



Memorial Sloan Kettering
Cancer Center

Managing Newly Diagnosed Multiple Myeloma in 2023

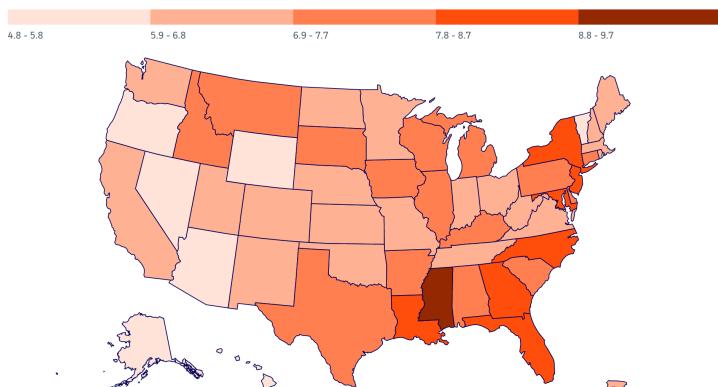
Saad Z. Usmani, MD MBA FACP
Chief of Myeloma Service



Multiple Myeloma: A Systemic Plasma Cell Malignancy

- Estimated new cases and deaths in 2022 in the United States¹
 - New cases: 34,470
 - Deaths: 12,640
- Percentage of patients surviving 5 years: 57.9%¹
- Median age at diagnosis: 69 years²
- MM is most common in men and Black adults²

Incidence rates, 2015-2019
by state, for myeloma



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CancerStatisticsCenter.cancer.org

1. <https://seer.cancer.gov/statfacts/html/mulmy.html> 2. Myeloma at a glance. American Cancer Society Cancer Statistics Center. American Cancer Society website. https://cancerstatisticscenter.cancer.org/?_ga=2.47184933.325832967.1600196335-611855784.1581698489#!/cancer-site/Myeloma.



Staging and Cytogenetic Risk-Assessment

Stage ¹	R-ISS ¹
I	Serum albumin $\geq 3.5 \text{ g/dL}^{-1}$ Serum $\beta2\text{M} < 3.5 \text{ mg/L}^{-1}$ No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum $\beta2\text{M} > 5.5 \text{ mg/L}^{-1}$ High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH

Risk ²	Features
Standard	Trisomies t(11;14) t(6;14)
High	t(4;14) t(14;16) t(14;20) Del(17p) <i>p53</i> mutation Gain/Amp 1q High plasma cell S-phase GEP high-risk signatures Circulating Plasma Cells Elevated LDH/EMD
Ultra-High Risk	2 or more features

Stage ¹	R2-ISS ³
I	0 Points (Low Risk, 19% pts)
II	0.5-1 Points (Low-Intermediate Risk, 31% pts)
III	1.5-2.5 Points (Intermediate-High Risk, 41% pts)
IV	3-5 Points (High Risk, 9 % pts)

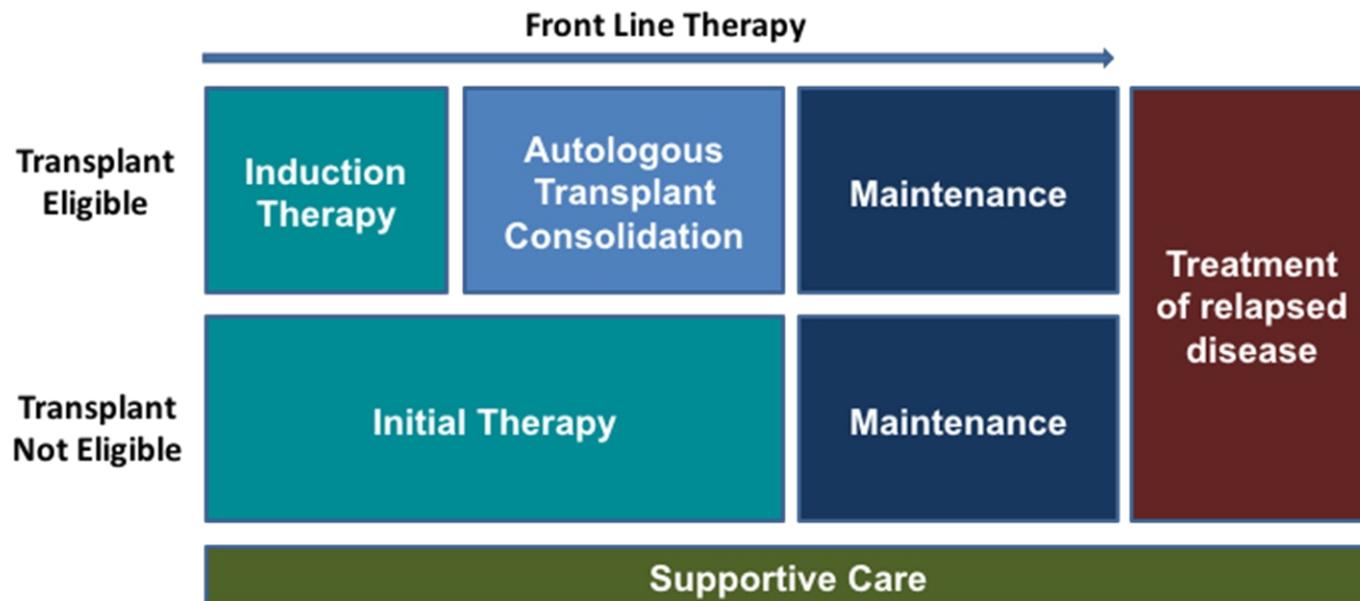
POINTS: ISS III= 1.5, ISS-II = 1, Del17p =1, elevated LDH =1, Chromosome 1q21+ = 0.5

High-Risk Consensus Definition for Trials ⁴
<ul style="list-style-type: none"> • R-ISS III • R-ISS II with 1q21+, Del17p, t(14;16), t(14;20) • Circulating PCs $\geq 5\%$ • Extramedullary disease

1. Palumbo A, et al. *J Clin Oncol.* 2015;33:2863-2869; 2. Costa LJ, Usmani SZ. *J Natl Compr Canc Netw.* 2020;18(12):1730-1737;
2. D'Agostino et al. *J Clin Oncol* 2022 ;40(29):3406-3418; 4; Davies F et al. *Blood Cancer Discovery* 2022

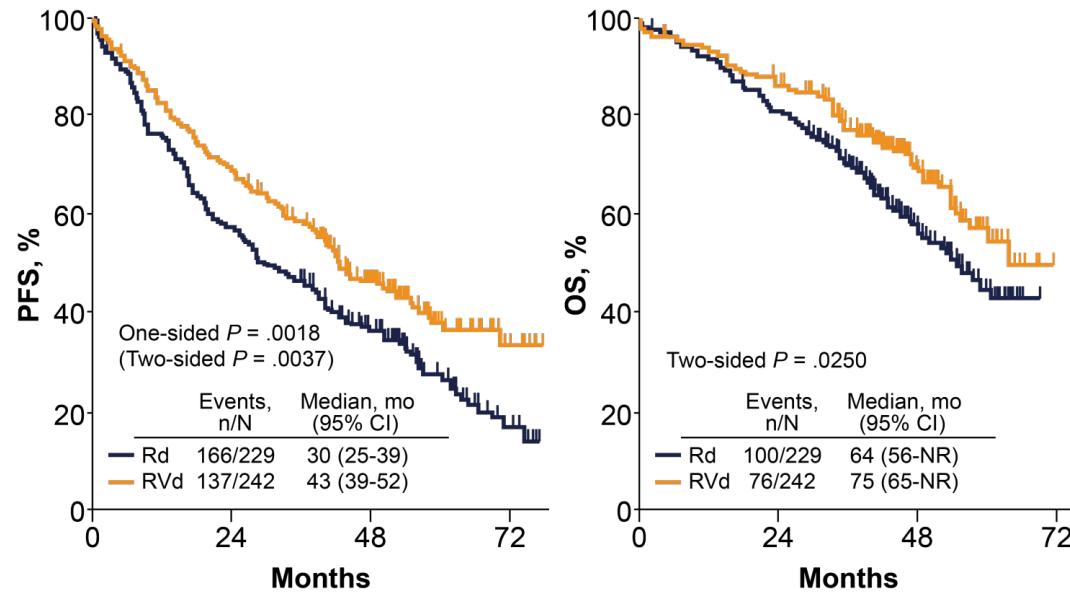


Treatment Paradigm For Newly Diagnosed Multiple Myeloma





SWOG So777: RVd Versus Rd in Patients Without Immediate Intent for ASCT¹

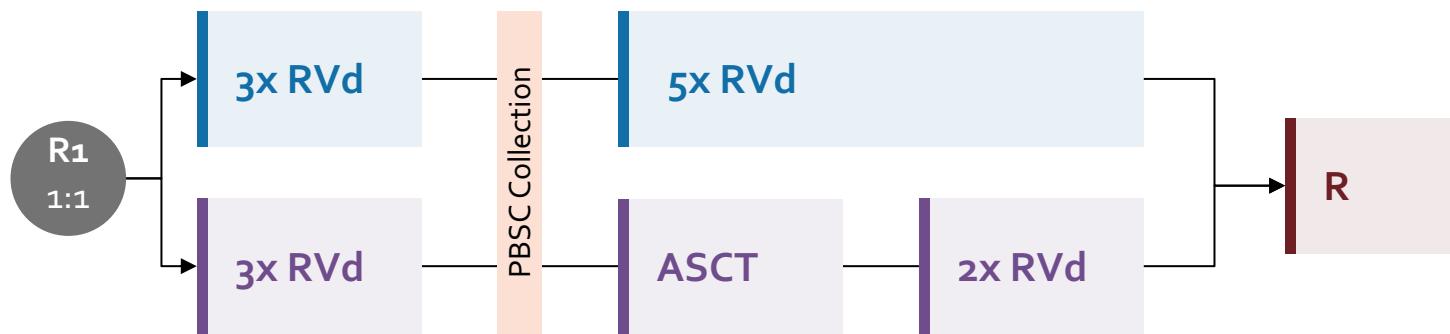


Initial Therapy

RVd for eight 21-d cycles vs Rd for six 28-d cycles in patients not intending to proceed to upfront transplant, followed by Rd in both arms (N = 525)



IFM 2009 Study: Early vs Late ASCT



RVd 21-day Cycles
R: 25 mg d 1–14
V: 1.3 mg/m² d 1, 4, 8, 11
d: 20 mg d 1, 2, 4, 5, 8, 9, 11, 12

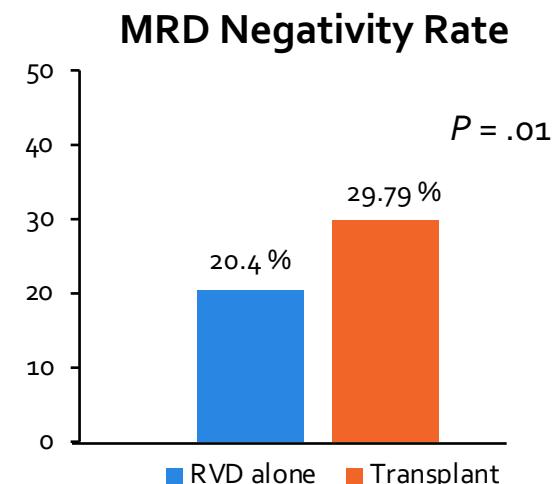
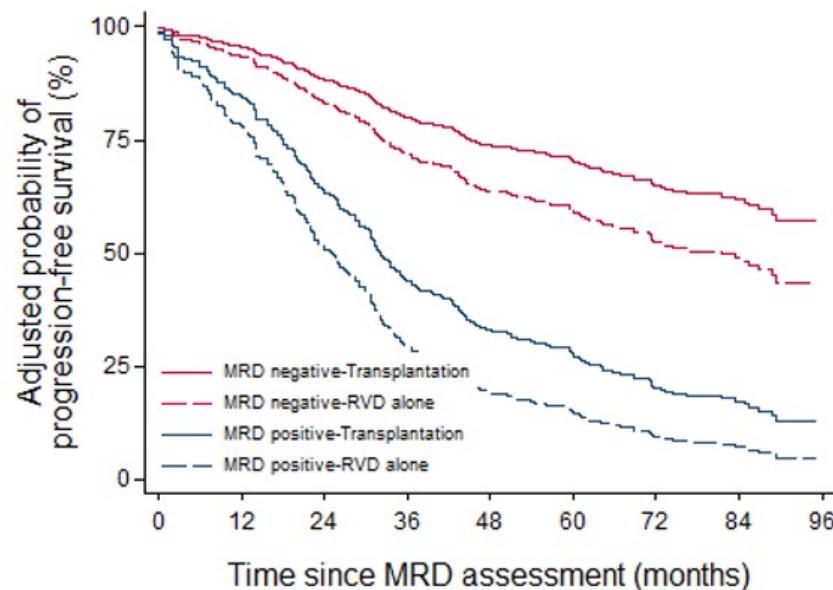
R Maintenance
R: 10–15 mg/d for 13 cycles

Primary endpoint: PFS
Secondary endpoints:
ORR, MRD, TTP, OS, safety

Attal M, et al. N Engl J Med. 2017;376:1311-1320.



Superior PFS With ASCT vs RVd Alone



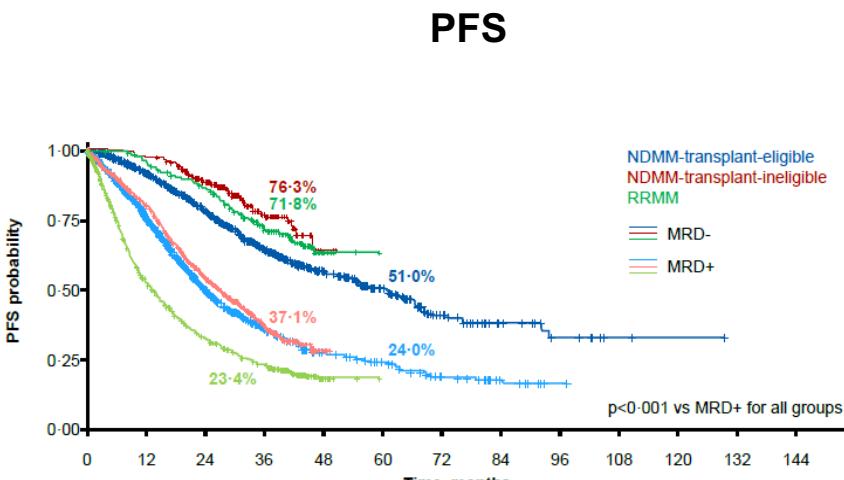
RVd + transplant was superior to RVd alone, even with undetectable MRD at 10^{-6}

MRD, minimal residual disease.

Perrot A. Presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020; Abstract 143.

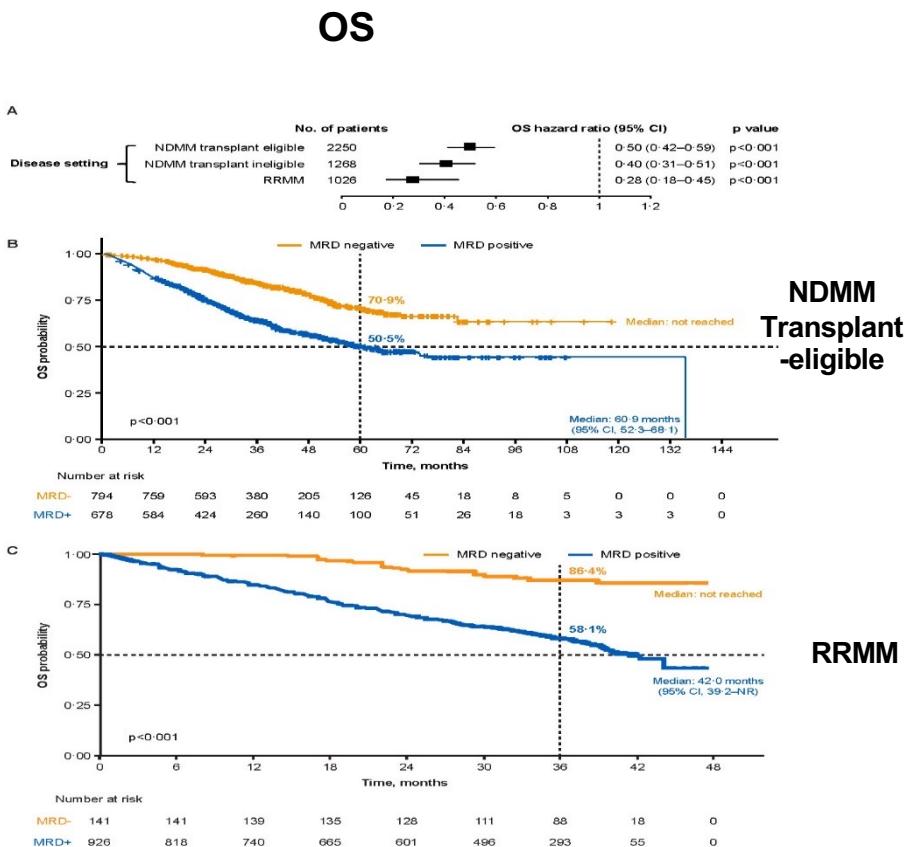


MRD Negativity and Survival Outcomes



Number at risk

MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0
MRD-	291	283	217	93	4	0							
MRD+	1328	983	516	133	5	0							
MRD-	164	155	135	97	10	0							
MRD+	960	456	269	179	11	0							

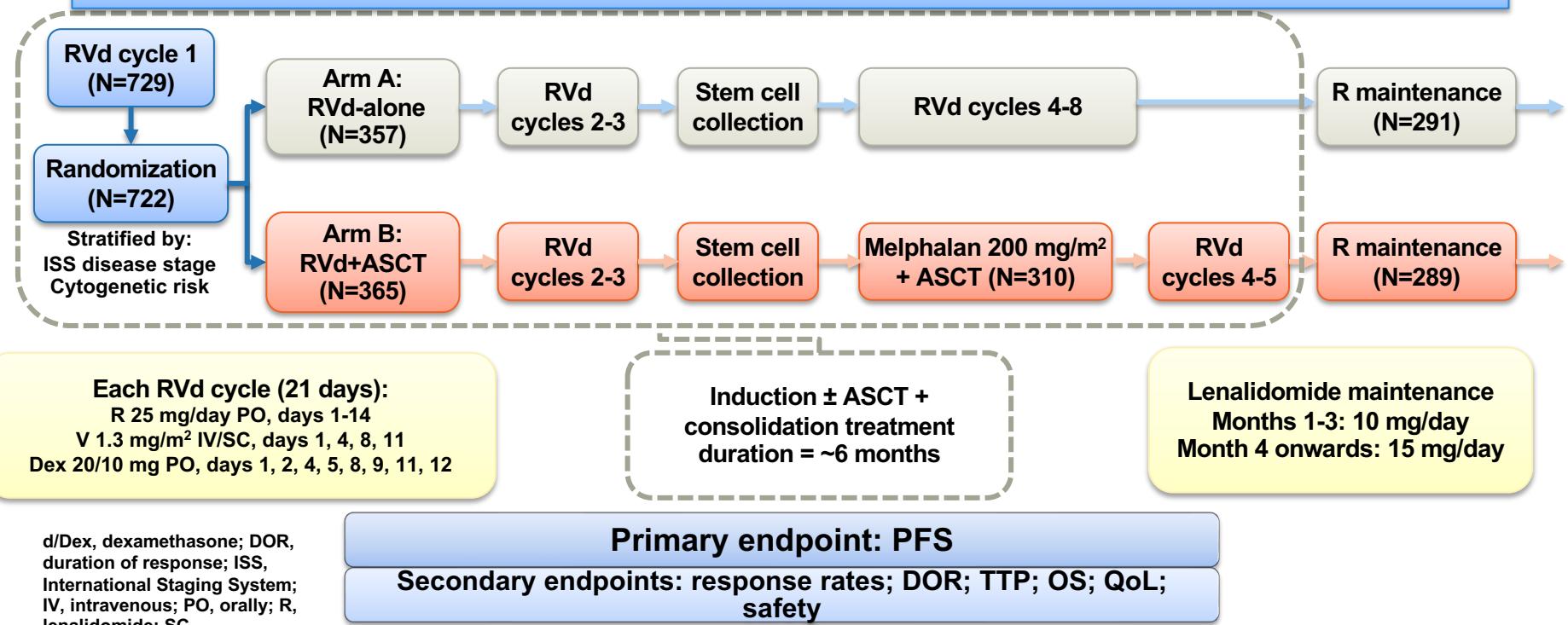


Munshi et al., Blood Adv 2020; 4: 5988-99.



DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy

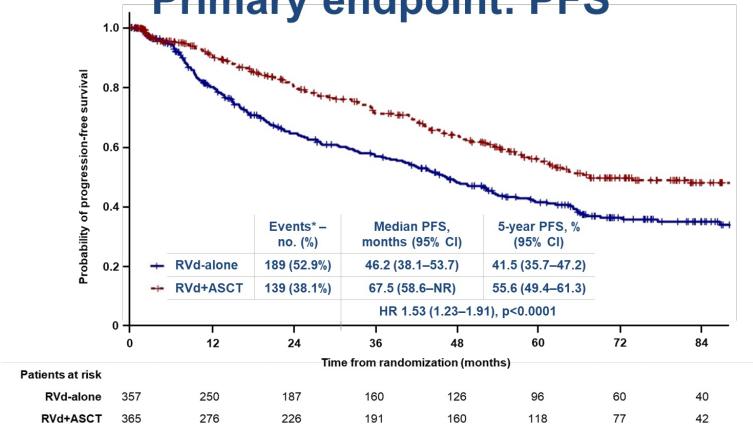


d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

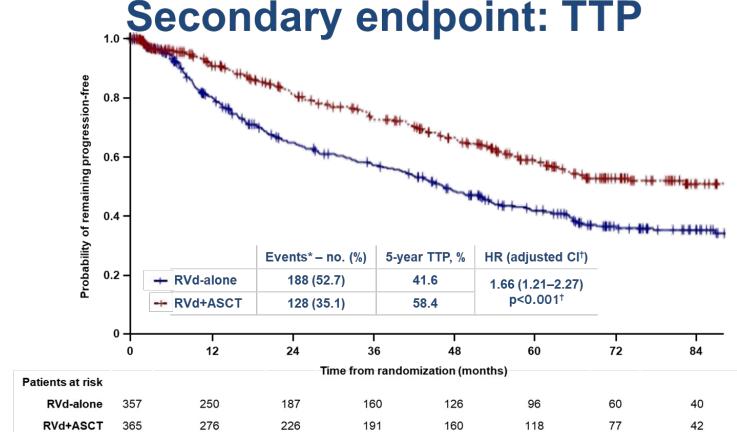


DETERMINATION: Endpoint Readouts (Median follow-up 70 months)

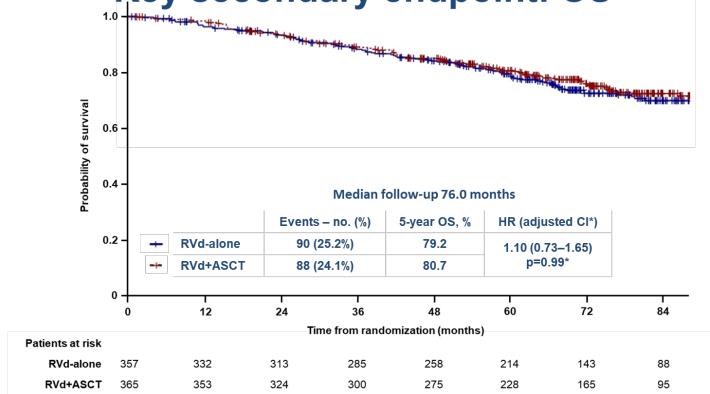
Primary endpoint: PFS



Secondary endpoint: TTP



Key secondary endpoint: OS



Second primary malignancies

5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):

- All : 9.7% vs 10.8%
- Invasive: 4.9% vs 6.5%
- Hematologic: 1.59% vs 3.52%

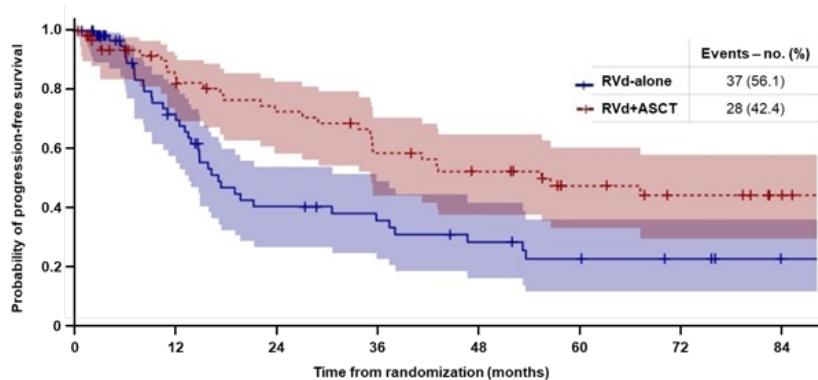
At time of data cutoff, among patients on the RVd-alone and RVd+ASCT arms who had hematologic SPMs, respectively:

- 6/7 vs 2/3 patients with ALL alive
- 6/10 patients with AML/MDS alive
- 1/2 patients with CLL/CML alive
- Overall, 7/9 RVd-alone vs 8/13 RVd+ASCT alive

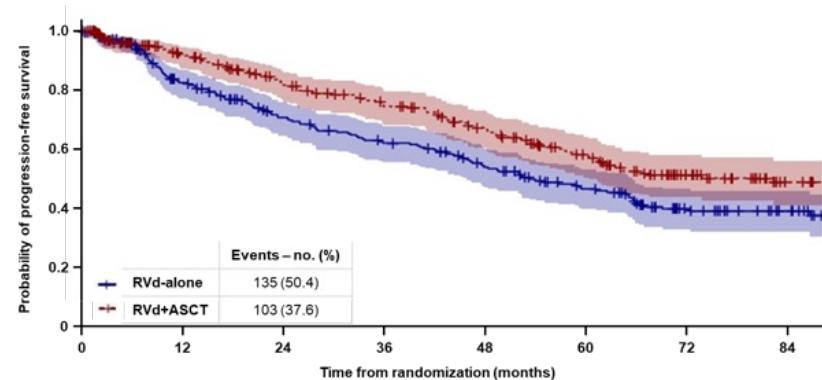
SPMs	RVd-alone (N=357)	RVd+ASCT (N=365)
Any, %	10.4	10.7
Any invasive SPM, %	5.3	6.8
Any hematologic SPM, %	2.5	3.6
ALL, n	7	3
AML/MDS, n	0	10
CLL/CML, n	2	0
Any solid tumor SPM, %	3.4	3.3
Any non-invasive solid tumor SPM, %	0	0.5
Any non-melanoma skin cancer, %	5.9	4.1



DETERMINATION Trial: PFS by Risk



Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	



Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

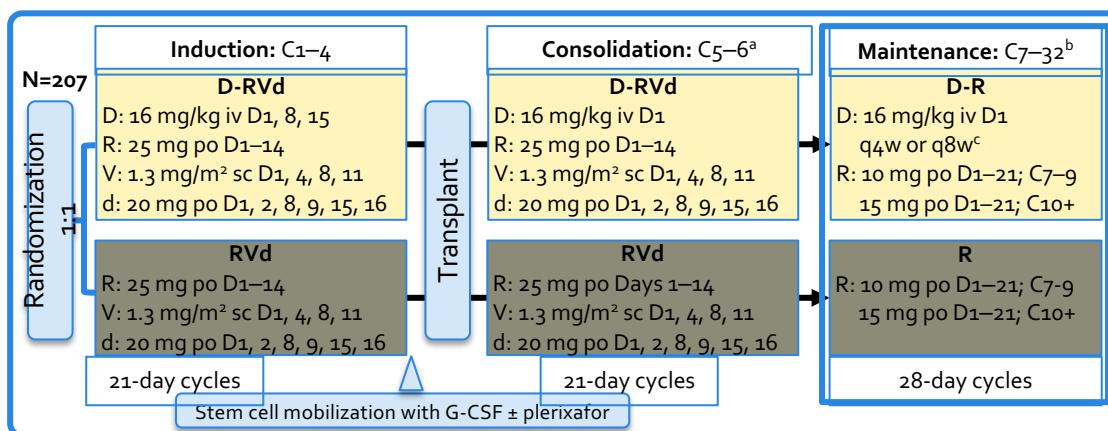
Richardson PG, et al. N Engl J Med. 2022 Jun 5. doi: 10.1056/NEJMoa2204925



GRiffin: Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Eligible NDMM – 24 Months of Maintenance

Study design

Key eligibility criteria: TE NDMM; 18–70 years; ECOG PS 0–2; CrCl ≥30 mL/min²



- Primary endpoint:** sCR by end of consolidation
- Secondary endpoints:** MRD negativity (NGS 10⁵), ORR, ≥VGPR, CR, PFS, OS

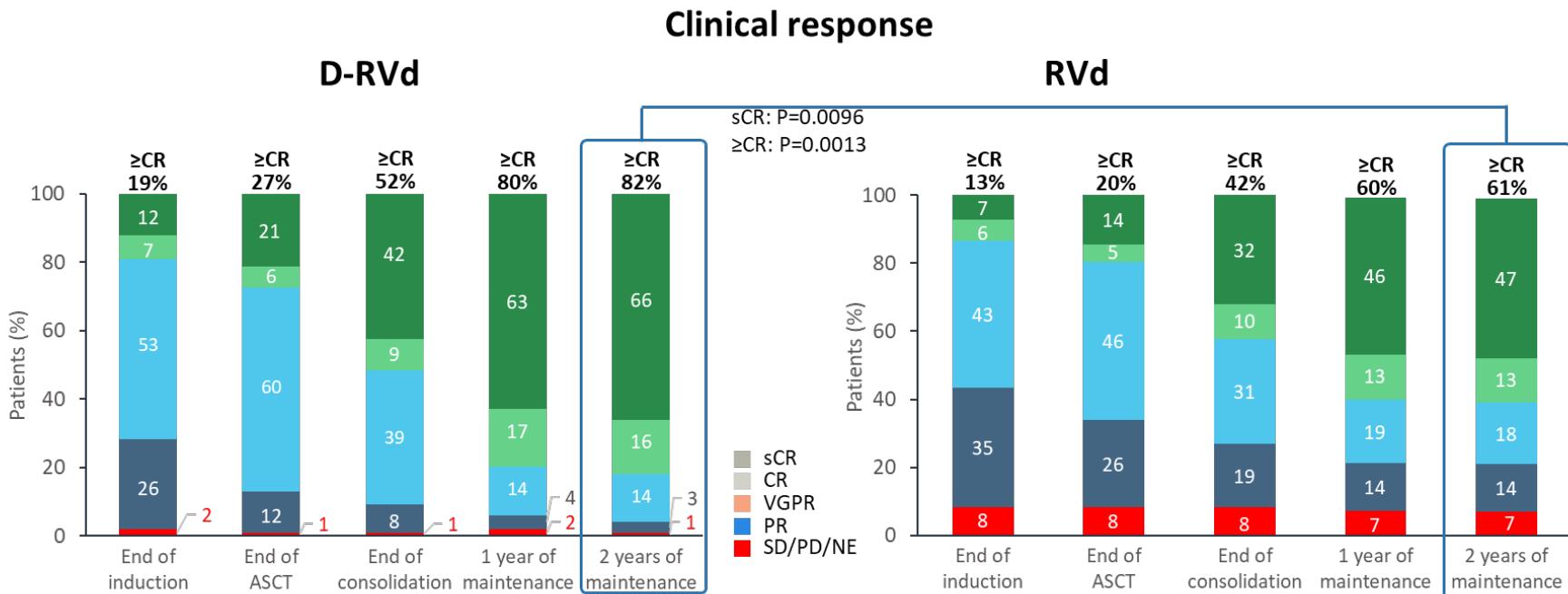
Patient disposition

n (%)	D-RVd (n=104)	RVd (n=103)
Treated with maintenance therapy	90 (87)	70 (68)
Completed maintenance therapy	67 (64)	44 (43)
Discontinued treatment during maintenance therapy	21 (20)	21 (20)
Adverse event	8 (8)	7 (7)
Progressive disease	3 (3)	7 (7)
Patient withdrawal	2 (2)	4 (4)
Lost to follow-up	2 (2)	0
Death	1 (1)	1 (1)
Other	5 (5)	2 (2)

^aConsolidation initiated 60–100 days post transplant; ^bPatients who complete maintenance cycles 7–32 may continue single-agent lenalidomide thereafter; ^cProtocol amendment allowed q4w dosing option. Phase 2 trial – patient enrollment between December 2016 and April 2018



GRiffin: Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Eligible NDMM – 24 Months of Maintenance

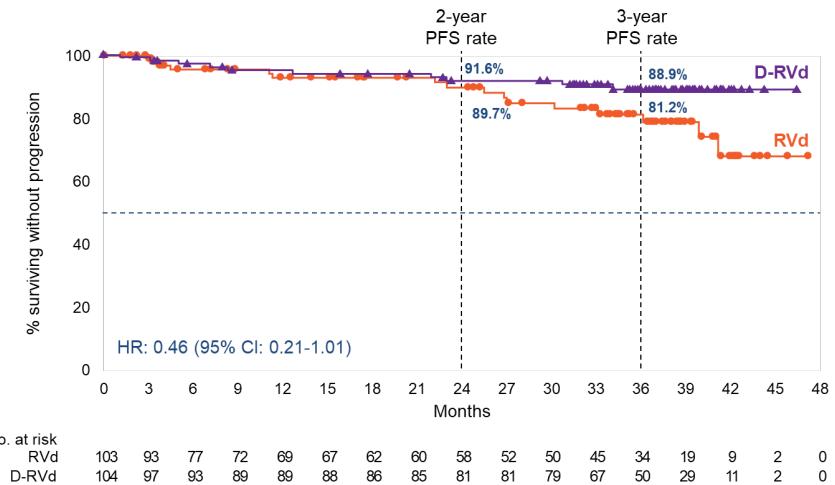
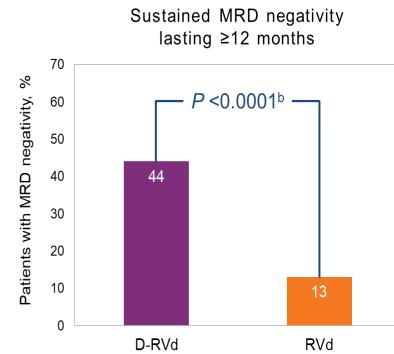
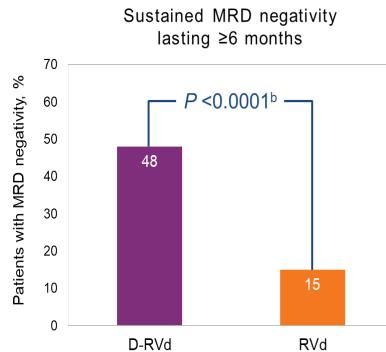


Laubach JP, et al. ASH 2021, Virtual Meeting. Abstract 79



GRiffin Update: MRD and PFS Data

- D-RVd Improved Rates of Durable MRD Negativity^a (10^{-5}) Lasting ≥ 6 Months or ≥ 12 Months Versus RVd



- Median follow-up: 38.6 months
- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR versus RVd/R
- The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy

^aThe threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status was based on BM aspirates by NGS per IMWG.

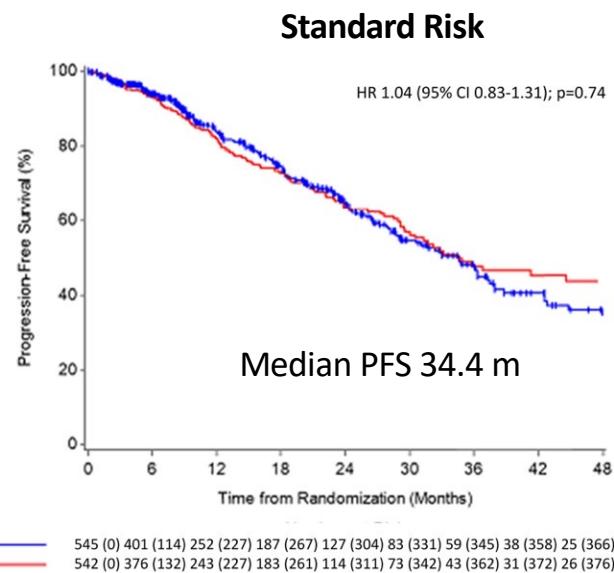
^bP values calculated by Fisher's exact test

Laubach et al. ASH 2021. Abstract 79.

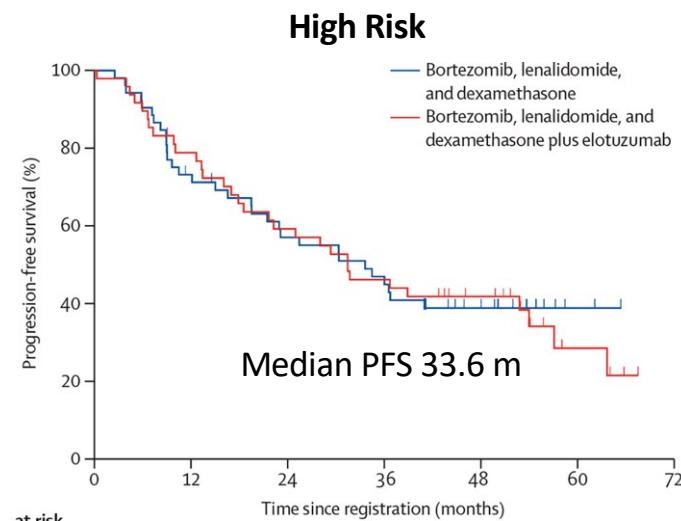


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Impact of PI/IMiD Maintenance in High-Risk MM



ENDURANCE: VRd or KRd with len maintenance
Kumar S et al Lancet Oncol 2021

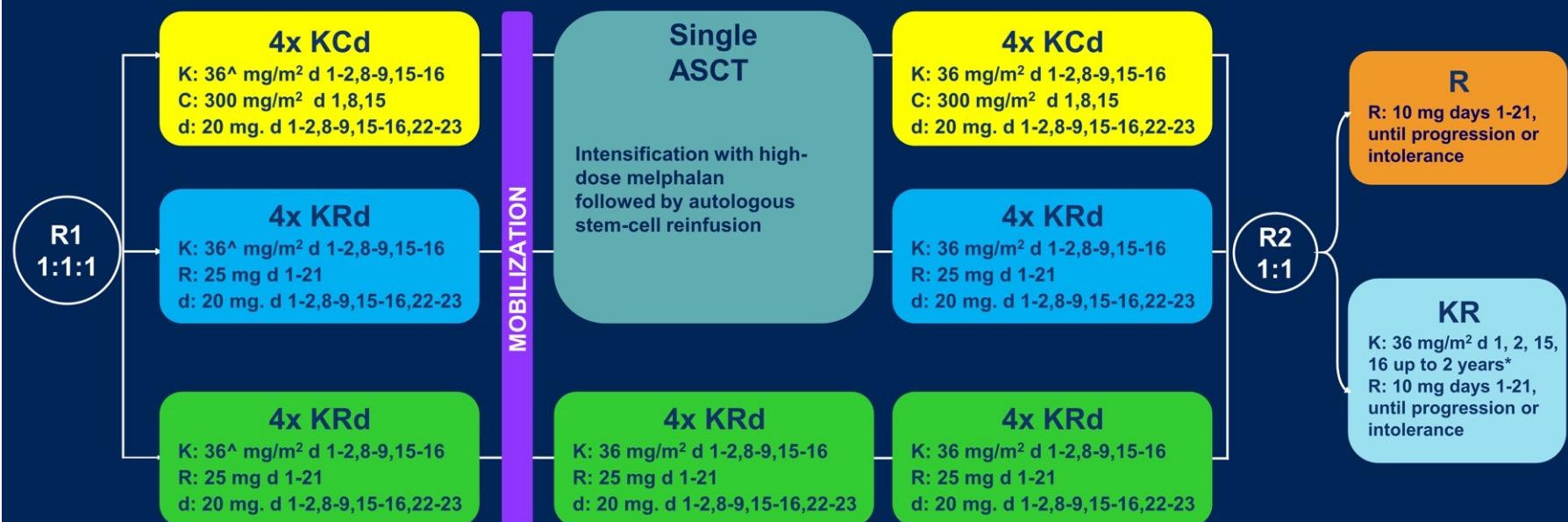


S1211: Elo VRd or VRd with VR maintenance
Usmani SZ et al Lancet Haematol 2021



Trial design

474 NDMM patients, transplant-eligible and younger than 65 years



[^]20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

NDMM, newly diagnosed multiple myeloma; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd.

Presented By:
Francesca Gay

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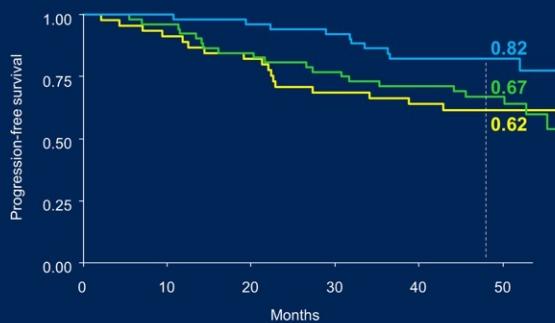


Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

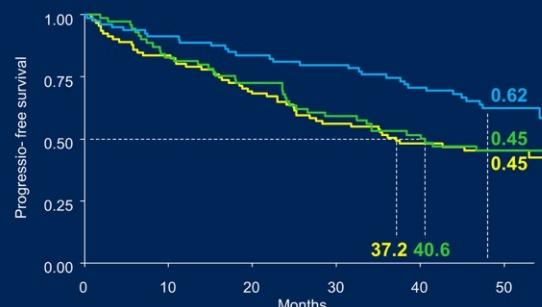
Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk
(N=153)



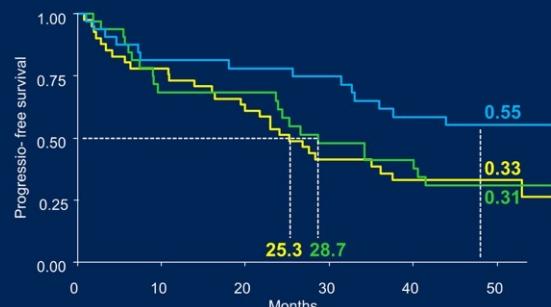
KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04
KRd_ASCT vs. KRd12: HR 0.46, p=0.04
KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

High risk
(N=243)



KRd_ASCT vs. KCd_ASCT: HR 0.57, p=0.01
KRd_ASCT vs. KRd12: HR 0.6, p=0.04
KRd12 vs. KCd_ASCT: HR 0.95, p=0.8

Double hit
(N=105)



KRd_ASCT vs. KCd_ASCT: HR 0.49, p=0.03
KRd_ASCT vs. KRd12: HR 0.53, p=0.07
KRd12 vs. KCd_ASCT: HR 0.91, p=0.75

Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; IQR, interquartile range.

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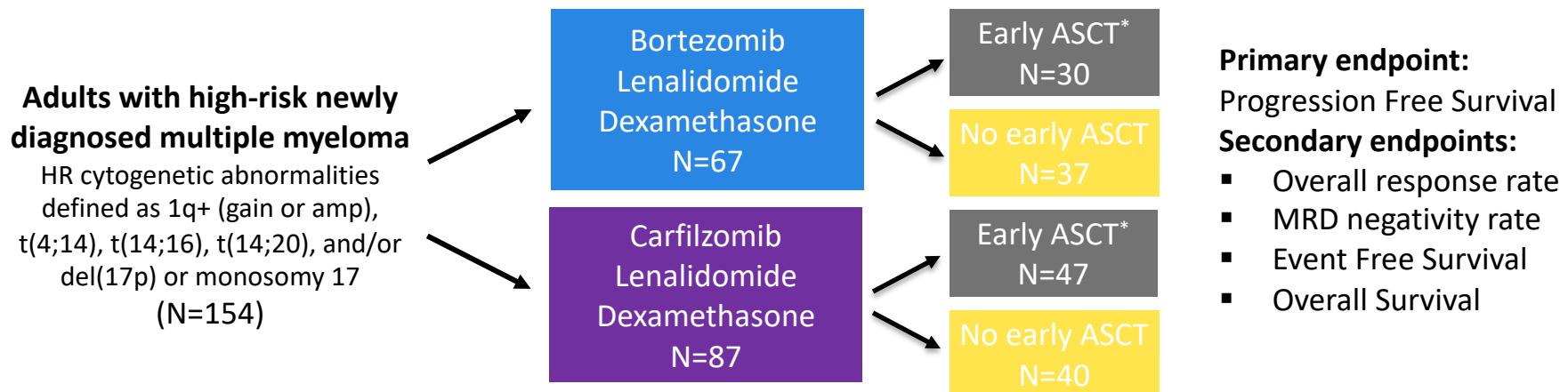
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Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Bortezomib, Lenalidomide, and Dexamethasone (VRd) as Induction Therapy in Newly Diagnosed HR-NDMM

- We conducted a retrospective chart review study with 154 consecutive HR-NDMM patients treated with KRd and VRd at Memorial Sloan Kettering Cancer Center.
- Time period: January 1, 2015 to December 31, 2019
- Date of last follow-up: Sept. 30, 2022



*Early ASCT: ASCT within 12 months of start of induction therapy without progressive disease
HR: high risk; NDMM: newly diagnosed multiple myeloma; VRd: Bortezomib, lenalidomide, dexamethasone; KRd: Carfilzomib, lenalidomide, dexamethasone; ASCT: Autologous stem cell transplant

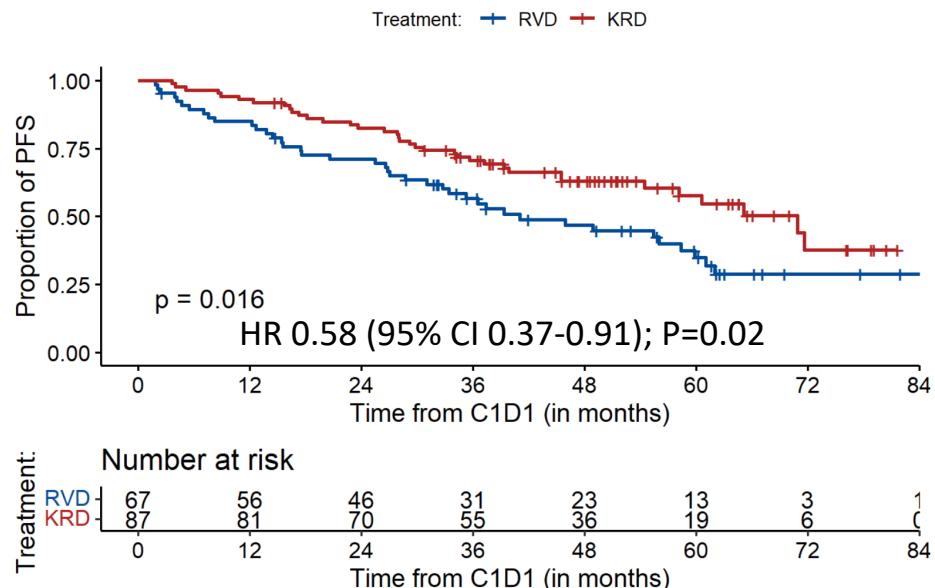
Primary endpoint:
Progression Free Survival
Secondary endpoints:

- Overall response rate
- MRD negativity rate
- Event Free Survival
- Overall Survival

Tan C et al, ASH 2022



Progression Free Survival



Median f/u for all patients: 55.8 mos (95%CI 50.9-62.6)

Median f/u VRd 61.7 mos (95%CI 53-67.1)

Median f/u K Rd 51.6 mos (95%CI 49.1-63.5)

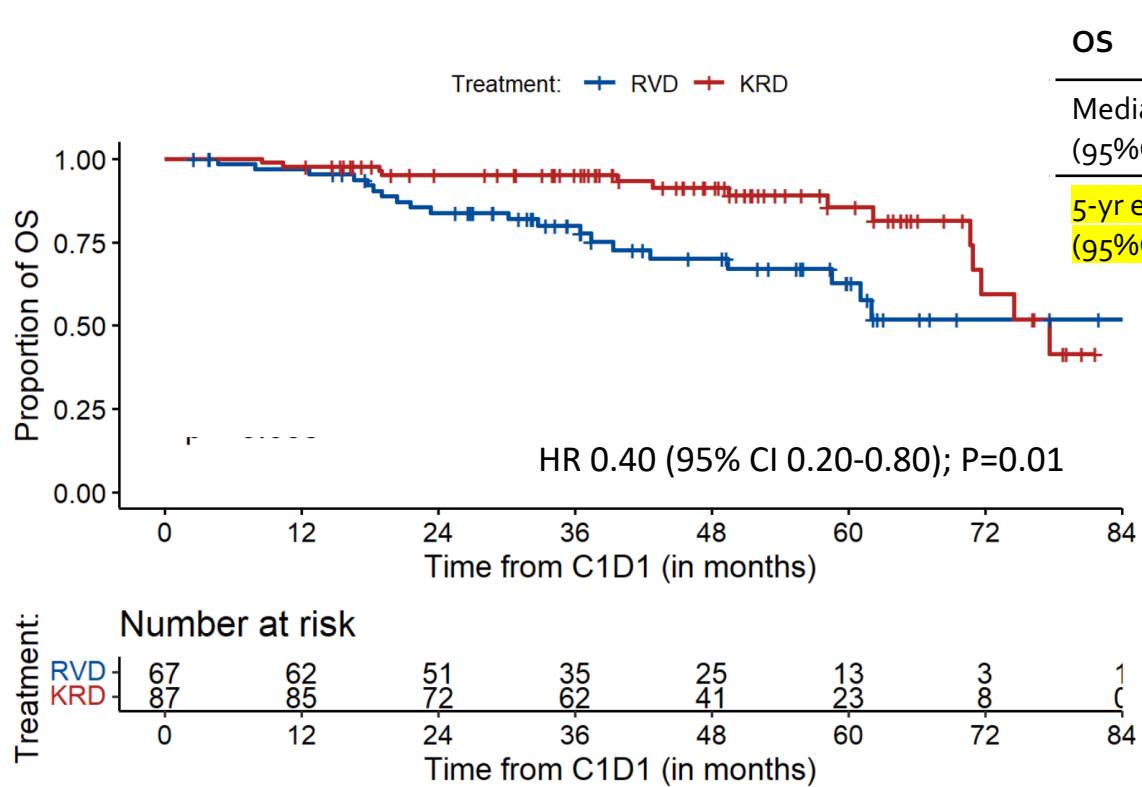
PFS	VRd (N=67)	KRd (N=87)
Median, mo (95%CI)	41 (32.8 – 61.1)	70.9 (58.2 – NR)*
5-yr estimate (95%CI)	35% (24% - 51%)	58% (47% - 71%)

*Median PFS is an estimate

Tan C et al, ASH 2022



Overall Survival



OS	VRd (N=67)	KRd (N=87)
Median, mo (95%CI)	NR	77.7 (70.9-NR)
5-yr estimate (95%CI)	63% (49%-80%)	85% (76%-96%)

Median f/u for all patients: 48.9 mos (95%CI 44.9-53)

Median f/u VRd: 49.3 mos (95%CI 36.6-59.8)

Median f/u KRd: 48.6 mos (95%CI 44.9-52.6)

Tan C et al, ASH 2022

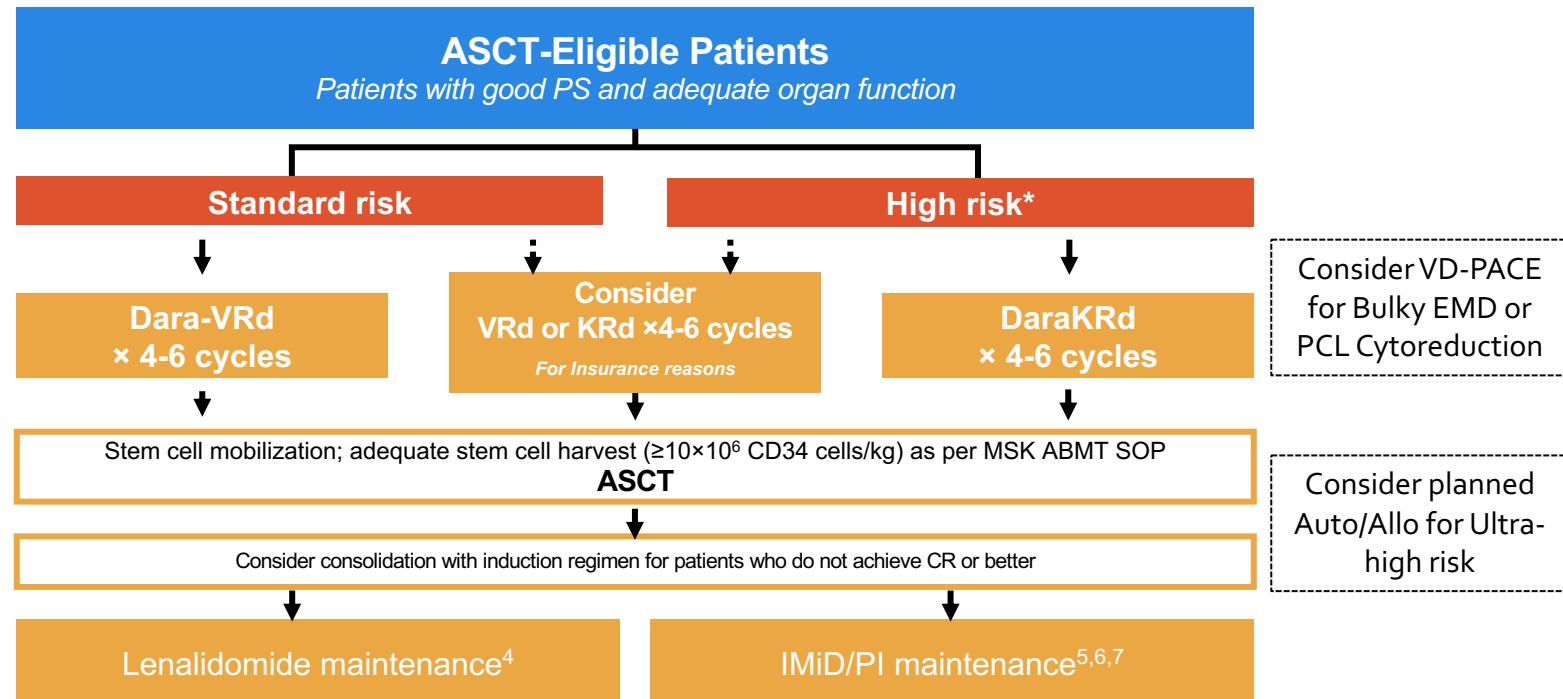


Daratumumab-KRd for NDMM

Study/Phase	Patient Characteristics	Responses	PFS data	Safety (Grade 3/4)
Landgren O et al JAMA Onc 2021 Phase II 8 cycles	N=41 High-risk = 49% (included gain 1q) Median age: 60 years	ORR = 100% ≥CR rate = 95% MRD-ve at 10^{-5} = 71%	1-year PFS rate 100%	Neutropenia 27%, Rash 9% Lung infection 7% Increased ALT 4% No TRM
Costa LJ et al JCO 2022 Phase II 4 cycles	N=123 High-risk = 57% (included gain 1q) Median age: 60 years	ORR = 100% ≥CR rate = 39% MRD-ve at 10^{-5} = 80%	2-year PFS rate 87%	Lung infection 6% VTE 3% No TRM
Bhutani M et al ASH 2022 Phase II 8 cycles	N=23 (of 39) High-risk = 43% (included gain 1q) Median age:	ORR = 100% ≥CR rate = 65% MRD-ve at 10^{-5} = 70%	Not reported	Hypophosphatemia 30% Neutropenia 13%, HTN 13% COVID19 7% No TRM



Approach to Transplant Eligible NDMM



ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; Tx, treatment.

*By R-ISS staging (R-ISS II/III) and/or cytogenetics (t[4;14], t[14;16], or del[17p]), elevated LDH, primary plasma cell leukemia

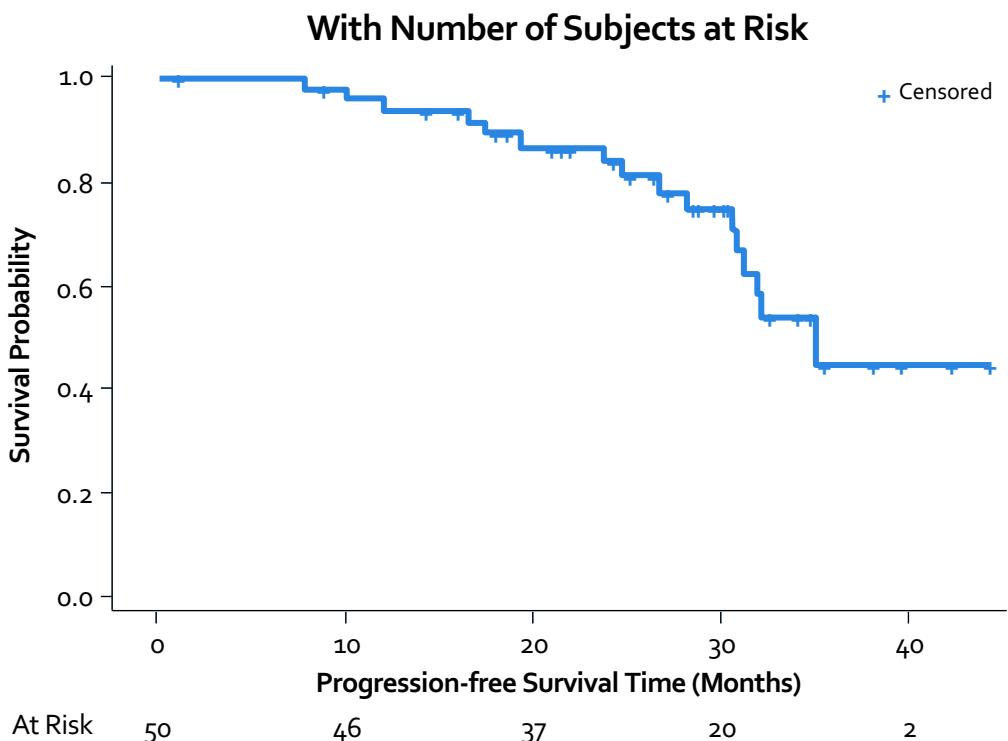
1. Attal. NEJM. 2017;376:1311. 2. Voorhees PM. Blood 2020. Gay. ASH 2020. Abstr 294. 4. McCarthy. J Clin Oncol. 2017;35:3279. 5. Nooka. Leukemia. 2014;28:690.

6. Dimopoulos. ASH 2018. Abstr 301. 7. Usmani. Lancet Haematol. 2021 Jan;8(1):e45-e54.



RVd-Lite

- Regimen (N=53)
 - Lenalidomide: 15 mg po days 1 to 21
 - Bortezomib: 1.3 mg/m² SC 1× weekly on days 1, 8, 15, 22
 - Dexamethasone
 - If ≤75 years, 20 mg 2× weekly
 - If >75 years, 20 mg 1× weekly
- Results
 - 86% ORR
 - 66% ≥VGPR
 - Median PFS: 35.1 months
 - Median OS: NR
 - Median follow-up: 30 months
 - Median age: 73 years (range: 65-91)
 - PN: 62%
 - Only 1 patient had grade 3 symptoms



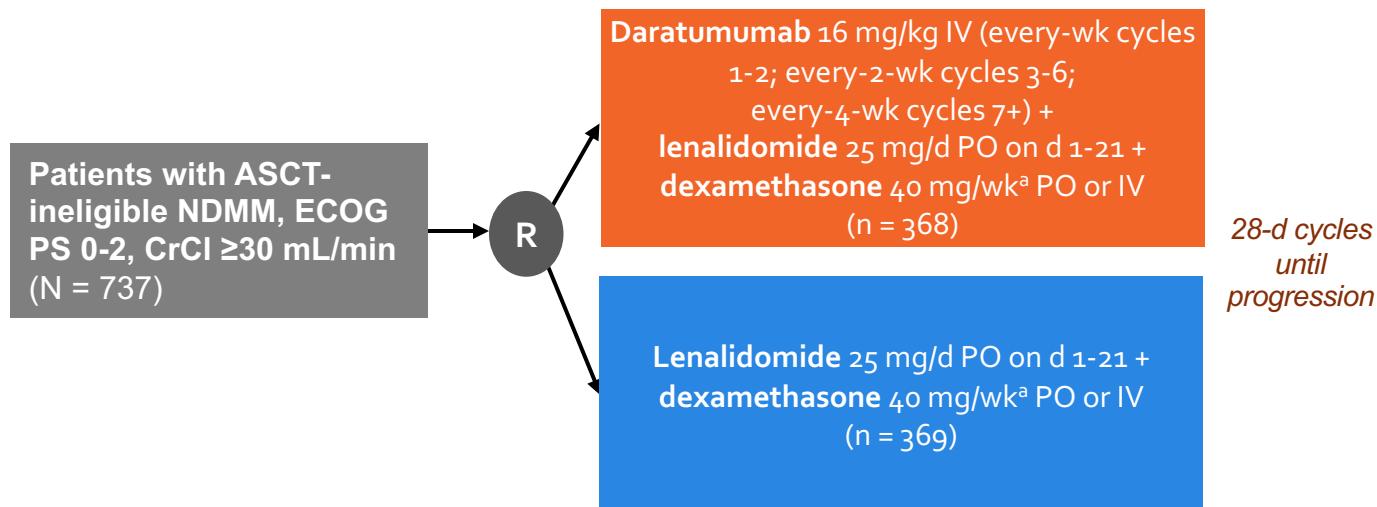
• PN, peripheral neuropathy.

O'Donnell et al. *Br J Haematol.* 2018;182:222-230.



Phase 3 MAIA Study: Daratumumab Plus Rd in NDMM

- Stratified by ISS (I vs II vs III), region (North America vs other), and age (<75 vs ≥75 y)
- Primary endpoint:** PFS
- Secondary endpoints:** ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, and safety



^a Reduced to 20 mg/wk if aged >75 y or BMI <18.5.
Facon T et al. *N Engl J Med.* 2019;380:2104-2115.



Demographics and Baseline Characteristics (ITT)

	D-Rd (n = 368)	Rd (n = 369)
Age		
Median (range), y	73 (50-90)	74 (45-89)
Distribution, n (%)		
<65 y	4 (1)	4 (1)
65-<70 y	74 (20)	73 (20)
70-<75 y	130 (35)	131 (36)
≥75 y	160 (43)	161 (44)
Male, n (%)	189 (51)	195 (53)
ECOG PS score,^a n (%)		
0	127 (35)	123 (33)
1	178 (48)	187 (51)
2 ^b	63 (17)	59 (16)
ISS stage,^c n (%)		
I	98 (27)	103 (28)
II	163 (44)	156 (42)
III	107 (29)	110 (30)

	D-Rd (n = 368)	Rd (n = 369)
Type of measurable disease, n (%)		
IgG	225 (61)	231 (63)
IgA	65 (18)	66 (18)
Other ^d	9 (2)	10 (3)
Detected in urine only	40 (11)	34 (9)
Detected as serum-free light chain only	29 (8)	28 (8)
Cytogenetic profile,^e n/total n (%)		
Standard risk	271/319 (85)	279/323 (86)
High risk	48/319 (15)	44/323 (14)
Median time since initial diagnosis of MM (range), months	0.95 (0.1-13.3)	0.89 (0-14.5)

Demographics and baseline characteristics were well balanced between arms

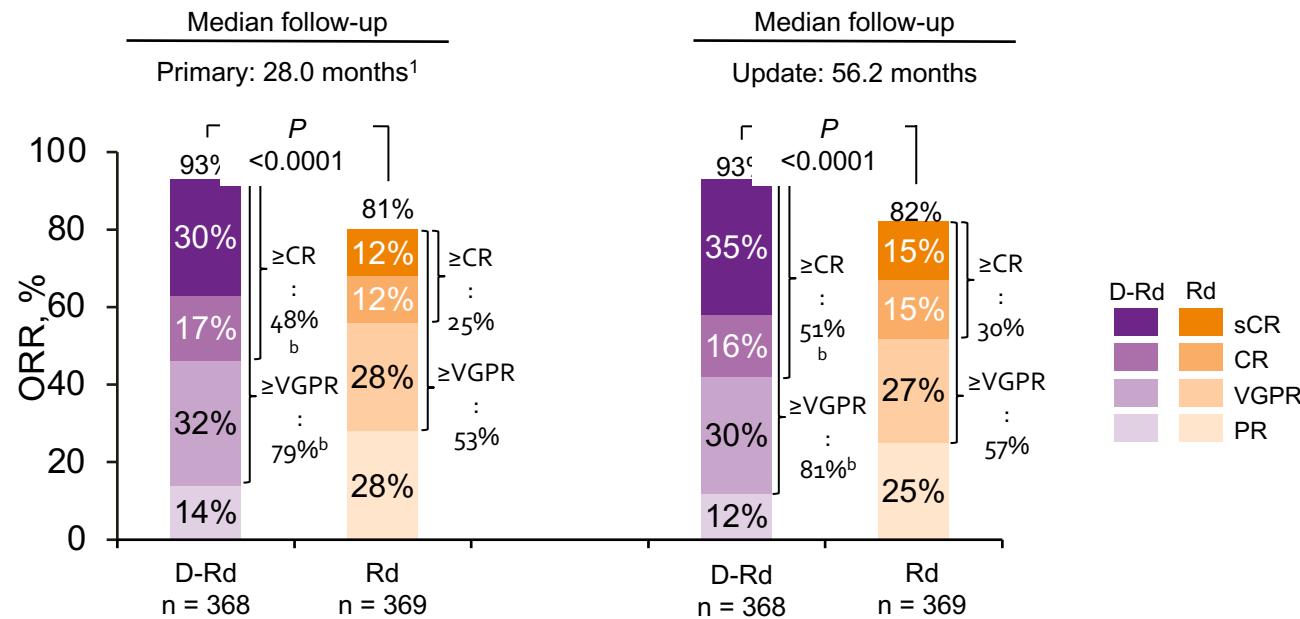
ITT, intention-to-treat.

^aECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. ^b2 patients had an ECOG PS score >2 (1 patient each with an ECOG PS score of 3 and 4). ^cISS stage is derived based on the combination of serum β₂-microglobulin and albumin; higher stages indicate more severe disease. ^dIncludes IgD, IgE, IgM, and biclonal. ^eCytogenetic abnormalities were identified by fluorescence in situ hybridization or karyotype testing; high risk was defined as having a t(4;14), t(14;16), and/or del17p abnormality.

Note: percentages may not add up to 100% due to rounding.



MAIA Phase III ORR^a



- D-Rd induced deeper responses, with significantly higher rates of ≥CR and ≥VGPR, compared with Rd
- With >28 months of additional follow-up, responses deepened with continued daratumumab therapy

VGPR, very good partial response; PR, partial response; OR, odds ratio.

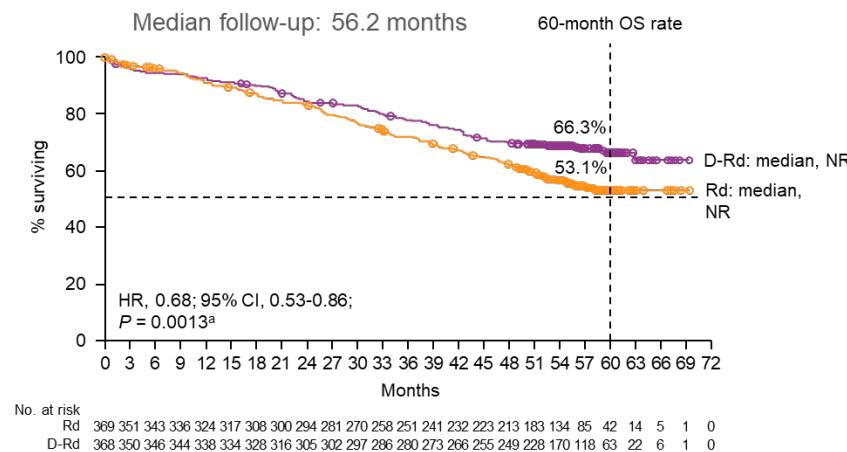
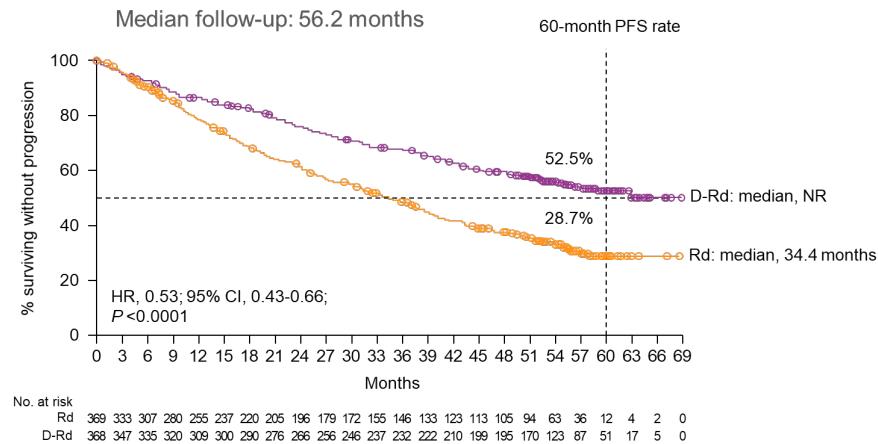
^aITT population. ^bP <0.0001; P values were calculated from the Cochran-Mantel-Haenszel Chi-Squared test.

1. Facon T, et al. *N Engl J Med.* 2019;380(22):2104-2115.

Note: percentages may not add up to the total due to rounding.



MAIA Phase III Updated PFS/OS



^a $P = 0.0013$ is statistically significant, crossing the prespecified stopping boundary of $P = 0.0414$.

NR, not reached; CI, confidence interval.



MSK Approach to Transplant Ineligible NDMM

ASCT-Ineligible Patients

Patients with poor PS not related to disease, ejection fraction <50%, pulmonary function test values <50%, concomitant multiorgan amyloidosis



RVd-Lite¹×8-12 cycles



DRd²

Consider DVd or VCd or Rd if VRd or DRd is not appropriate
(eg, renal failure or other comorbidities)



**Lenalidomide
maintenance
until progression³**

**IMiD/PI maintenance
until progression for high
risk⁴**



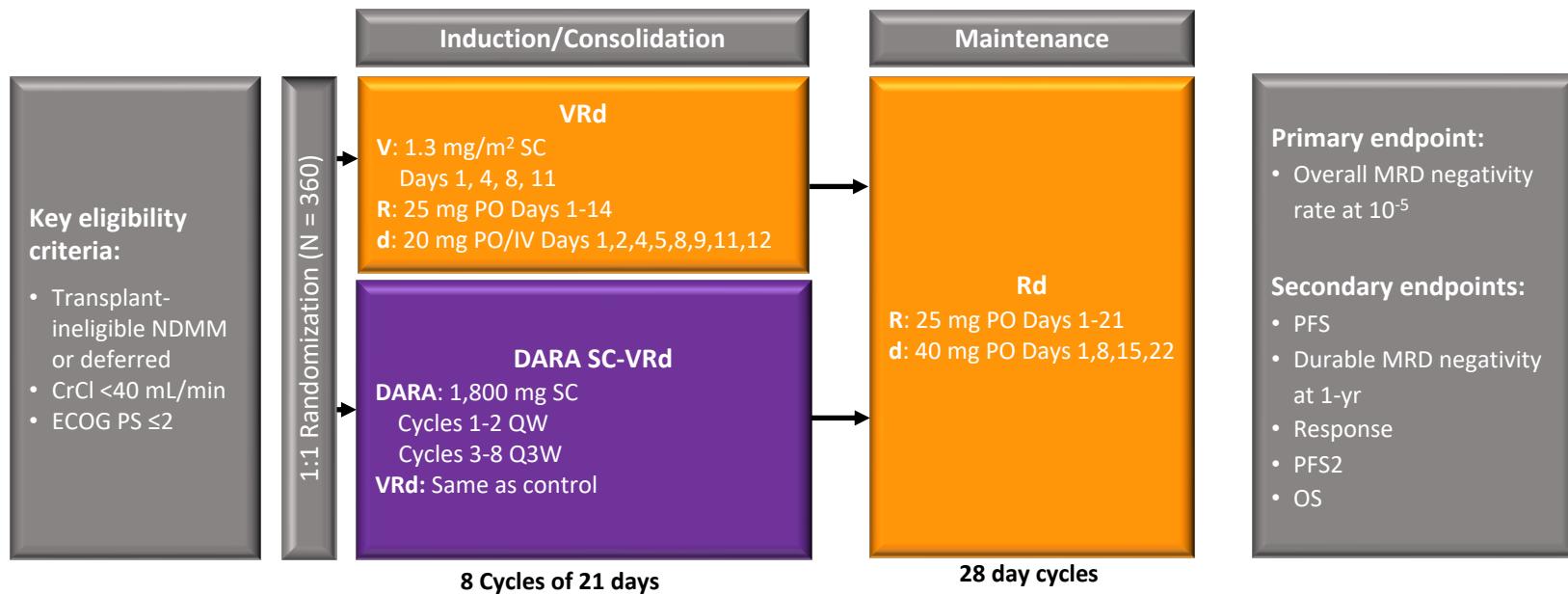
**Continue treatment
until progression**

- DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; VRd-Lite, modified VRd regimen.
- Adjust dosing of lenalidomide based on renal function. Consider empiric age-adjusted dose reductions for all regimens, as needed.⁴
- 1. O'Donnell. Br J Haematol. 2018;182:222. 2. Facon. ASH 2018. Abstr LBA-2. 3. Larocca. ASH 2018. Abstr 305. 4. Usmani. Lancet Haematol. 2021 Jan;8(1):e45-e54.



CEPHEUS: Study Design

- Phase 3 study of DARA-VRd versus VRd in transplant-ineligible NDMM



Zweegman S, et al. Trials in Progress Poster presented at ASCO Annual meeting. May 31-June 4, 2019. Chicago, IL. Abstract TPS8066.
ClinicalTrials.gov Identifier: NCT03652064. Accessed 24 February 2022



Approach to NDMM

Transplant eligible

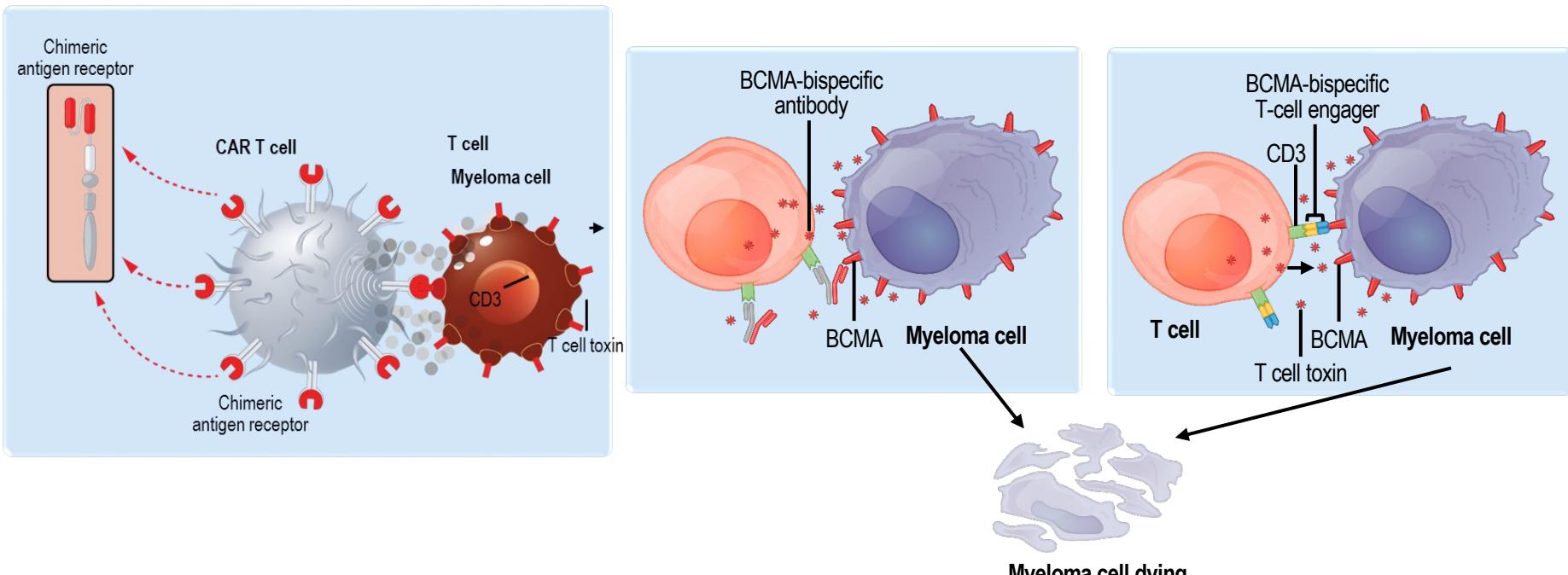
- Induction : Dara-RVd, Dara-KRd, Dara-VTd, RVd, KRd, CyBorD
- Maintenance: R, VR, Dara-R, Dara
- Expected PFS/OS:
 - Standard Risk: 80 months/130+ months
 - High Risk: 40 months/80+ months

Transplant Ineligible

- DRd, VRd-lite/RVd-lite
- Expected PFS/OS:
 - Standard Risk: 36-60+ months/90+ months
 - High Risk: 24-30 months/60-72 months



The Promise of T-cell redirection



CAR, chimeric antigen receptor; MM, multiple myeloma.
CAR T-cell therapy is not yet FDA-approved for patients with MM.

Adapted from Cho S-F et al. *Front Immunol.* 2018;9:1821.



Memorial Sloan Kettering
Cancer Center™

MSKCC Myeloma Service



Saad Z. Usmani (Chief)
High-Risk Disease , Disparities
TCE, CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics



Carlyn Tan
MM Precursor diseases
Supportive Care
Bone Health



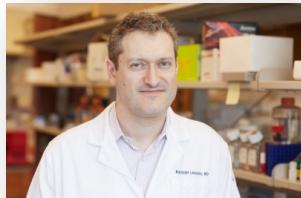
Urvi Shah
MM Precursor Disease
Nutrition & Modifiable
Risk Factors
Early Relapse



Kylee MacLachlan
MM Precursor Disease,
NDMM Trials
Genomics, Immune
Profiling



Neha Korde
NDMM Clinical Trials
Digital Wearables
Supportive Care



Alex Lesokhin
RRMM Immunotherapy
TCE, Checkpoints Inhibitors
Neoantigens
Microbiota, Immune
Profiling



Hani Hassoun
MM Supportive Care
Alliance Liaison
NDMM/RRMM Trials
Elderly and Frail



Sham Mailankody
RRMM Trials with
CAR T Cells
High-Risk Disease



Malin Hultcrantz
RRMM Trials in TCR
Antibody drug conjugates
Epidemiology



Sridevi Rajeeve
NDMM Clinical Trials
Digital Wearables
Cellular therapies



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MSKCC Myeloma TCT Program



Sergio Giralt
Allo/Auto HCT for
MM
New Regimens
CAR T Cells



David Chung
T Cell exhaustion
Auto HCT + Vaccines
MM Immunotherapies



Gunjan Shah
HCT Toxicities
Precision Drug Dosing
CAR T Cells
Salvage Auto and Allo HCT



Saad Z. Usmani
High-Risk Disease Biology/Trials
CAR T Cells
Auto HCT for MM



Michael Scordo
HCT Toxicities
Precision Drug Dosing
CAR T Cells



Heather Landau
Amyloidosis
HCT Toxicities
Homebound HCT
Precision Drug Dosing
Novel Regimens for Salvage
Auto



Oscar Lahoud
Auto HCT and CAR T Cells
Post HCT Therapies



Parastoo Dahi
Auto HCT and CAR T Cells
Post HCT Therapies