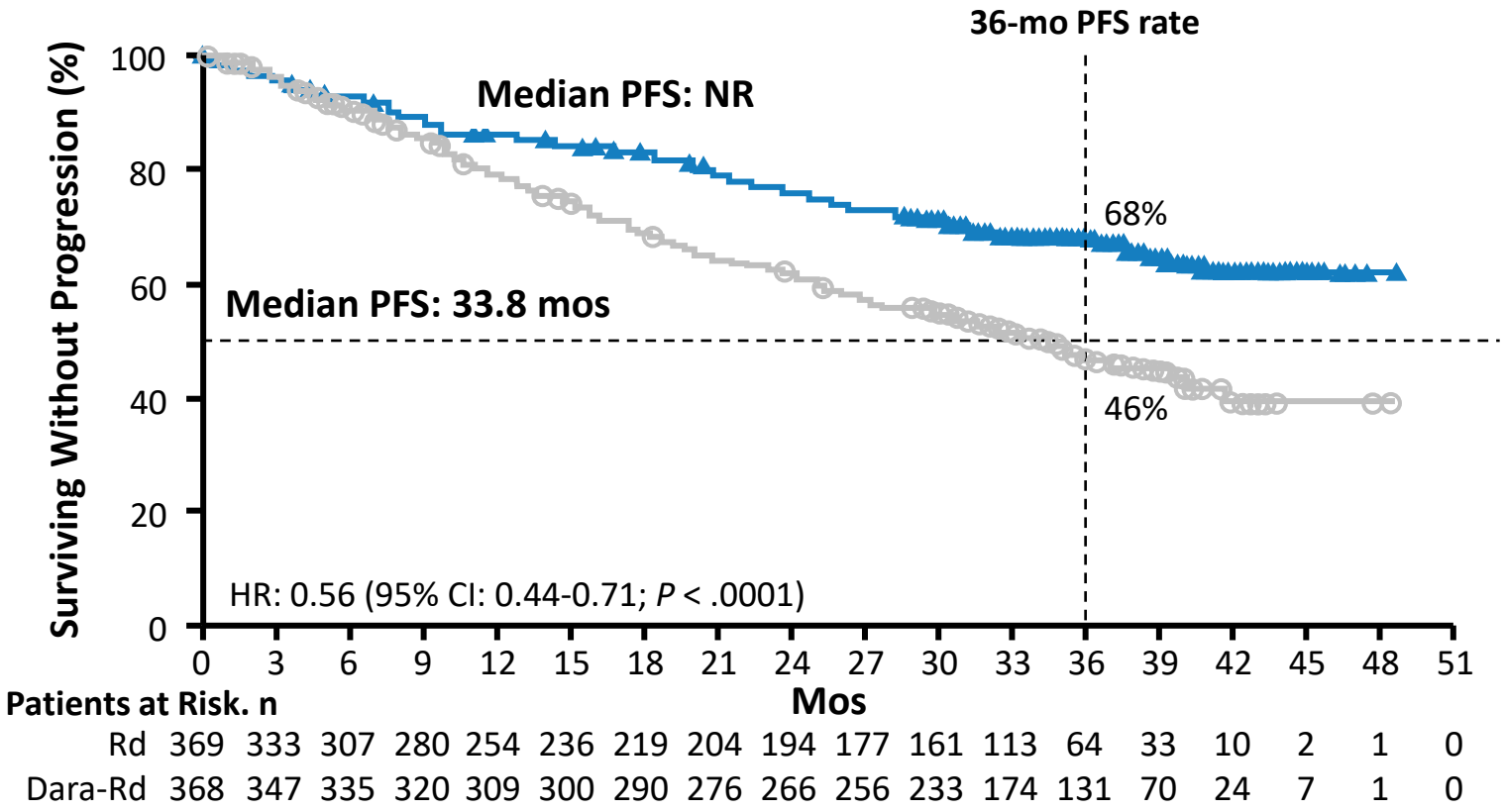
*Reduced to 20 mg/wk if > 75 yrs of age or BMI < 18.5.

Facon. NEJM 2019;380:2104.

MAIA: Response and Survival With Dara-Rd vs Rd in NDMM

Response, %	Dara-Rd	Rd
ORR	92.9	81.3
▪ PR	13.6	28.2
▪ VGPR	31.8	28.2
▪ CR	17.1	12.5
▪ sCR	30.4	12.5
▪ ≥ VGPR	79.3	53.1
MRD negative*	29	9
Sustained MRD neg†	11	2
Median DoR, mos	NR	40.7

*NGS 10^{-5} sensitivity.
†MRD negative for ≥ 12 mos.



Median duration of follow-up: 36.4 mos

MRD negative in patients with high-risk cytogenetics: 2% vs 23%
in <75 y MRD neg was 28% vs 19% in older pts
Median PFS in patients with high-risk cytogenetics
- **29.6 mos vs NR (HR: 0.57; 95% CI: 0.32-1.04)**

Bahlis. ASH 2019. Abstr 1875.
Facon. NEJM 2019;380:2104.

PI/IMiD-Based Triplets vs Quadruplets

Daratumumab-Based Quads: Depth of Response

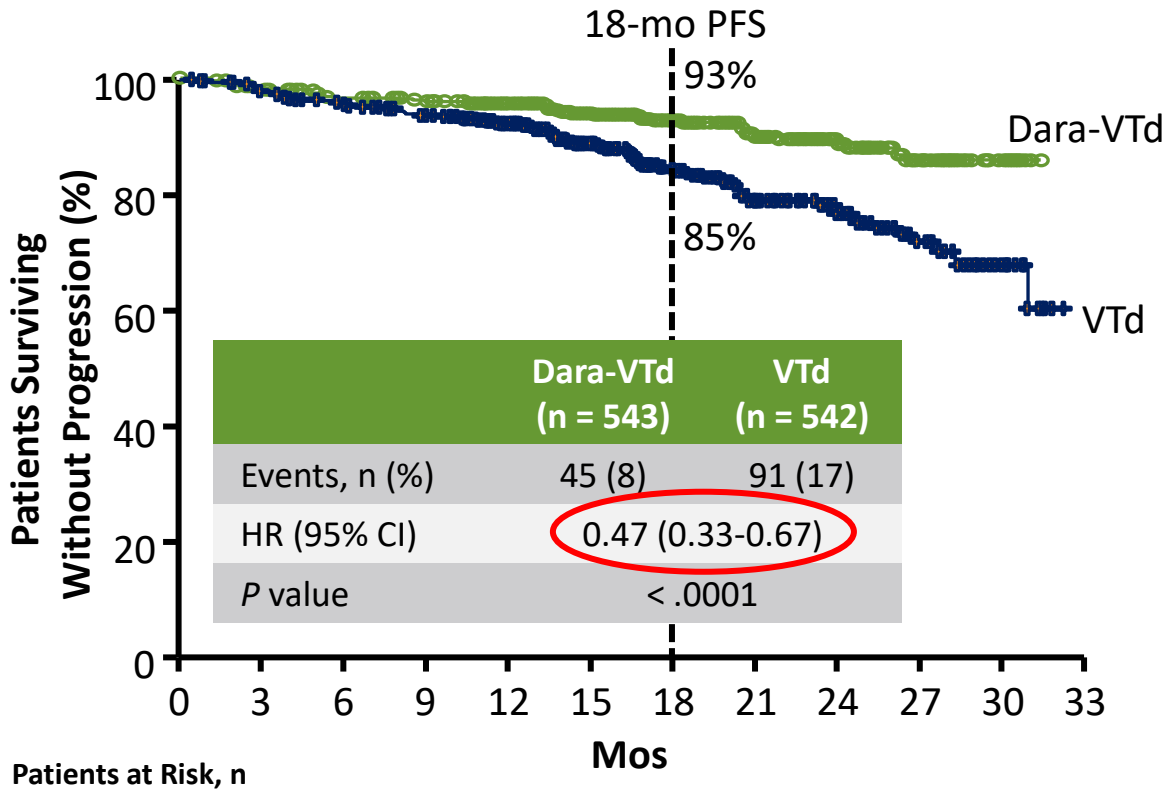
Trial	Regimen	N	Depth of Response, %						
			Post Induction		Post ASCT		Post Consolidation		
			sCR	≥ VGPR	sCR	≥ VGPR	sCR	≥ VGPR	MRD-
CASSIOPEIA[1]	VTd	542	6.5	56.1	9.4	67.4	20.3	78.0	44
	Dara-VTd	543	7.4	64.9	13.4	76.7	28.9	83.4	64
GRIFFIN[2]	VRd	103	7.2	56.7	14.4	66.0	32.0	73.2	20.4
	Dara-VRd	104	12.1	71.7	21.2	86.9	42.4	90.9	51.0
MASTER[3]	Dara-KRd	81	39	91	81	100	95	100	82

1. Moreau. Lancet. 2019;394:29. 2. Voorhees. ASH 2019. Abstr 691. 3. Costa. ASH 2019. Abstr 860.

CASSIOPEIA: Survival With Dara-VTd vs VTd

Primary and final PFS analysis of Part 1

PFS

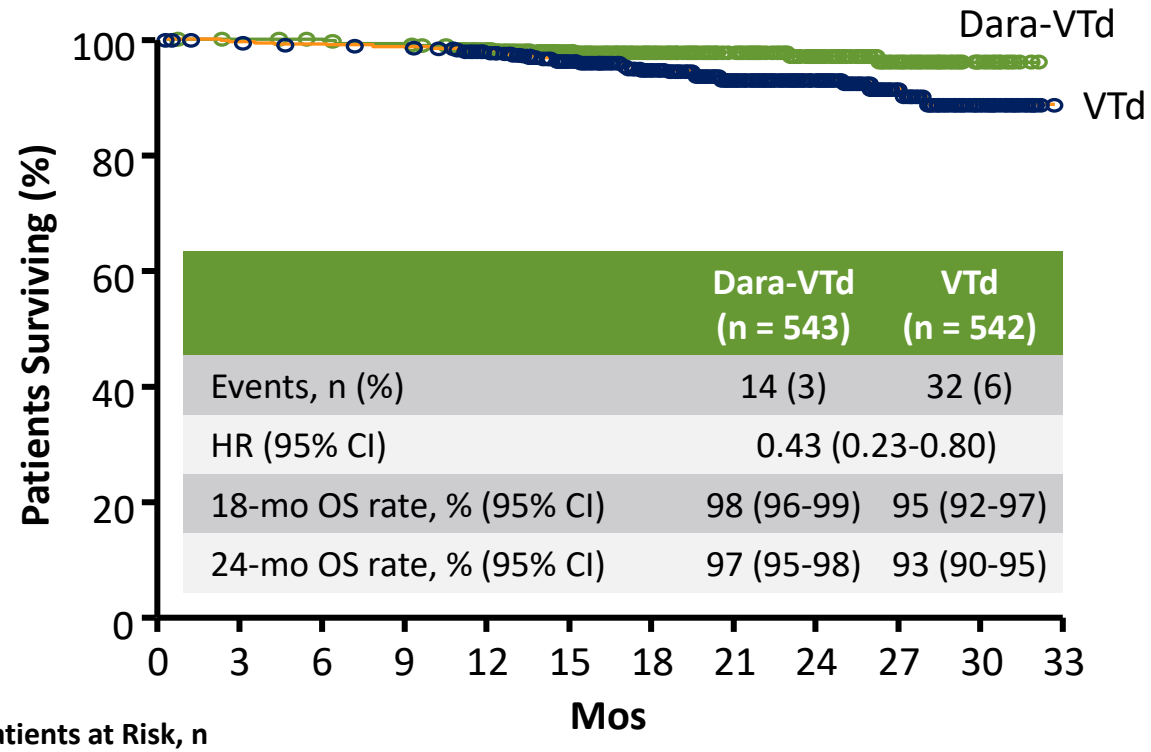


	Dara-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	< .0001	

Patients at Risk, n

Dara-VTd	543	520	501	492	442	346	261	185	122	61	14	0
VTd	542	519	497	475	413	319	233	163	104	50	14	0

OS



	Dara-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-mo OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-mo OS rate, % (95% CI)	97 (95-98)	93 (90-95)

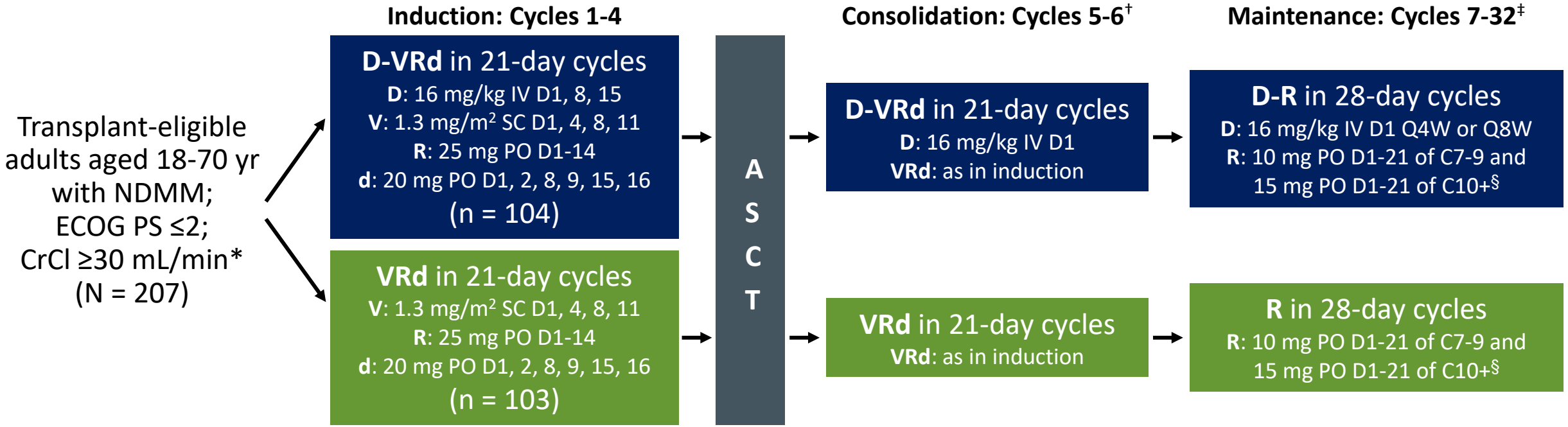
Patients at Risk, n

Dara-VTd	542	535	531	528	480	371	283	206	131	71	17	0
VTd	543	539	535	532	485	388	292	212	137	75	17	0

- Median follow-up: 18.8 mos (range: 0-32.2).ORR 93% and MRD negativity 66% with DVTd vs 84 and 44% with VTd

GRIFFIN: VRd ± Dara in Patients With NDMM Eligible for ASCT

- Multicenter, open-label, randomized phase II trial

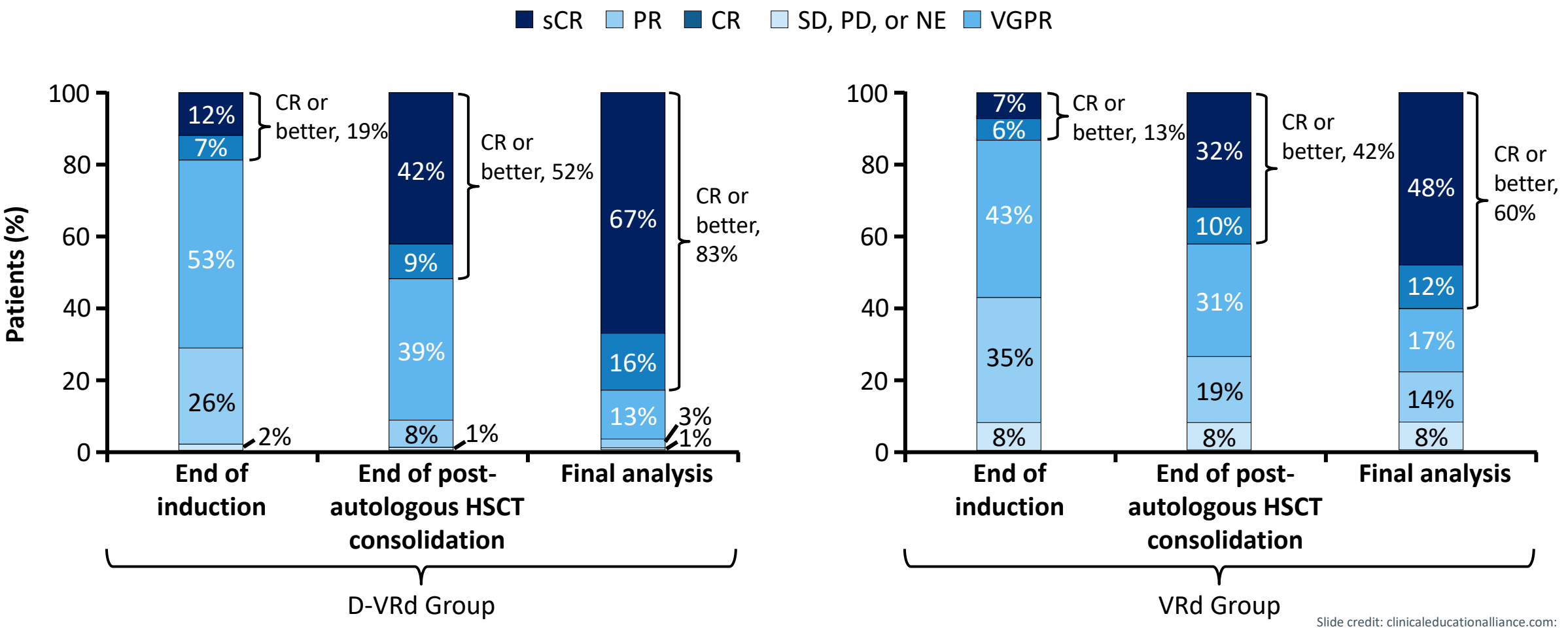


*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

- **Primary endpoint:** sCR by end of consolidation with 1-sided α = 0.1
- **Key secondary endpoints:** rates of MRD negativity, ORR, ≥ VGPR, CR, PFS, OS

NCT02874742. Voorhees. Lancet Haematol. 2023;10:e825.

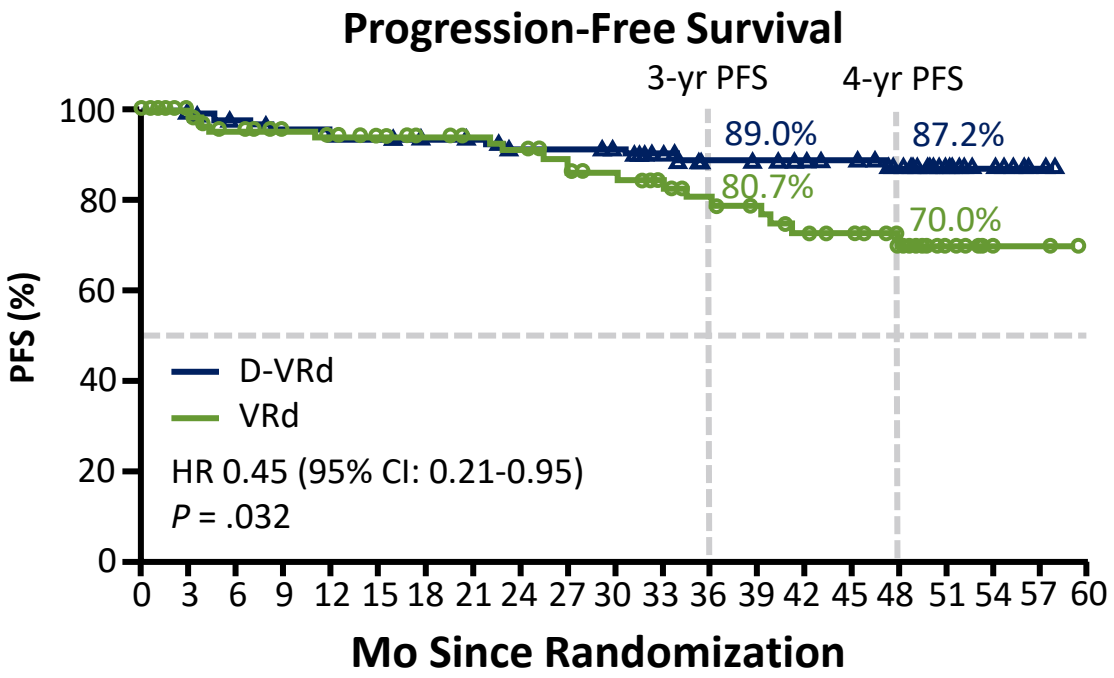
GRIFFIN: Response Rates

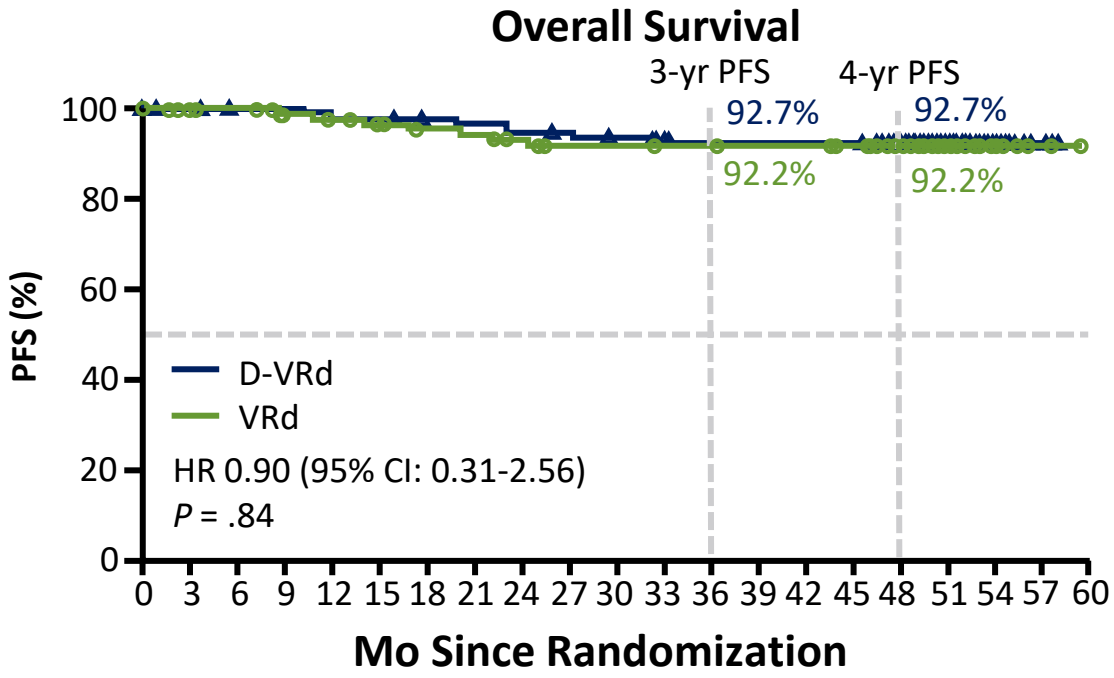


Voorhees. Lancet Haematol. 2023;10:e825.

Slide credit: clinicaleducationalliance.com:

GRIFFIN: Progression-Free and Overall Survival

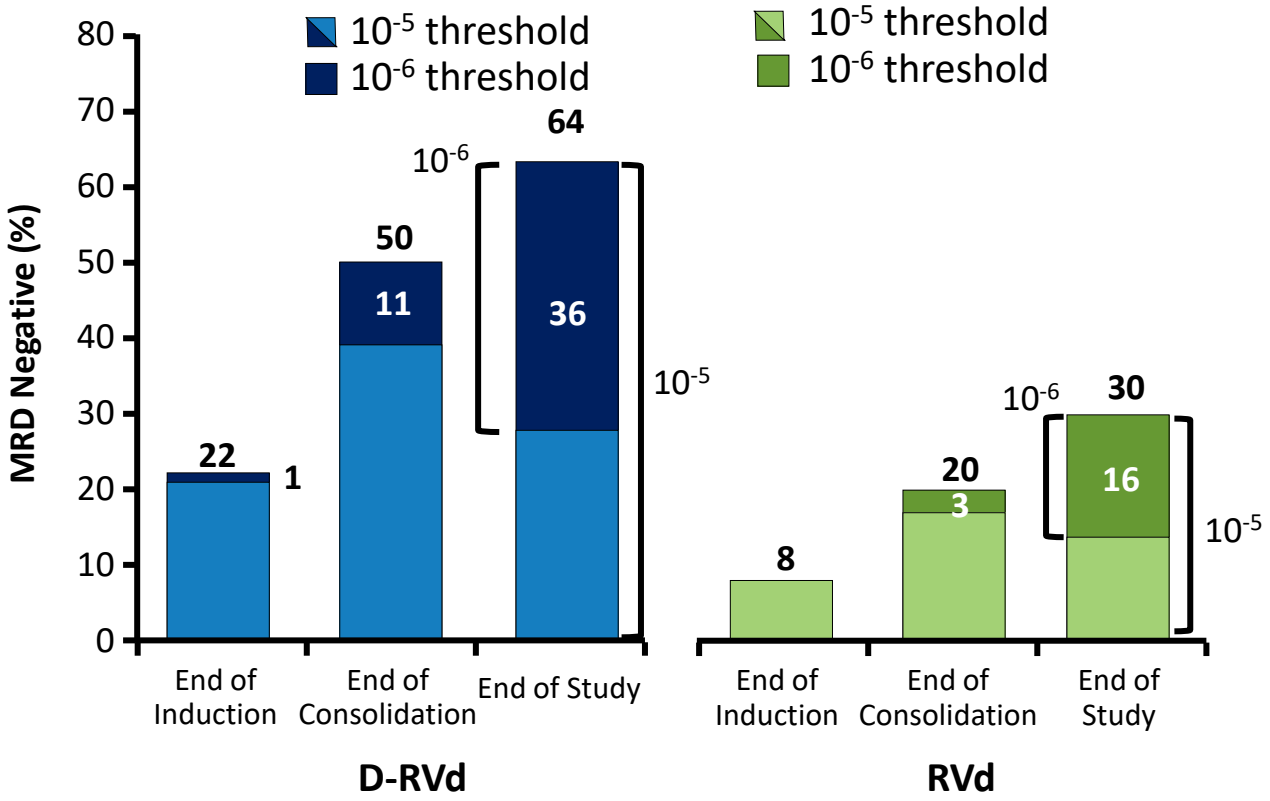




Voorhees. Lancet Haematol. 2023;10:e825.

GRIFFIN: MRD-Negativity Rates Over Time

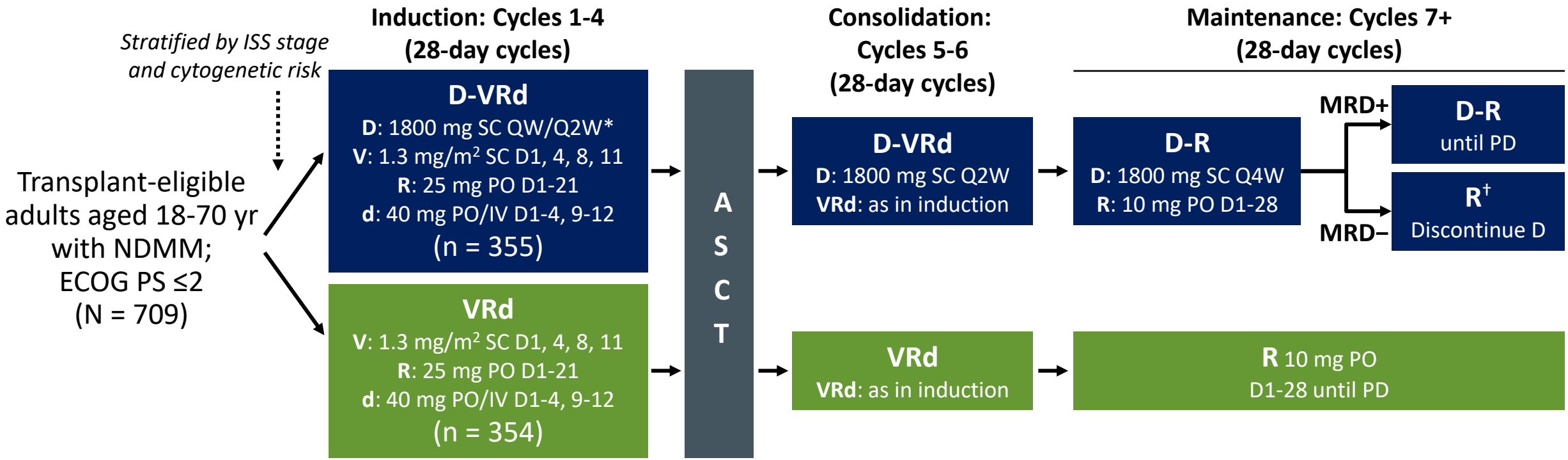
- Negative MRD rates were higher for D-RVd compared with RVd and continued to deepen and improve over time



Voorhees. Lancet Haematol. 2023;10:e825.

PERSEUS: Primary Analysis of Phase III Trial With VRd ± Daratumumab in Patients With NDMM Eligible for ASCT

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo

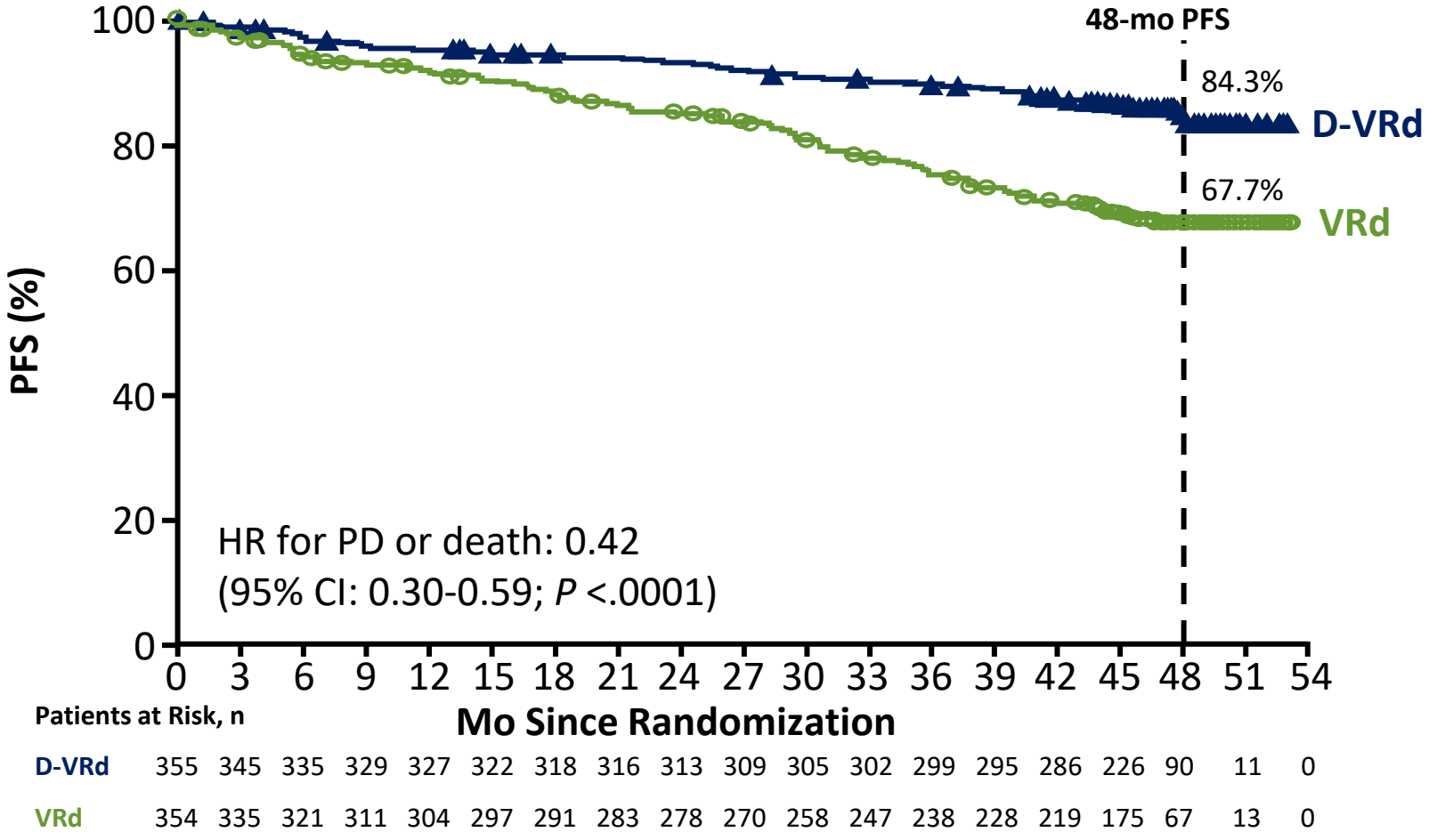


*QW during cycles 1-2, Q2W during cycles 3-4. †D discontinued after ≥24 mo in patients with ≥ CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥ CR rate, MRD negativity rate, OS

Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2024;390:301.

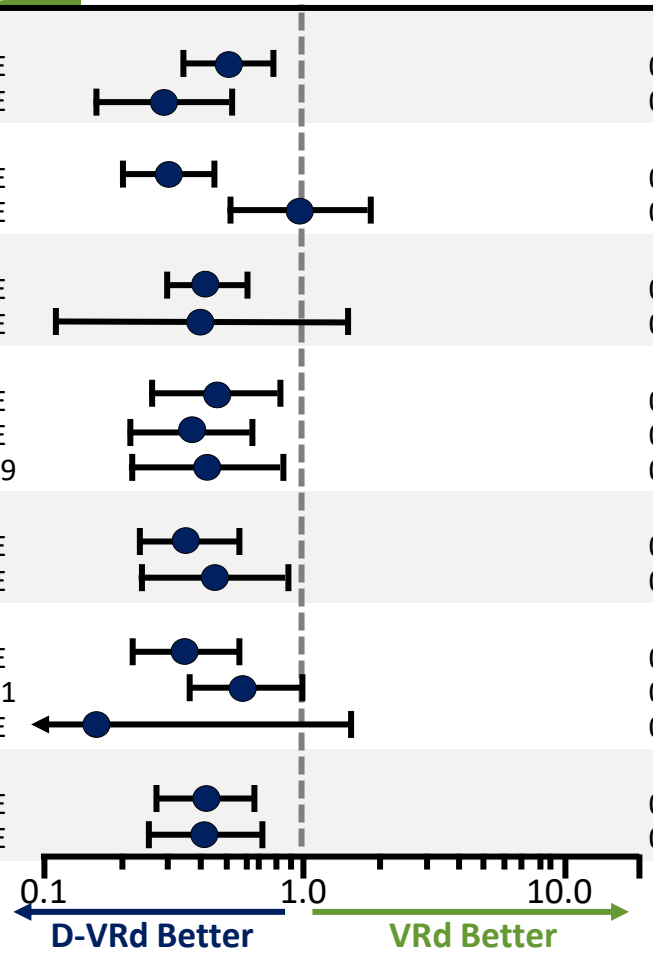
PERSEUS Primary Analysis: PFS (Primary Endpoint)



Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2024;390:301.

PERSEUS Primary Analysis: PFS Subgroup Analysis

Subgroup	PD or Death		Median PFS		Hazard Ratio for PD or Death (95% CI)
	D-VRd n/N	VRd n/N	D-VRd mo	VRd mo	
Sex					
▪ Male	36/211	61/205	NE	NE	0.51 (0.34-0.77)
▪ Female	14/144	42/149	NE	NE	0.29 (0.16-0.53)
Age					
▪ <65 yr	30/261	84/267	NE	NE	0.30 (0.20-0.46)
▪ ≥65 yr	20/94	19/87	NE	NE	0.97 (0.52-1.81)
Race					
▪ White	47/330	95/323	NE	NE	0.42 (0.30-0.60)
▪ Other	3/25	8/31	NE	NE	0.40 (0.11-1.50)
ISS disease stage					
▪ I	18/186	35/178	NE	NE	0.46 (0.26-0.81)
▪ II	19/114	43/125	NE	NE	0.37 (0.22-0.64)
▪ III	13/55	25/50	NE	41.9	0.42 (0.22-0.83)
Type of multiple myeloma					
▪ IgG	28/204	58/185	NE	NE	0.36 (0.23-0.57)
▪ Non-IgG	13/78	31/96	NE	NE	0.46 (0.24-0.88)
Cytogenetic risk					
▪ Standard	25/264	62/266	NE	NE	0.35 (0.22-0.56)
▪ High	24/76	38/78	NE	44.1	0.59 (0.36-0.99)
▪ Indeterminate	1/15	3/10	NE	NE	0.16 (0.02-1.56)
ECOG performance-status score					
▪ 0	28/211	60/230	NE	NE	0.42 (0.27-0.66)
▪ ≥1	22/134	43/124	NE	NE	0.41 (0.25-0.69)



Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2024;390:301.

Slide credit: clinicaleducationalliance.com:

PERSEUS Primary Analysis: Safety

	TEAEs,* n (%)	D-VRd (n = 351)		VRd (n = 347)	
		Any Gr	Gr 3/4	Any Gr	Gr 3/4
	Any	349 (99.4)	321 (91.5)	344 (99.1)	297 (85.6)
Hematologic	Neutropenia	243 (69.2)	218 (62.1)	204 (58.8)	177 (51.0)
Hematologic	Thrombocytopenia	170 (48.4)	102 (29.1)	119 (34.3)	60 (17.3)
Hematologic	Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Hematologic	Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
	Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
	Peripheral sensory neuropathy	188 (53.6)	15 (4.3)	179 (51.6)	14 (4.0)
	Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
	Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
	Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)

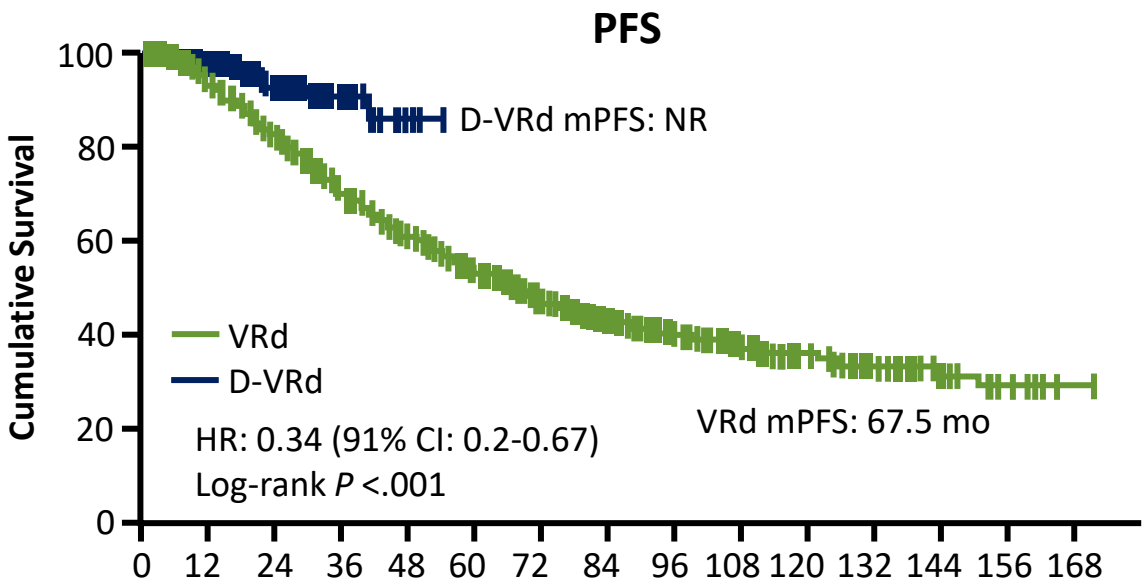
TEAEs,* n (%)	D-VRd (n = 351)		VRd (n = 347)	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infections	305 (86.9)	124 (35.3)	266 (76.7)	95 (27.4)
▪ COVID-19	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
▪ URI	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
▪ Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)

*Any grade occurring in ≥25% or grade 3/4 occurring in ≥10%

- Any grade and grade 3/4 IRRs occurred in 6% (n = 21) and 0.9% (n = 3) of patients in the D-VRd arm, respectively
- Secondary malignancies occurred in 10.5% (n = 37) of patients in the D-VRd arm and 7.2% (n = 25) in the VRd arm

Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2024;390:301.

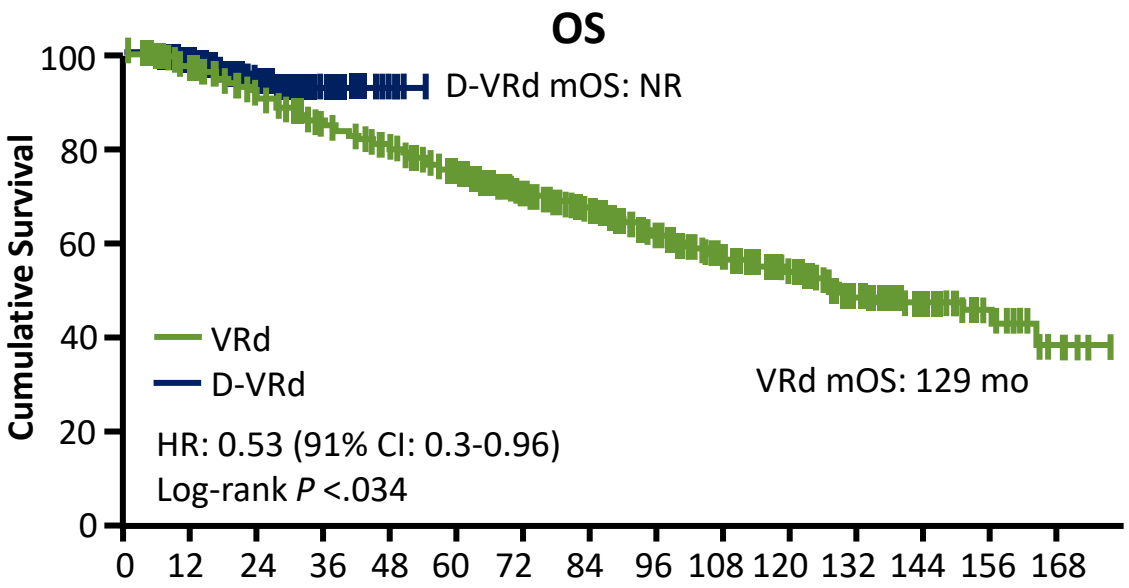
D-VRd vs VRd: Progression-Free and Overall Survival



1-yr PFS, D-VRd vs VRd: 98% vs 93%

2-yr PFS, D-VRd vs VRd: 93% vs 82%

Median follow-up D-VRd: 18 mo, VRd: 87 mo



1-yr OS, D-VRd vs VRd: 99% vs 97%

2-yr OS, D-VRd vs VRd: 94% vs 91%

Median follow-up D-VRd: 18 mo, VRd: 96 mo

Joseph. ASH 2023. Abstr 647.

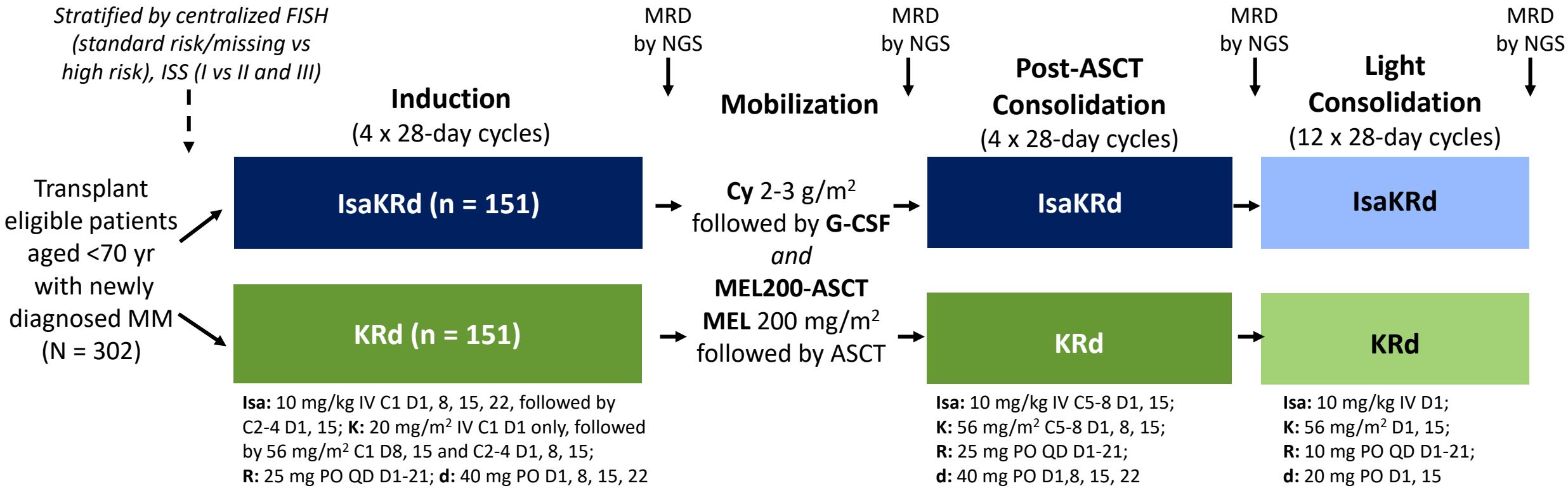
Conclusions: Newly Diagnosed, MM

- A triplet is better than a doublet in some cases
  - Addition of bortezomib to Rd backbone improved depth of response and PFS; OS benefit with bortezomib
  - Given favorable safety profile of D-Rd and availability of VRd-lite, role of doublet therapy in ASCT-ineligible MM should be restricted to the most frail patients
- Treatment choice influenced by comorbidities
  - More neuropathy with bortezomib than carfilzomib
  - More cardiovascular toxicity with carfilzomib than bortezomib
- Daratumumab and PIs have a role in MM with high-risk cytogenetics

- 4-drug therapy remains the purview of clinical trials

IsKia EMN24: Phase III Trial of IsaKRd vs KRd in Transplant-Eligible Patients With NDMM

- Open-label, randomized phase III trial



- **Primary endpoint:** MRD negativity by NGS after postASCT consolidation
- **Secondary endpoints:** MRD negativity after induction, PFS, sustained MRD negativity

Gay. ASH 2023. Abstr 4. NCT04483739.

Slide credit: clinicaleducationalliance.com:

IsKia EMN24: Baseline Characteristics

Characteristic*	IsaKRd (n = 151)	KRd (n = 151)
Median age, yr (IQR)	61 (55-66)	60 (54-63)
Female sex, n (%)	72 (48)	67 (44)
Cytogenetic risk as per IMWG, n (%)		
▪ Standard	115 (82)	113 (81)
▪ High†	25 (18)	26 (19)
▪ *Missing*	*11*	*12*
HRCA risk: 0 vs 1 vs 2+ HRCAs, n (%)‡		
▪ 0 HRCAs	78 (56)	75 (54)
▪ 1 HRCA	49 (35)	49 (35)
▪ 2+ HRCAs	13 (9)	15 (11)
▪ *Missing*	*11*	*12*

Characteristic*	IsaKRd (n = 151)	KRd (n = 151)
R-ISS, n (%)		
▪ I	50 (35)	48 (34)
▪ II	82 (58)	85 (59)
▪ III	10 (7)	10 (7)
▪ *Missing*	*9*	*8*
R2-ISS, n (%)		
▪ I	34 (24)	35 (25)
▪ II	45 (32)	47 (34)
▪ III	52 (37)	51 (37)
▪ IV	8 (6)	6 (4)
▪ *Missing*	*12*	*12*

*% calculated on number of patients whose data were available. †High risk: t(4;14), t(14;16), or del(17p). ‡del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3q23), gain (1q21) or amp(1q21).

Gay. ASH 2023. Abstr 4.

IsKia EMN24: Postconsolidation MRD Negativity (ITT) and Response

Outcome	IsaKRd (n = 151)	KRd (n = 151)	Odds Ratio	*P* Value
Postconsolidation MRD negativity by NGS, %				
▪ 10^{-5} cutoff	77	67	1.67	.049
▪ 10^{-6} cutoff	67	48	2.29	<.001
Postconsolidation response, %				
▪ ≥ VGPR	94	94	—	—
▪ ≥ CR	74	72		
▪ sCR	64	67		

- MRD negativity rates improved over time, with higher rates of 10^{-5} and 10^{-6} MRD negativity observed after each treatment phase (induction, transplantation, consolidation)
- Increase in MRD negativity rate in IsaKRd arm observed in all subgroups analyzed, including high-risk and very high-risk disease.

Gay. ASH 2023. Abstr 4.

IsKia EMN24: Safety

TRAEs, n (%)	IsaKRd (n = 151)		KRd (n = 151)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
≥1 hematologic toxicity	83 (55)	61 (40)	67 (44)	46 (30)
▪ Anemia	32 (21)	5 (3)	28 (19)	5 (3)
▪ Neutropenia	62 (41)	55 (36)*	39 (26)	33 (22)*
▪ Thrombocytopenia	51 (34)	22 (15)	38 (25)	25 (17)
≥1 nonhematologic toxicity	136 (90)	61 (41)	129 (85)	56 (37)
▪ Infections†	55 (36)	23 (15)	49 (32)	17 (11)
▪ SARS-CoV-2 infection	39 (26)	3 (2)	28 (19)	2 (1)
▪ Asthenia/fatigue	37 (25)	5 (3)	40 (26)	3 (2)
▪ Dyspnea	20 (13)	2 (1)	9 (6)	1 (<1)
▪ Rash	33 (22)	5 (3)	40 (26)	5 (3)
▪ Peripheral neuropathy	22 (15)	0 (0)	25 (17)	0 (0)
▪ Infusion-related reactions	30 (20)	5 (3)	2 (1)	0 (0)
▪ Cardiac disorders	11 (7)	1 (<1)	19 (13)	5 (3)
▪ Vascular disorders	29 (19)	7 (5)	33 (22)	15 (10)
Hypertension	5 (3)	2 (1)	6 (4)	3 (2)
Thromboembolism	12 (8)	4 (3)	16 (11)	9 (6)
▪ Gastrointestinal disorders	79 (52)	10 (7)	73 (48)	8 (5)
Nausea	36 (24)	4 (3)	31 (21)	2 (1)
Vomiting	18 (12)	2 (1)	12 (8)	1 (<1)
Diarrhea	41 (27)	6 (4)	37 (25)	5 (3)

*P = .008. †Excluding COVID-19.

Gay. ASH 2023. Abstr 4.

Selecting Treatment for MM: General Principles

Patient	Disease	Treatment
▪ Age/frailty ▪ Performance status ▪ Lifestyle ▪ Patient preference ▪ Caregiver support ▪ Comorbidities – Renal status – Neuropathy – Cardiac – Diabetes – Cytopenias	▪ Disease burden: ISS – Rate of progression – Marrow burden – CRAB symptoms – Extramedullary disease ▪ Biology – LDH – Cytogenetics: • t(4;14) • del(17p) • t(14;16) • amp(1q) • t(11;14)	▪ Toxicity – Myelosuppression – Infections – Neuropathy – Secondary cancers – Ocular toxicity ▪ Cost ▪ Administration route ▪ Relapsed vs refractory ▪ Depth/duration of response to any prior treatment

Holstein SA. Oncology (Williston Park). 2022;36:430. NCCN. clinical practice guidelines in oncology: multiple myeloma v3.2024.

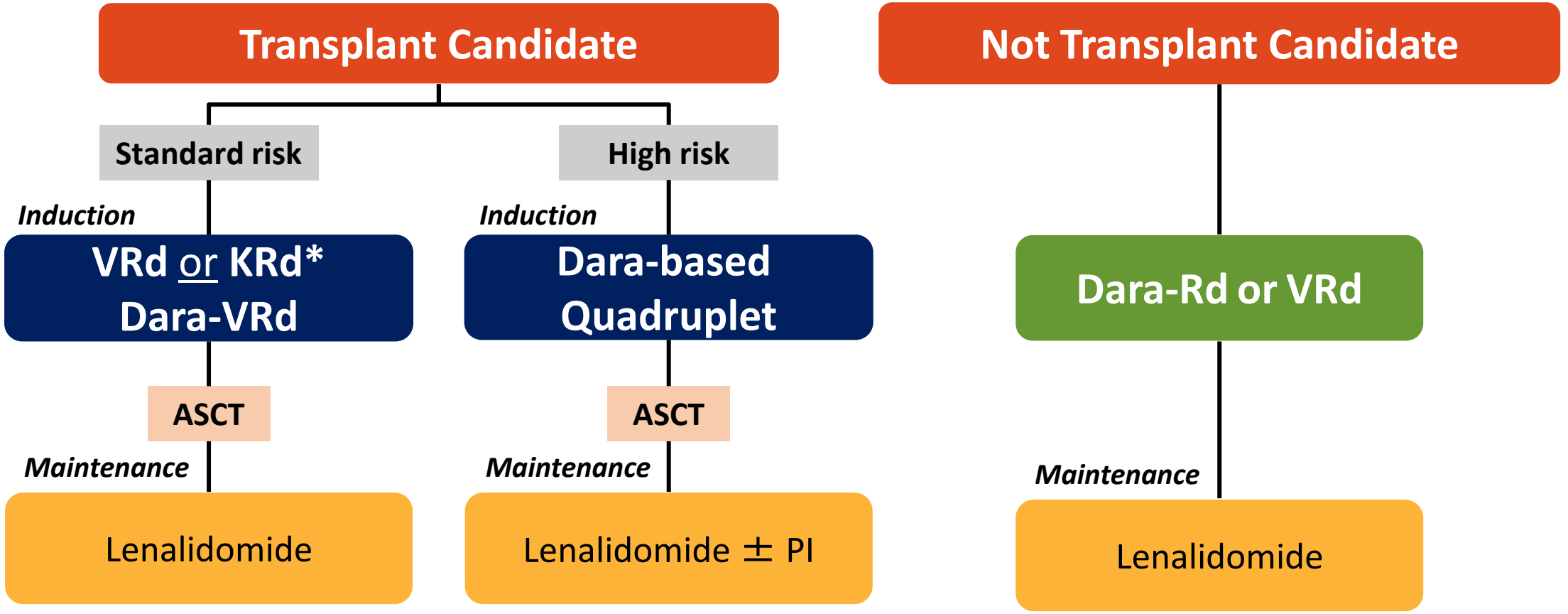
Factors to Consider When Determining Transplant Eligibility

- Age
- Comorbidities
  - Hypertension, ischemic heart disease, diabetes
  - Renal insufficiency
  - Osteoporosis
  - Psychological issues
- Frailty
- Altered drug metabolism
- Limited social support
- Limited independence/mobility

Derudas. Hematol Rep. 2020;12:8956.

Transplant-Ineligible Patients

Proposed Treatment Algorithm for Newly Diagnosed Multiple Myeloma



*Ixazomib may be substituted for carfilzomib in select patients.

Adapted from NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. v.2.2024. nccn.org.

Slide credit: clinicaleducationalliance.com:

Treatment Considerations for ASCT-Ineligible Patients

Patient Population	Considerations
Fit patients	Use standard 3-drug regimens with available dose reductions to improve tolerability (Dara-Rd, VRd-lite)
Frail, unfit patients	Consider starting with doublet therapy (Rd, Vd) and adding third agent if tolerable Geriatric assessment
Renal dysfunction	Lenalidomide dose adjusted based on CrCl
Cardiac dysfunction	Avoid carfilzomib Use thromboprophylaxis with lenalidomide-based therapy
Peripheral neuropathy	Administer bortezomib SC and use weekly dosing Consider induction with IRd

Consider risk of thromboembolic events, infection, bone health, and disease monitoring throughout

Derudas. Hematol Rep. 2020;12:8956. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.1.2024. nccn.org.

Combination Therapy in Patients With Newly Diagnosed Transplant-Ineligible Multiple Myeloma

Outcome	SWOG S0777[1]	VRd-lite[2]	MAIA[3]	CLARION[4]	TOURMALINE-MM2[5]
Study regimen	VRd vs Rd (n = 264*)	VRd lite† (n = 50)	DRd vs Rd (n = 368)	KMP vs VMP (n = 955)	IRd vs Rd (n = 351)
Study phase	III	II	III	III	III
Study population	69% intent to transplant	100% ineligible for transplant	100% ineligible for high-dose CT and transplant	100% ineligible for transplant	100% ineligible for transplant
Median f/u, mo	84	61	64.5	~22‡	53.3§
ORR, %	90.2 vs 78.8	86	92.9 vs 81.6	84.3 vs 78.8	82.1 vs 79.7
Median PFS, mo	41 vs 29 (*P* = .003)	41.9	61.9 vs 34.4 (*P* <.0001)	22.3 vs 22.1	35.3 vs 21.8 (*P* = .073)
Median OS, mo	NR vs 69 (*P* = .0114)	NR	NR vs 65.5 (*P* = .0003)	NR vs NR	NR vs NR (HR: 0.998)

*Efficacy analysis, n = 235; response analysis, n = 215. †V: 1.3 mg/m^2 SC QW, R: 15 mg PO on Days 1-21, d: 20 mg PO on Days 1, 2, 8, 9, 15, 16, 22, 23 (9 cycles) followed by consolidation (6 cycles) for 35-day cycles. ‡For OS assessment, ~27 mo. §For OS assessment, ~58 mo.

1. Durie. Blood Cancer J. 2020;10:53. 2. O'Donnell. ASH 2019. Abstr 3178. 3. Kumar. ASH 2022. Abstr 4559. 4. Facon. Blood. 2019;133:1953. 5. Facon. Blood. 2021;137:3616.

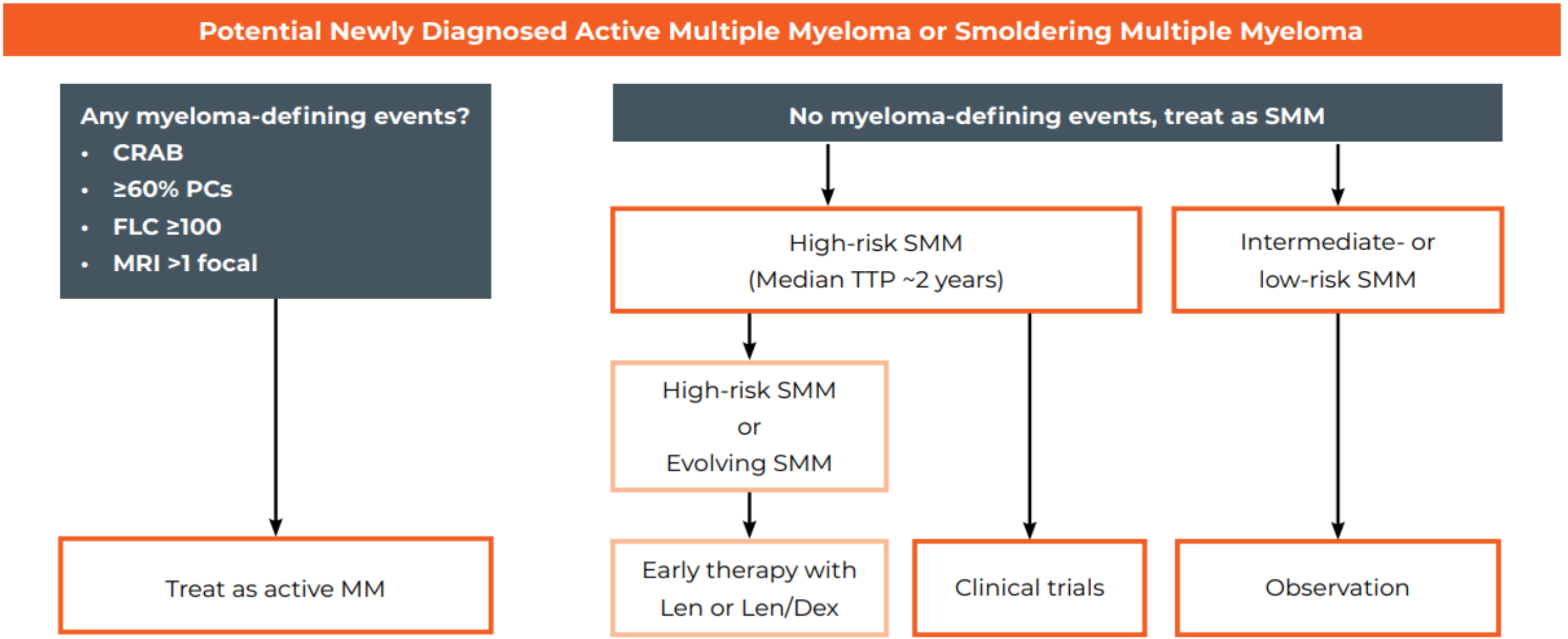
Moving CAR T-Cell Therapy and Bispecific Antibodies to Earlier Therapy Lines

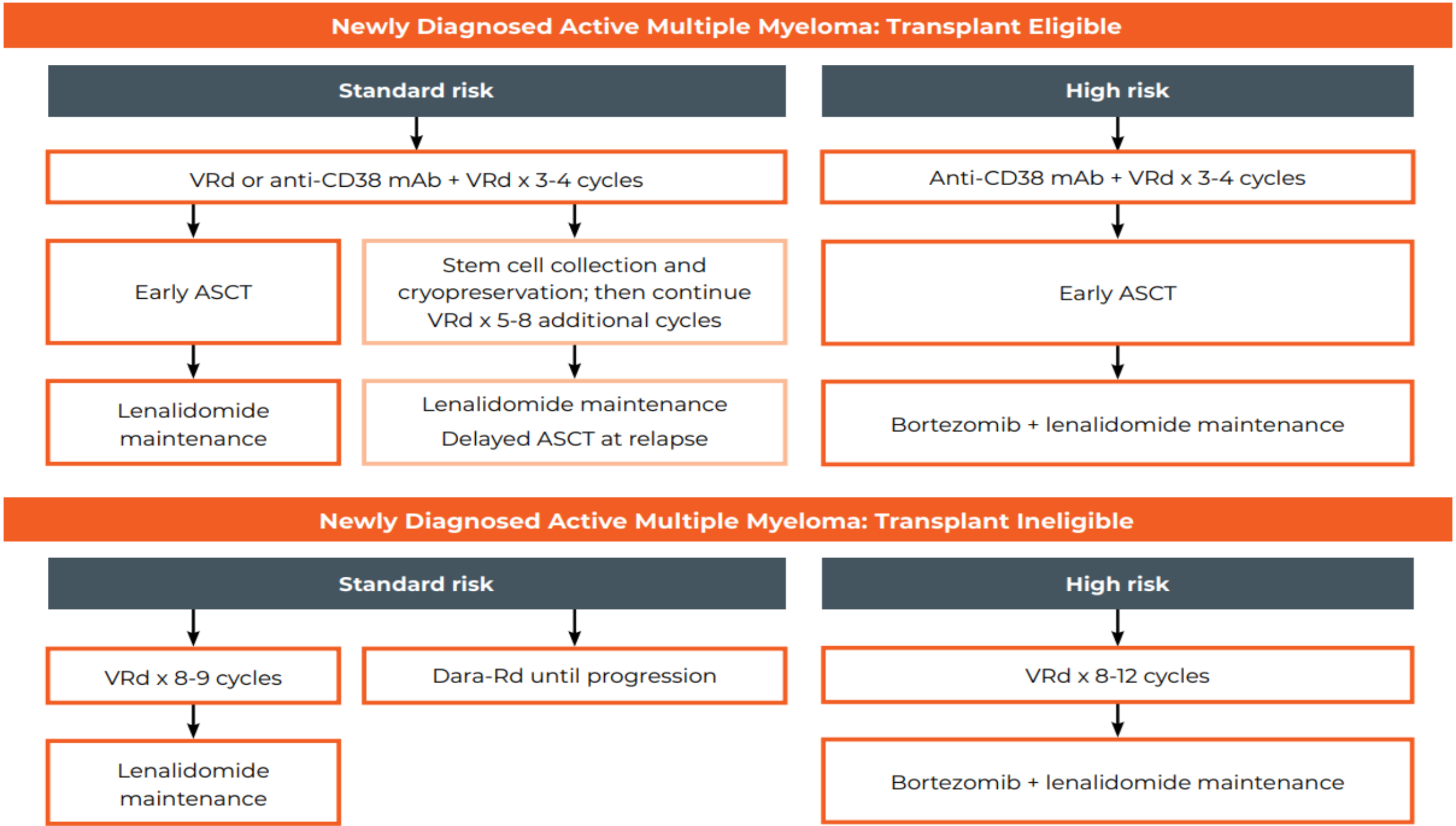
Trial	Phase	Population	Regimen	Estimated Primary Completion*
CARTITUDE-5 (NCT04923893)	III	NDMM, ASCT not planned	VRd → Cilta-cel vs VRd → Rd	June 2026
CARTITUDE-6 (NCT05257083)	III	NDMM	Dara-VRd → Cilta-cel vs Dara-VRd → ASCT	June 2033
KarMMa-4 (NCT04196491)	I	High-risk NDMM	Ide-cel → R maintenance	June 2023 (Actual)
MajesTEC-4 (NCT05243797)	III	NDMM, transplant eligible	Induction → ASCT → Teclistamab + R or Teclistamab vs R	April 2028
MajesTEC-7 (NCT05552222)	III	NDMM, ASCT ineligible or not planned	Teclistamab + Dara-R vs Talquetamab + Dara-R vs Dara-Rd	April 2031
MagnetisMM-6 (NCT05623020)	III	NDMM, transplant ineligible	Elranatamab + Dara-R vs Dara-Rd	March 2028
MagnetismMM-7 (NCT05317416)	III	NDMM, MRD positive post ASCT	ASCT → Elranatmab vs ASCT → R	August 2027

*As of April 17, 2024.

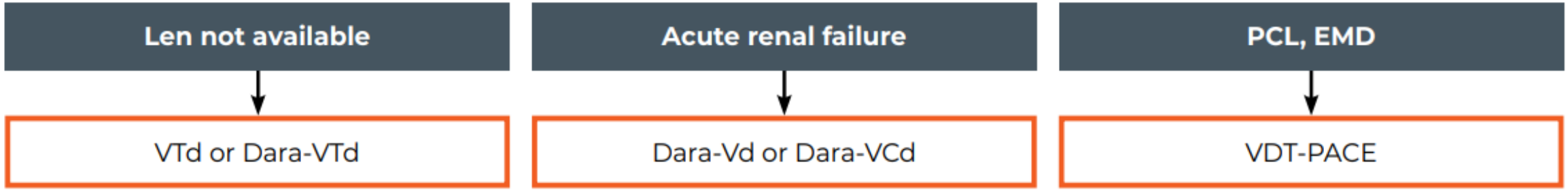
ClinicalTrials.gov.

16th Annual CCO/IMF Hematology Symposium:
2024 Myeloma Treatment Algorithm

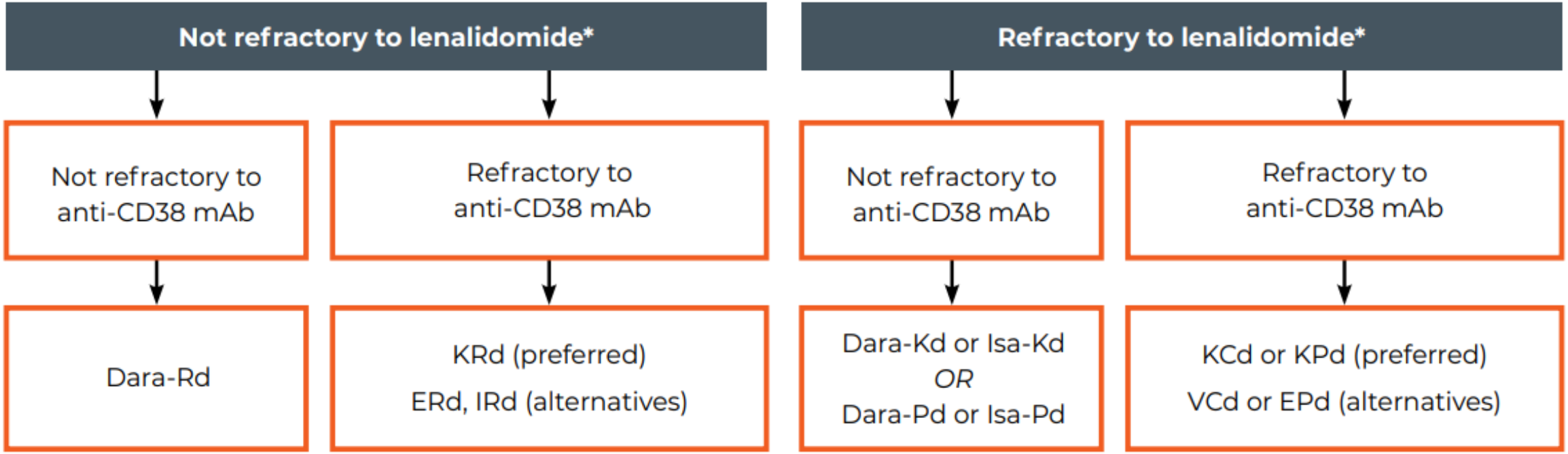



Newly Diagnosed Active Multiple Myeloma: Transplant Eligible
Standard risk
VRd or anti-CD38 mAb + VRd x 3-4 cycles
Early ASCT
Lenalidomide maintenance
Stem cell collection and cryopreservation; then continue VRd x 5-8 additional cycles
Lenalidomide maintenance
Delayed ASCT at relapse
High risk
Anti-CD38 mAb + VRd x 3-4 cycles
Early ASCT
Bortezomib + lenalidomide maintenance
Newly Diagnosed Active Multiple Myeloma: Transplant Ineligible
Standard risk
VRd x 8-9 cycles
Lenalidomide maintenance
Dara-Rd until progression
High risk
VRd x 8-12 cycles
Bortezomib + lenalidomide maintenance

Newly Diagnosed Active Multiple Myeloma: Special Settings



Multiple Myeloma at First Relapse



*Consider salvage ASCT in patients eligible for ASCT who have not had transplant before; consider second ASCT if eligible and had >36-month response duration with maintenance to first ASCT.

Adverse Event Management and Supportive Care for NDMM

Slide credit: clinicaleducationalliance.com:

Select Adverse Events and Prophylaxis by Drug Class

Proteasome Inhibitors	Immunomodulatory Agents	Anti-CD38 Monoclonal Antibodies	Corticosteroids
▪ Herpes zoster prophylaxis ▪ Peripheral neuropathy (bortezomib) ▪ Monitor/manage cardiac conditions carefully (carfilzomib) ▪ Thromboprophylaxis (carfilzomib)	▪ Prophylactic anticoagulation – 81-mg aspirin for patients with no risk factors – Warfarin or LMWH for higher-risk individuals – Possible role for DOACs ▪ 2 birth control methods required ▪ Cytopenias	▪ Premedicate with corticosteroids, antipyretics, antihistamines, and H2 antagonist (for isatuximab) ▪ Herpes zoster prophylaxis ▪ Consider *Pneumocystis jiroveci* pneumonia prophylaxis per institutional practice ▪ Interference with blood typing and response monitoring ▪ Evaluate hepatitis B viral serologies at baseline	▪ Hyperglycemia ▪ Fatigue ▪ Hyperactivity ▪ Infection risk ▪ Muscle wasting

Kurtin. J Adv Pract Oncol. 2013;4:307. Raje. J Natl Compr Canc Netw. 2014;12:502. NCCN. Multiple Myeloma. v.3.2024. myeloma.org/dexamethasone-side-effects. Daratumumab PI. isatuximab PI.

Myelosuppression With MM Treatments

- Myeloma and some treatment regimens associated with myelosuppression, including thrombocytopenia, anemia, and neutropenia
  - Increased risk of infection
  - Potential for decreased QoL and treatment interruption
- Dose modification guidelines available in prescribing information
- Growth factor support may be considered

Brigle. Clin J Oncol Nurs. 2017;21 (5 suppl):60.

Managing Infections With MM Treatments

- Myelosuppression with MM treatments increase the risk of infections
- Increase risk of
  - Viral infection with PIs and monoclonal antibodies
  - Fungal infection with high-dose steroids
- Patient education emphasizing importance of alerting treating clinicians of potential infection can reduce unnecessary antibiotics

Infection

- Stay current on vaccinations, including COVID-19, annual influenza, and pneumococcal vaccines
- VZV or HSV prophylaxis when receiving PIs, mAbs
- PJP prophylaxis if using high-dose dexamethasone
- Antibacterial and antifungal prophylaxis while neutropenic
- Consider IVIG for recurrent, life-threatening infections; use only when warranted

Brigle. Clin J Oncol Nurs. 2017;21 (5 suppl):60. Kambhampati. Blood Adv. 2022;6:2045. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2024. nccn.org. Raje. J Natl Compr Canc Netw. 2014;12:502.

Thrombotic Events With MM Treatments

- Thrombotic events are a concern for patients who are receiving IMiDs, and they may also occur with carfilzomib treatment
- Educate patients on preventive strategies and early detection
- Risk factors include older age, history of thrombotic event, BMI ≥30 kg/m^2, prior central venous catheter or pacemaker, immobilization, CV/renal disease, diabetes, trauma, blood clotting disorders, hyperviscosity, acute infection.

Thromboprophylaxis Recommendations

- Low risk (<2 risk factors): 81-325 mg aspirin
- High risk (≥2 risk factors) *or* IMiD + high-dose dexamethasone: LMWH or **therapeutic** warfarin (target INR 2-3)
- Possible role for DOACs

Delforge. Blood. 2017;129:2359. Noonan. Clin J Oncol Nurs. 2017;21 (5 suppl):37.
NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.1.2024. nccn.org.

IMiDs: Drug Interactions and Teratogenicity

- **Drug interactions**
  - Drugs that affect kidney function
  - Drugs that may increase the risk of thrombosis
    - Erythropoietic agents
    - Estrogen-containing therapies

- **Teratogenicity**
  - Drug available only through REMS program
  - Ensure compliance with REMS program requirements
    - Pregnancy testing
    - Contraception requirements
      - Females with childbearing potential: 2 methods of contraception
      - Males: use of condom during sexual intercourse; must not donate sperm
    - Participation in telephone surveys
    - Must not donate blood or blood products

Lenalidomide PI.

Maintaining Bone Health in Patients With MM

- All patients should receive bisphosphonates or denosumab
- Bisphosphonates: pamidronate and zoledronic acid
  - Greater risk for ONJ with zoledronic acid
  - Monitor for renal impairment on bisphosphonates
- SC denosumab preferred when renal disease is present
- Baseline dental exam and ONJ monitoring while using bone-modifying therapy

Raje. J Natl Compr Canc Netw. 2014;12:502. Bernstein. Cells. 2022;11:2308.

Selected Patient Resources

- General Myeloma/Cancer Resources
  - American Cancer Society
  - CANCERcare
  - International Myeloma Foundation
  - Leukemia and Lymphoma Society
  - LIVESTRONG
  - MedLine Plus
  - MMRF

- Financial Assistance
  - CancerCare Copayment Assistance Foundation
  - Cancer Financial Assistance Coalition
  - Center for Medicare and Medicaid Services
  - HealthWell Foundation
  - Pharmaceutical manufacturer websites
  - Rx Assist
- Psychological/Social
  - Association of Oncology Social Work
  - Cancer Hope Network
  - Cancer.net
  - Cancer Support Community

myeloma.org/cancer-organizations-resources.

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