Memorial Sloan Kettering Cancer Center

Transplanting the MRD Negative Myeloma Patients for a Deeper Remission After Initial Therapy

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

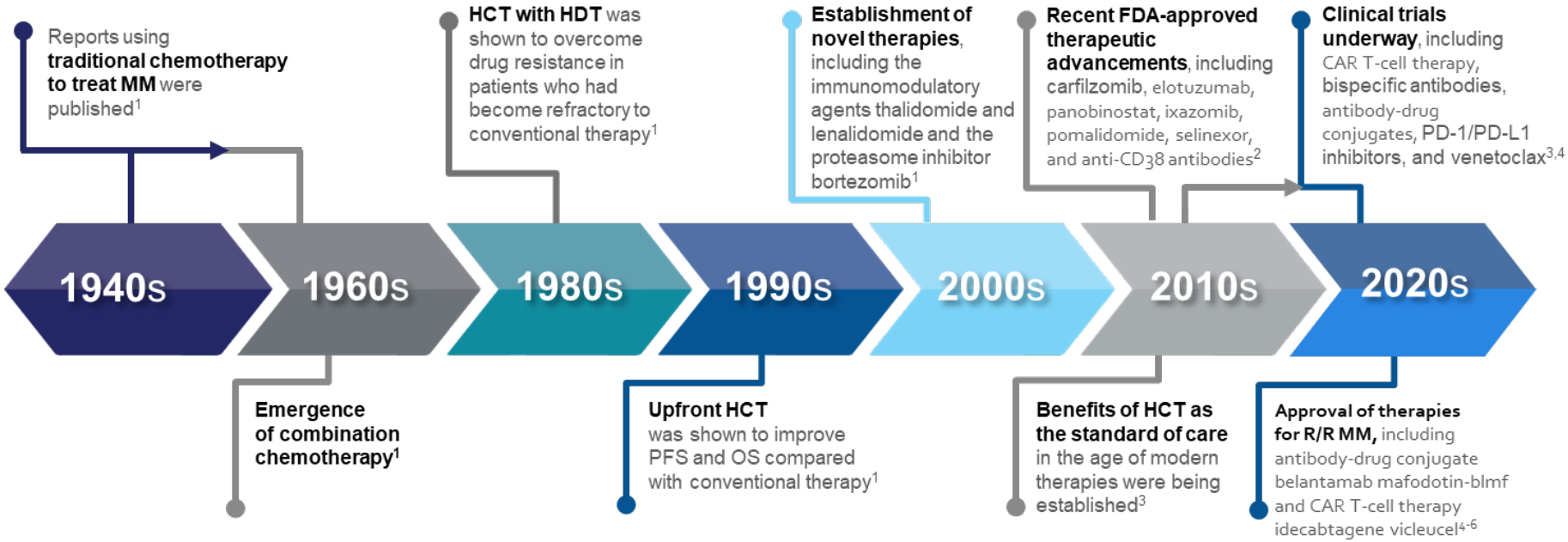
Memorial Sloan Kettering Cancer Center

Disclosures

- Research funding: Amgen, Array Biopharma, BMS, Celgene, GSK, Janssen, Merck, Pharmacyclics, Sanofi, Seattle Genetics, SkylineDX, Takeda.
- Consulting: Abbvie, Amgen, BMS, Celgene, EdoPharma, Genentech, Gilead, GSK, Janssen, Oncopeptides, Sanofi, Seattle Genetics, SecuraBio, SkylineDX, Takeda, TeneoBio.
- Speaker: Amgen, BMS, Janssen, Sanofi.

Memorial Sloan Kettering Cancer Center

History of MM Treatments



CAR, chimeric antigen receptor; HDT, high-dose therapy; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; R/R, relapsed/refractory.

1. Laubach J, et al. *Annu Rev Med.* 2011;62:249-264. **2.** Rajkumar SV. *Am J Hematol.* 2020;95(5):548-567. **3.** Palumbo A, et al. *N Engl J Med.* 2014;371(10):895-905. **4.** Zanwar S, et al. *Blood Cancer J.* 2020;10(8):84. doi: 10.1038/s41408-020-00350-x. **5.** US Food and Drug Administration. FDA granted accelerated approval to belantamab mafodotin-blmf for multiple myeloma. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma. Updated August 6, 2020. Accessed May 6, 2021. **6.** US Food and Drug Administration. FDA approves first cell-based gene therapy for adult patients with multiple myeloma. https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-multiple-myeloma. Updated March 27, 2021. Accessed May 17, 2021.

Memorial Sloan Kettering Cancer Center

Staging and Cytogenetic Risk-Assessment

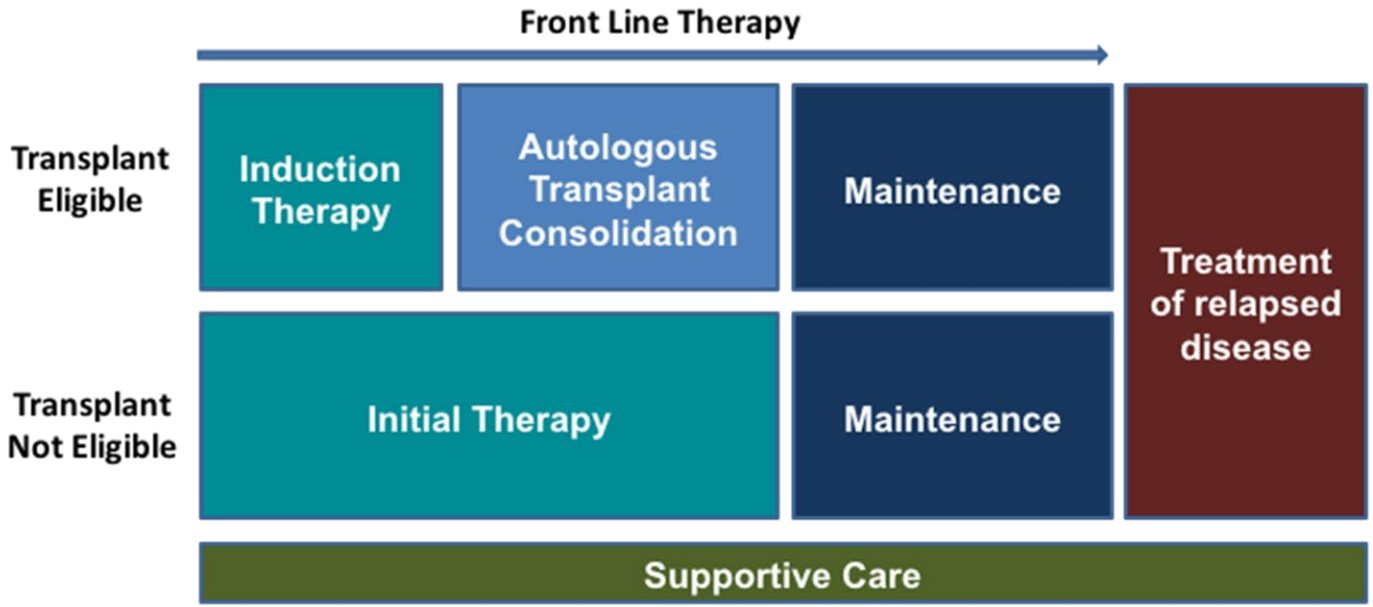
Stage[1]	R-ISS[1]
I	Serum albumin ≥3.5 g/dL^{-1} Serum β2M <3.5 mg/L^{-1} No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum β2M >5.5 mg/L^{-1} High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH

Risk[2]	Features
Standard	Trisomies t(11;14) t(6;14)
High	t(4;14) t(14;16) t(14;20) Del(17p) *p53* mutation Gain/Amp 1q High plasma cell S-phase GEP high-risk signatures Circulating Plasma Cells

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.

Memorial Sloan Kettering Cancer Center

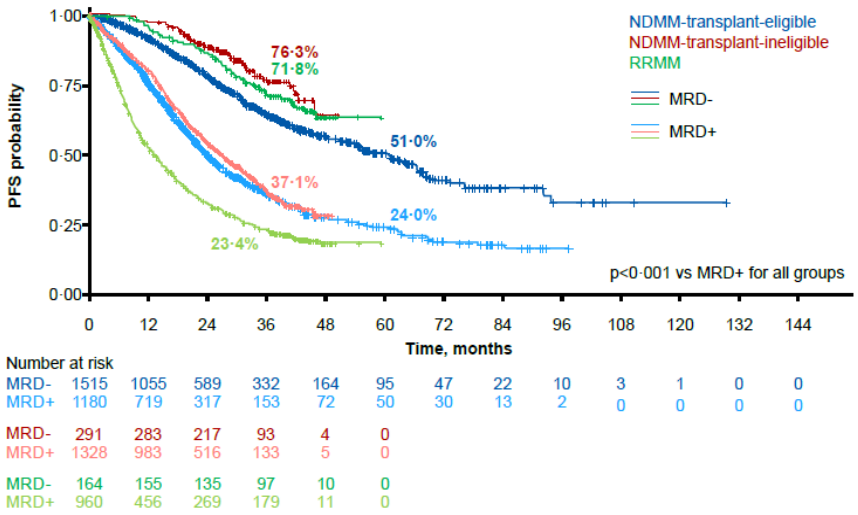
Treatment Paradigm For Newly Diagnosed Multiple Myeloma



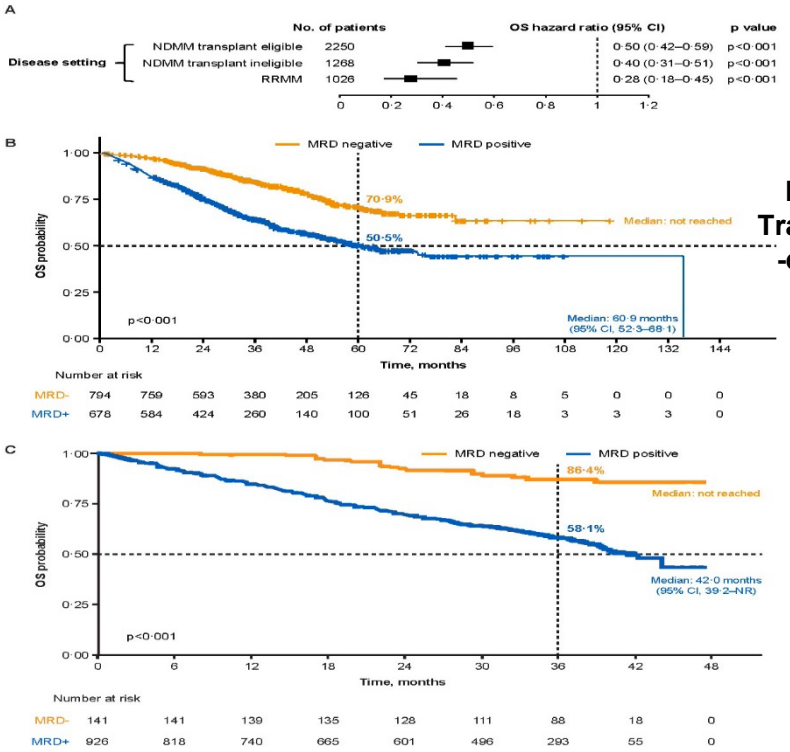
Memorial Sloan Kettering Cancer Center

MRD Negativity and Survival Outcomes

PFS



OS



NDMM Transplant -eligible

RRMM

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

Memorial Sloan Kettering Cancer Center

Approach to NDMM

Transplant eligible

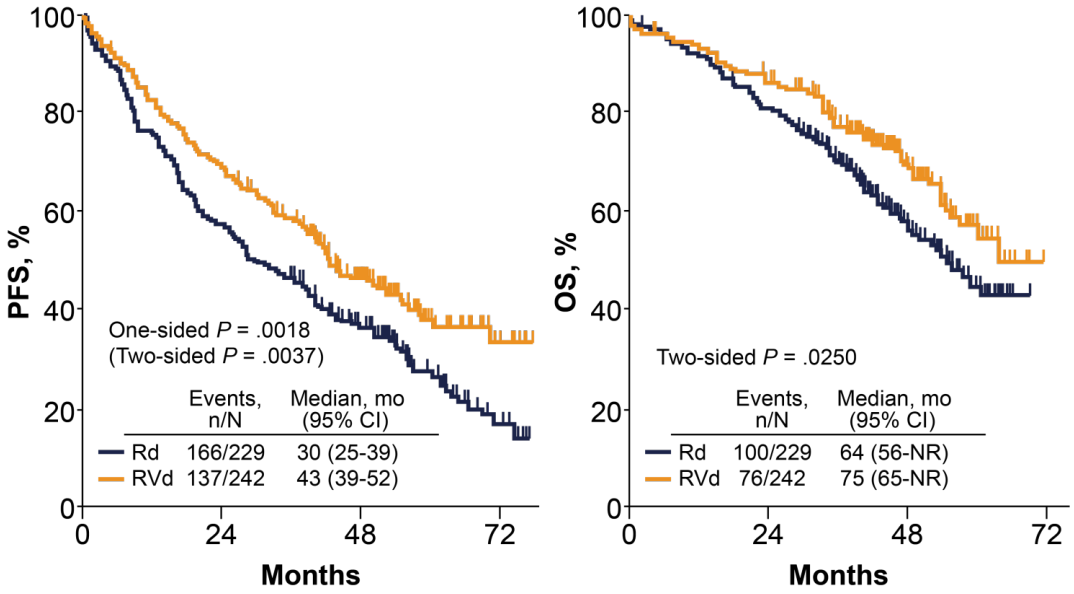
- Induction : Dara-RVd, Dara-KRd, Dara-VTd, RVd, KRd, CyBorD
- Maintenance: R, VR, Dara-R, Dara
- Expected PFS/OS:
  - Standard Risk: 80 months/130+ months
  - High Risk: 40 months/80+ months

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

Memorial Sloan Kettering Cancer Center

SWOG S0777: RVd Versus Rd in Patients Without Immediate Intent for ASCT[1]



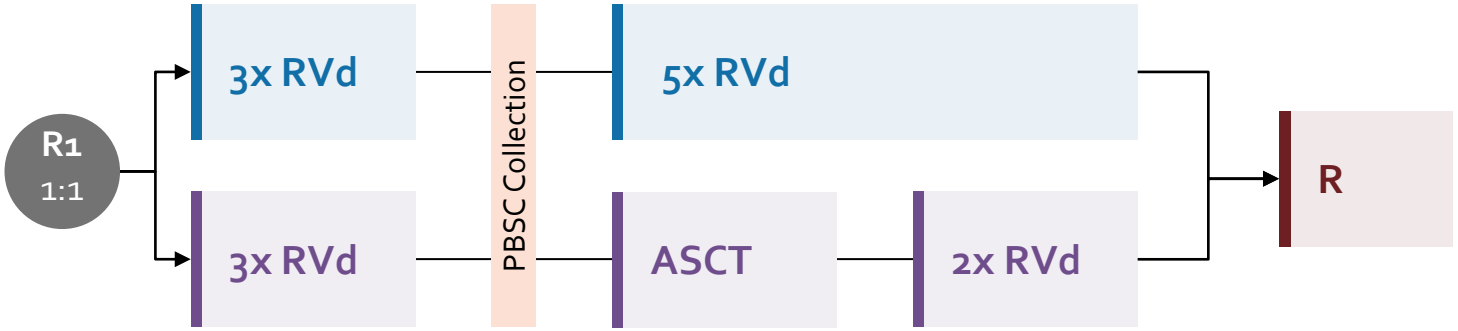
Initial Therapy

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)

Durie B et al. *Lancet*. 2017;389:519-527.

Memorial Sloan Kettering Cancer Center

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

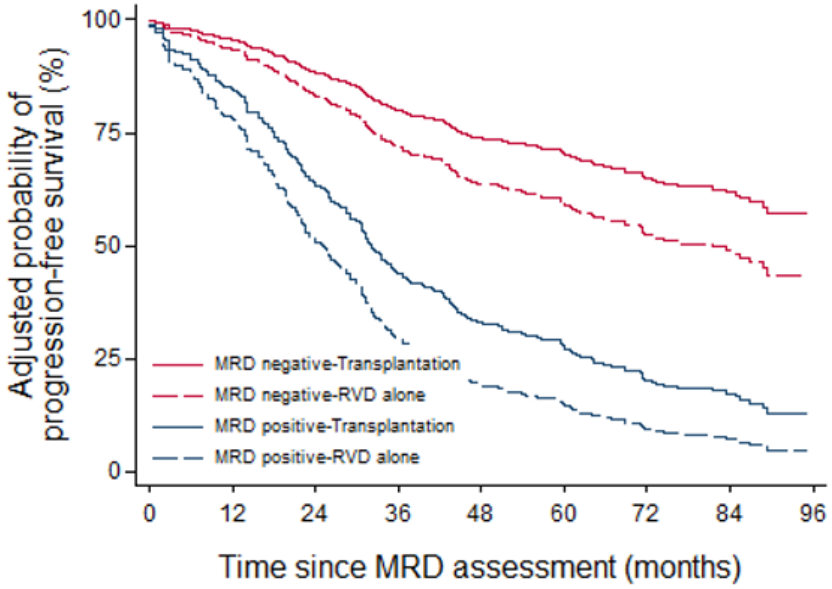
R Maintenance
R: 10-15 mg/d for 13 cycles

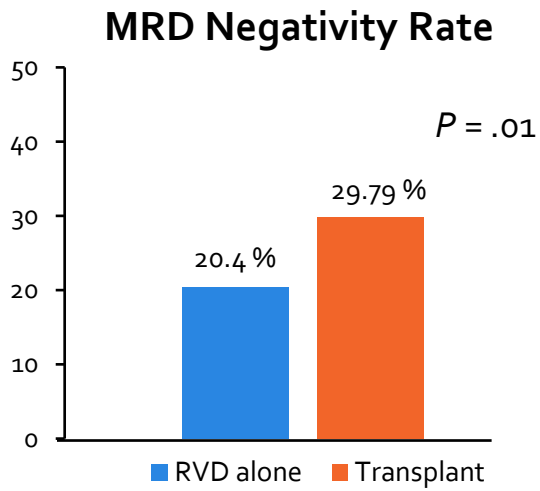
Primary endpoint: PFS
Secondary endpoints:
ORR, MRD, TTP, OS, safety

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

Memorial Sloan Kettering Cancer Center

Superior PFS With ASCT vs RVd Alone





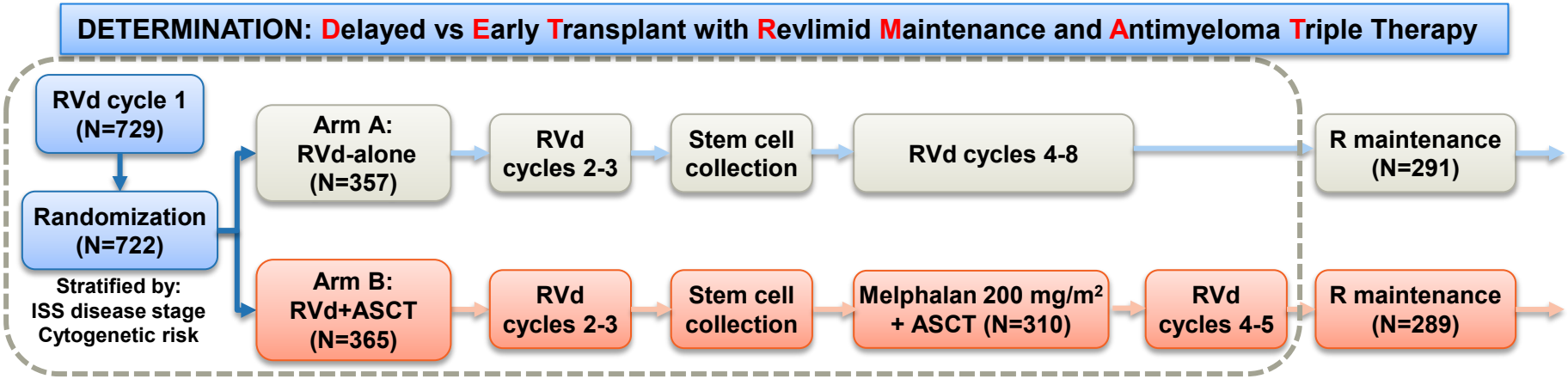
RVd + transplant was superior to RVd alone, even with undetectable MRD at 10^{-6}

MRD, minimal residual disease.

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

Memorial Sloan Kettering Cancer Center

DETERMINATION: study design and patient disposition



Each RVd cycle (21 days):
R 25 mg/day PO, days 1-14
V 1.3 mg/m^2 IV/SC, days 1, 4, 8, 11
Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

Lenalidomide maintenance
Months 1-3: 10 mg/day
Month 4 onwards: 15 mg/day

Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

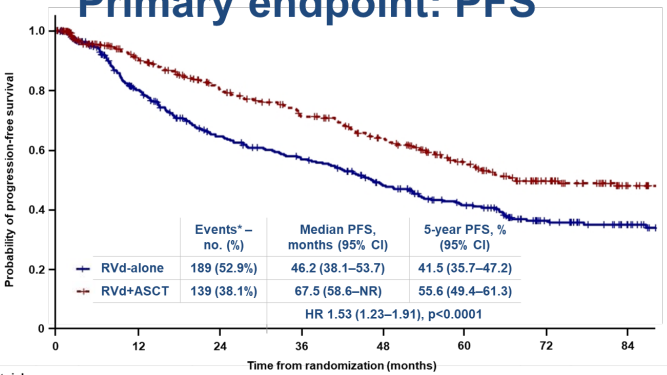
- d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

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

Memorial Sloan Kettering Cancer Center

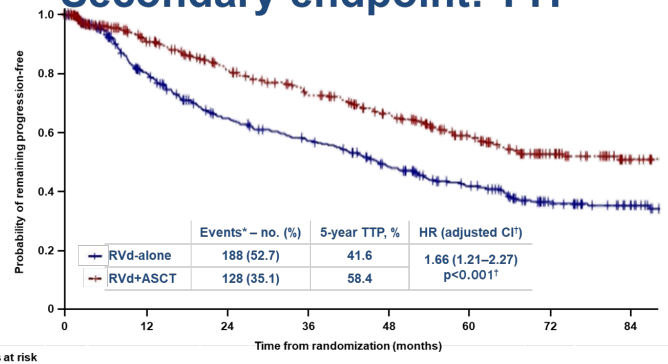
DETERMINATION: Endpoint Readouts
(Median follow-up 70 months)

Primary endpoint: PFS



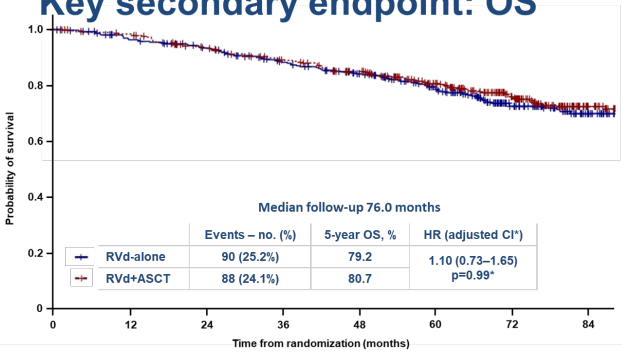
Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

Secondary endpoint: TTP



Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

Key secondary endpoint: OS



Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

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%

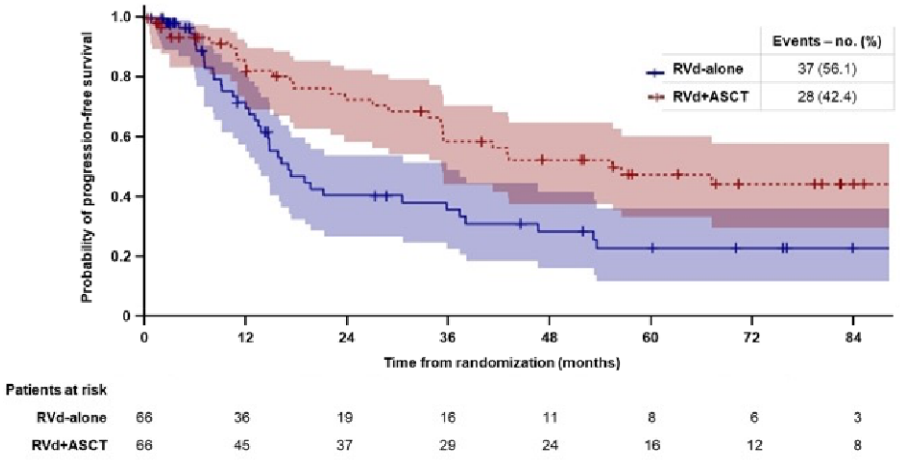
At time of data cutoff, among patients on the RVd-alone and RVd+ASCT arms who had hematologic SPMs, respectively:

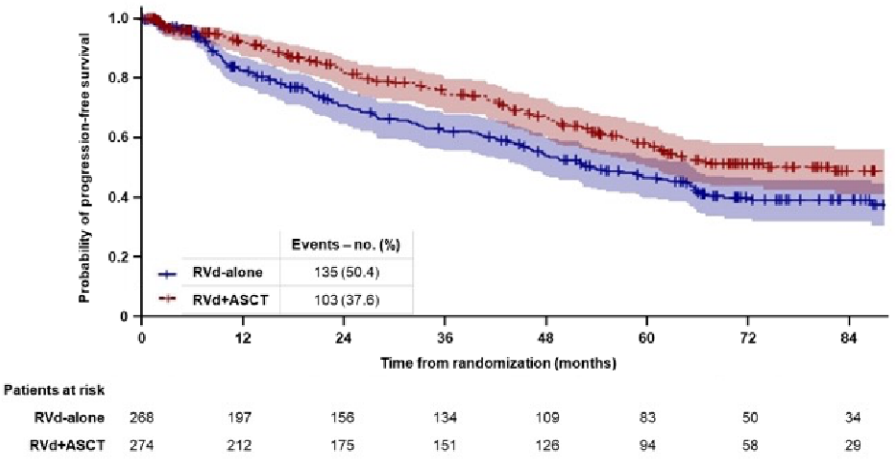
- 6/7 vs 2/3 patients with ALL alive
- 6/10 patients with AML/MDS alive
- 1/2 patients with CLL/CML alive
- Overall, 7/9 RVd-alone vs 8/13 RVd+ASCT alive

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

Memorial Sloan Kettering Cancer Center

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

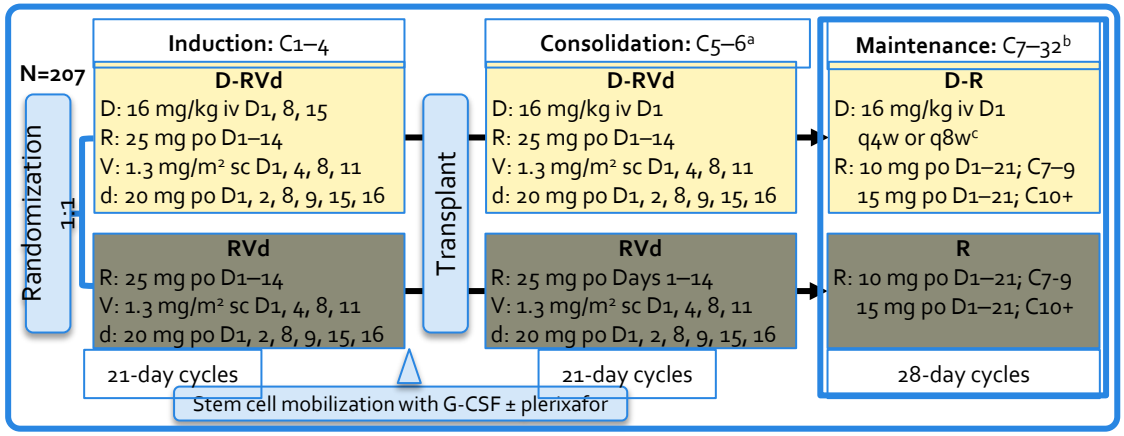
Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Memorial Sloan Kettering Cancer Center

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/min[2]



- **Primary endpoint:** sCR by end of consolidation
- **Secondary endpoints:** MRD negativity (NGS 10^{-5}), ORR, ≥VGPR, CR, PFS, OS

Patient disposition

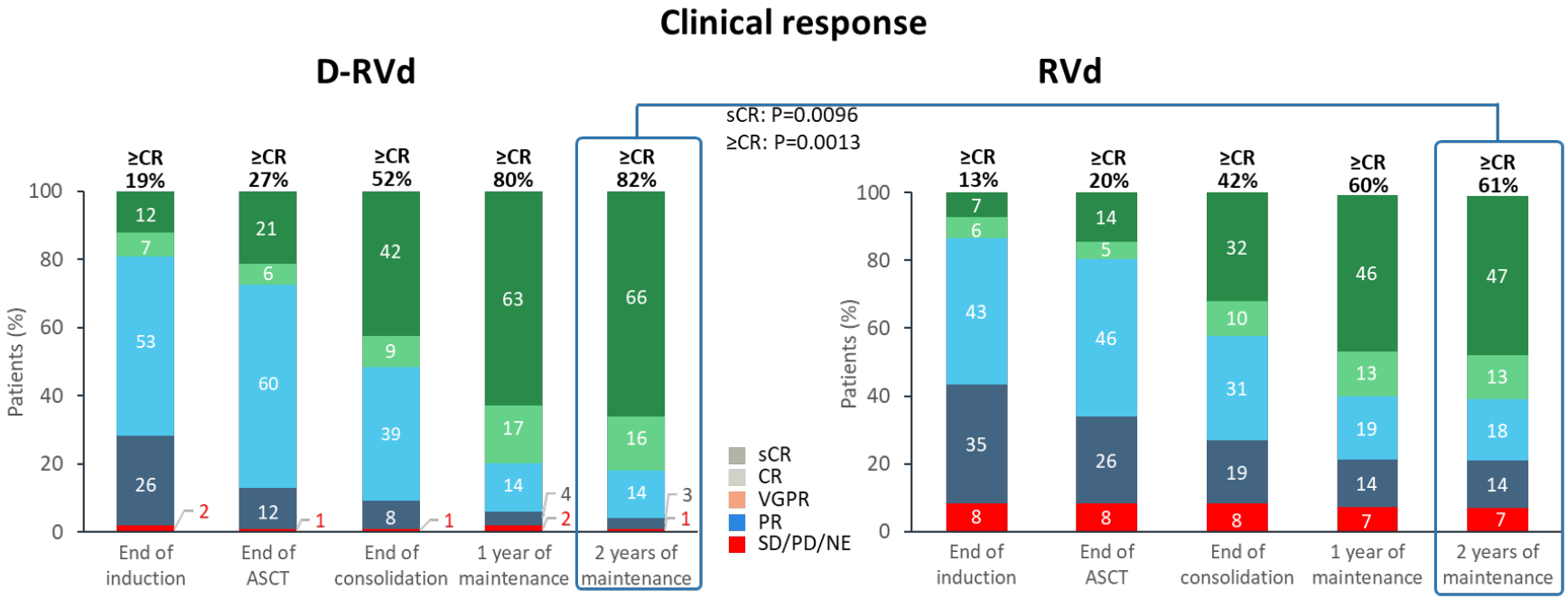
n (%)	D-RVd (n=104)	RVd (n=103)
Treated with maintenance therapy	90 (87)	70 (68)
Completed maintenance therapy	67 (64)	44 (43)
Discontinued treatment during maintenance therapy	21 (20)	21 (20)
Adverse event	8 (8)	7 (7)
Progressive disease	3 (3)	7 (7)
Patient withdrawal	2 (2)	4 (4)
Lost to follow-up	2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

[a]Consolidation initiated 60–100 days post transplant; [b]Patients who complete maintenance cycles 7–32 may continue single-agent lenalidomide thereafter; [c]Protocol amendment allowed q4w dosing option. Phase 2 trial – patient enrollment between December 2016 and April 2018

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

Memorial Sloan Kettering Cancer Center

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



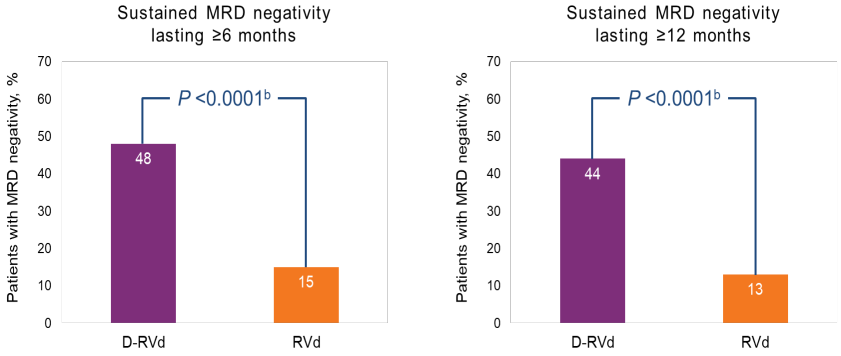
Laubach JP, et al. ASH 2021, Virtual Meeting. Abstract 79

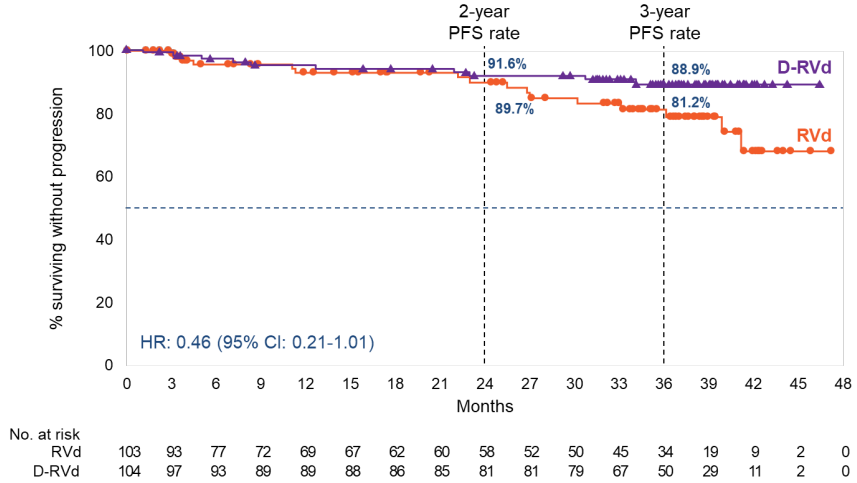
Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Memorial Sloan Kettering Cancer Center

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

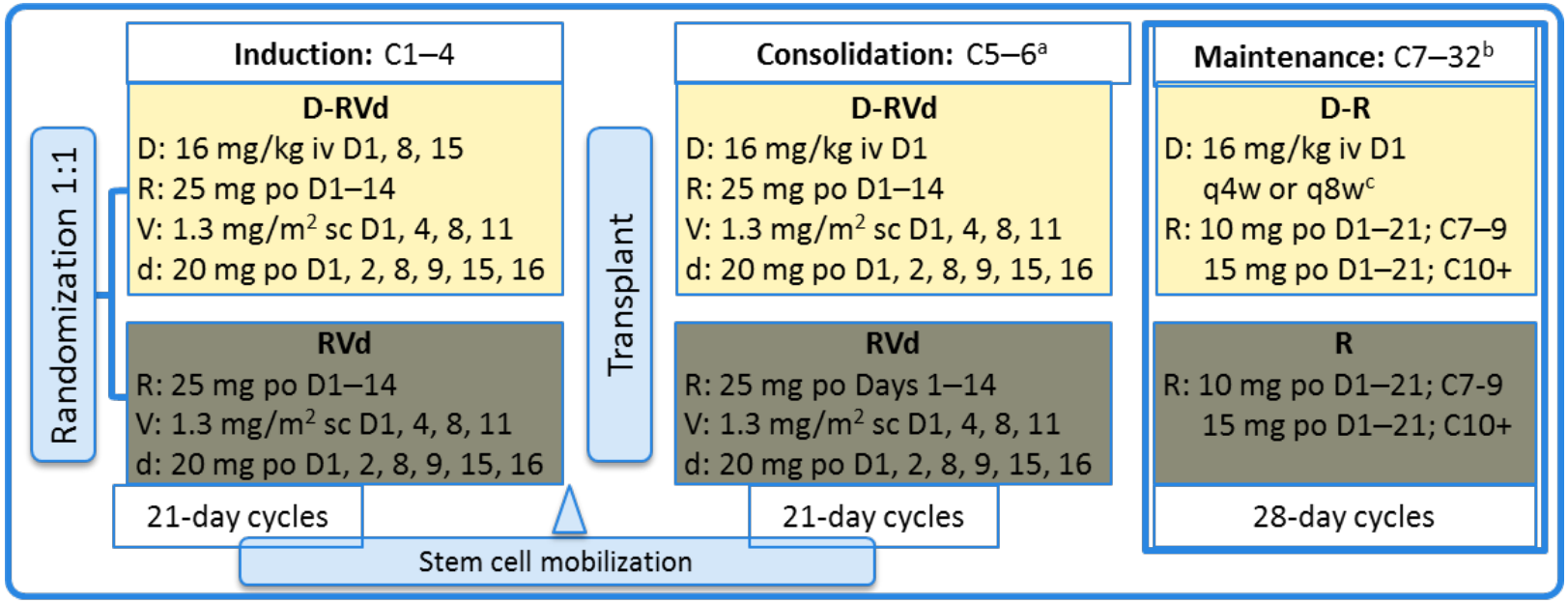
[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status was based on BM aspirates by NGS per IMWG. [b]P values calculated by Fisher's exact test

Laubach et al. ASH 2021. Abstract 79.

Memorial Sloan Kettering Cancer Center

PERSEUS: Study Design

Phase 3 trial, n=690



https://www.clinicaltrials.gov/ct2/show/NCT03710603

Memorial Sloan Kettering Cancer Center

Key Questions Towards Curing Myeloma

- Combine the molecular and immunobiology of disease evolution and progression in MM
  - Recognize patients at precursor state and intervene early.
  - Pick different strategies for different disease biology and immune status.

- Use MRD as guide for treatment strategy and duration.
  - Marrow: Sustained MRD-ve at 10^{-5} vs 10^{-6} , 12 months apart to de-escalate.
  - Imaging: Incoporate PET-CT (functional imaging) response in addition to the sustained MRD-ve status

- Optimal sequencing of existing therapies and incorporation of select novel MoAs based on disease biology.
  - Pay attention to supportive care, short-term and long-term sequelae of treatments.

Memorial Sloan Kettering Cancer Center

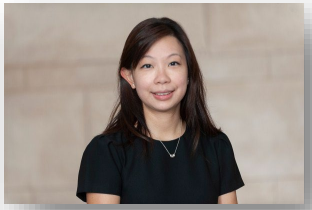
Conclusions & Future Directions

- Recognize MM is not one disease, need small enrichment design clinical trials for high-risk disease.
- Achieving and sustaining MRD negativity matters.
- Daratumumab-based quadruplets have become accepted standard of care
  - Higher MRD-ve rates
  - Safe, but attention to infection risk
- New studies are starting to focus on sustained MRD negativity-based duration of therapy for NDMM.
  - Achieving functional cure appears very promising in the next decade.

Memorial Sloan Kettering Cancer Center

MSKCC Myeloma Service

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

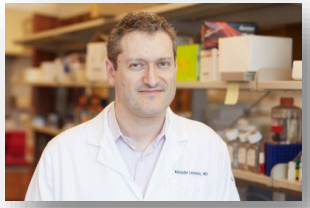


Carlyn Tan
MM Precursor diseases
Supportive Care
Bone Health

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

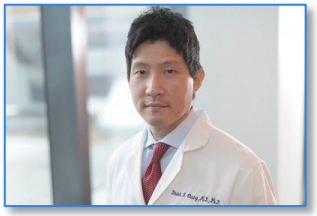
Sham Mailankody
RRMM Trials with CAR T Cells
High-Risk Disease

Malin Hultcrantz
RRMM Trials in TCR
Antibody drug conjugates
Epidemiology

Memorial Sloan Kettering Cancer Center

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