Memorial Sloan Kettering Cancer Center

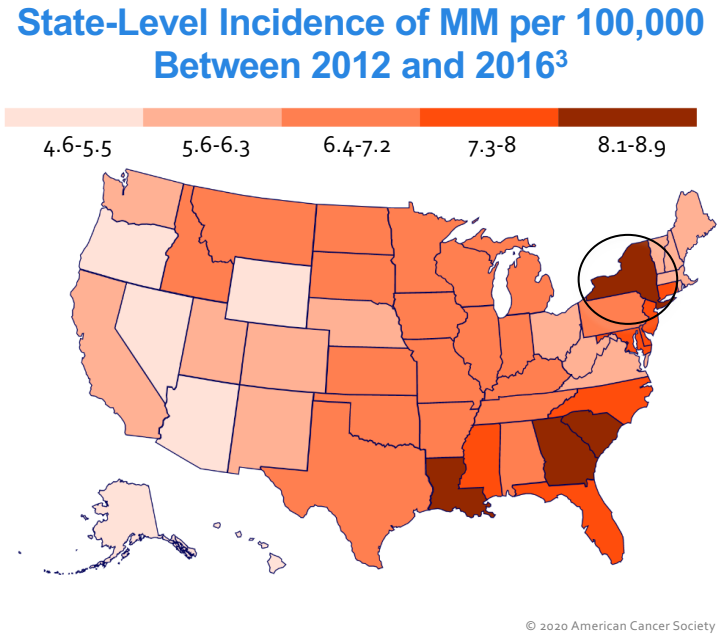
Managing Newly Diagnosed Multiple Myeloma in 2022: Triumphs & Opportunities

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

Memorial Sloan Kettering Cancer Center

Multiple Myeloma: A Systemic Plasma Cell Malignancy

- Estimated new cases and deaths in 2021 in the United States[1]
  - New cases: 34,920
  - Deaths: 12, 410
- Percentage of patients surviving 5 years: 55.6%[2]
- Median age at diagnosis: 69 years[2]
- MM is most common in men and Black adults[2]



1. Plasma cell neoplasms (including multiple myeloma) treatment (PDQ®)-Health Professional Version. National Cancer Institute website. http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional#Section_4. Updated February 11, 2021. Accessed May 6, 2021. **2.** SEER Cancer Stat Facts: Myeloma. National Cancer Institute website. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed May 6, 2021. **3.** 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. Accessed May 6, 2021.

Memorial Sloan Kettering Cancer Center

Realities of Health Care Access

- **Blacks have a twofold higher incidence of mortality** from multiple myeloma compared with whites.
- Black and Hispanic patients with multiple myeloma are **less likely to utilize stem cell transplantation and bortezomib treatment** compared with whites; they also receive novel treatments later after their diagnosis compared with whites.
- Notably, a new study shows that Blacks **may have a higher survival rate** than whites when all patients have **equal access to novel treatments.**

AACR Cancer Disparities Progress Report 2020

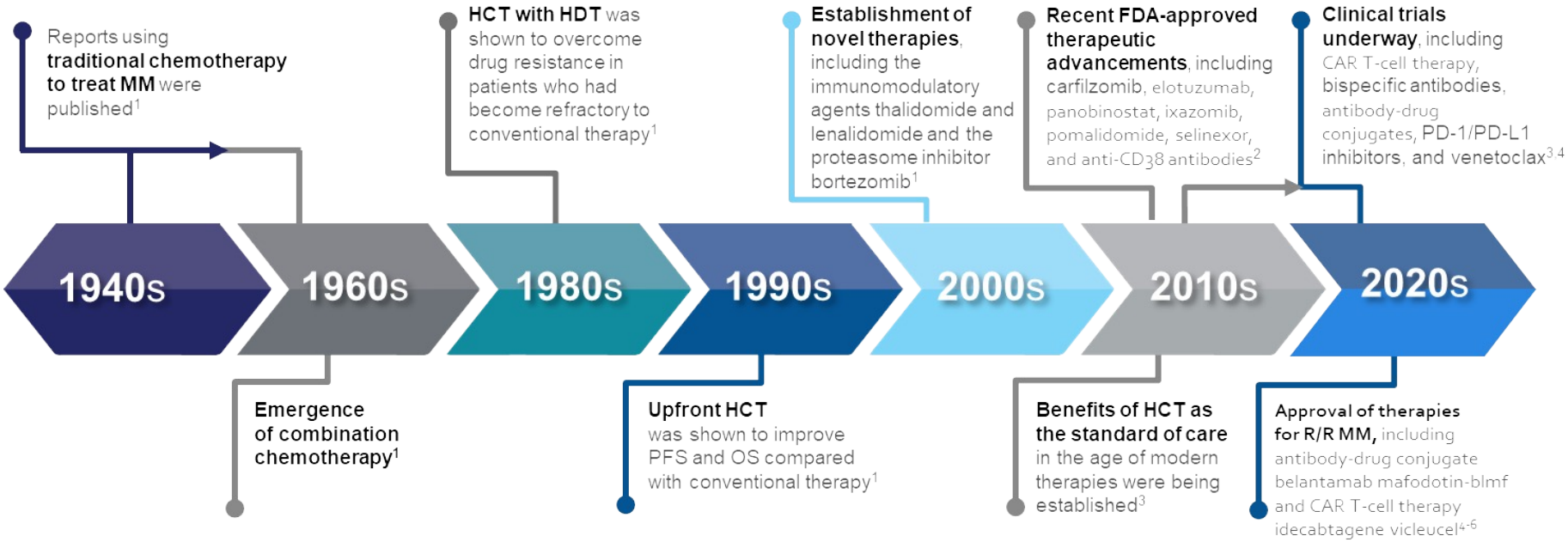
MM Is Not One Disease

- MGUS to Active MM transition period is different among patients. Diagnosis is made at variable time-points during the transition, so degree of end organ damage is different.
- Management strategies have improved MM survival from 2-3 years in the 2000s to ≥ 10 years in the 2020s.
- Advances in understanding myeloma biology has led to new therapeutic targets.
  - MM Pathways
  - BM microenvironment
  - Immune regulation and modulation
- Picking the right strategy that gives the highest likelihood of the best depth of response in the first year of diagnosis is extremely important for survival outcomes.

Martinez-Lopez J et al Blood 2011
Usmani et al Leukemia 2012

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.

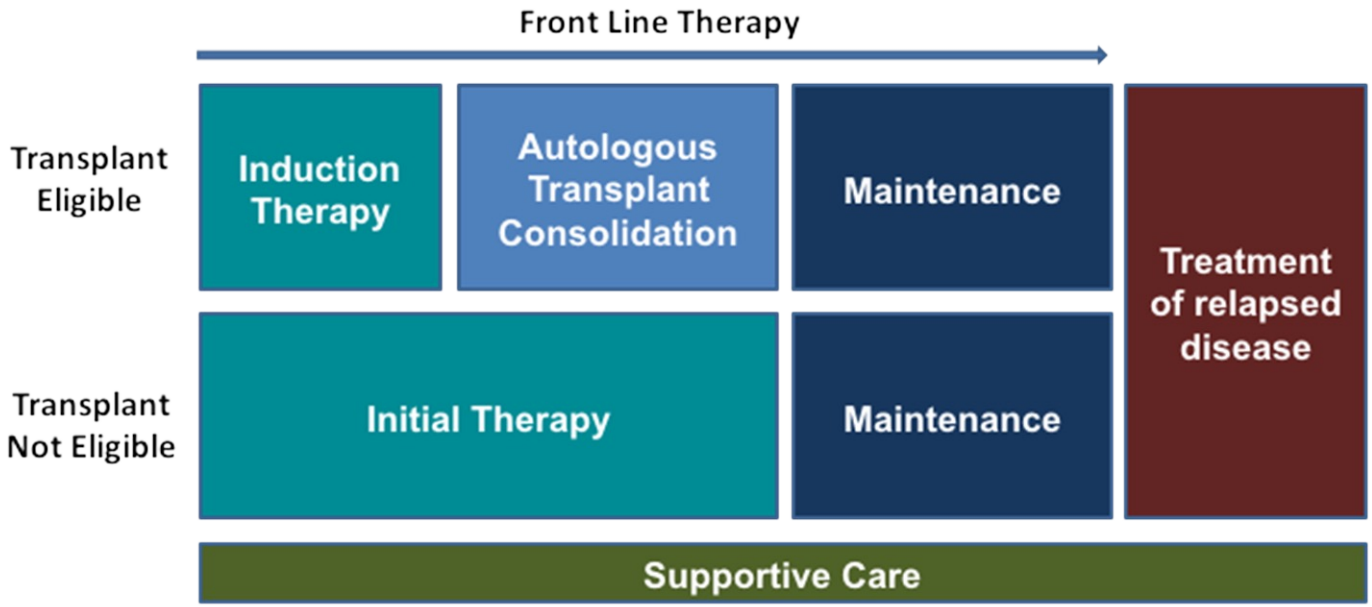
Memorial Sloan Kettering Cancer Center

Blind Spots

- Poor assessment of MM disease biology at diagnosis and relapse:
  - Highly dependent on the quality of random pelvic bone biopsy
    - Can fix by creating SOP for sample 'pecking order'.
  - No assessment of FDG avid focal bone lesions or EMD
    - Can fix by concomitant biopsy of such lesions as 'routine' practice, not patient friendly.
  - Only examine at finite timepoints
    - Harder fix as biopsies are not patient friendly, this is not CLL ☺.
  - This leads to the 'unexpected' poor responders or unexpected 'early relapse' we see in the clinics.
- We are still learning how to incorporate immunome and BM microenvironment status in MM patient assessment.
- We are still optimizing how best to assess depth of response/detect MRD status.

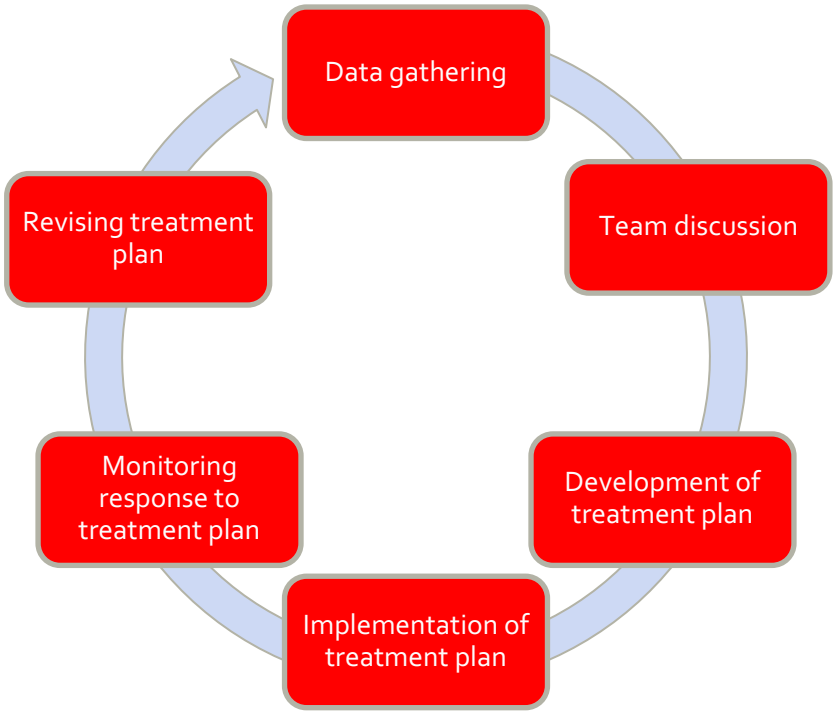
Memorial Sloan Kettering Cancer Center

Treatment Paradigm For Newly Diagnosed Multiple Myeloma



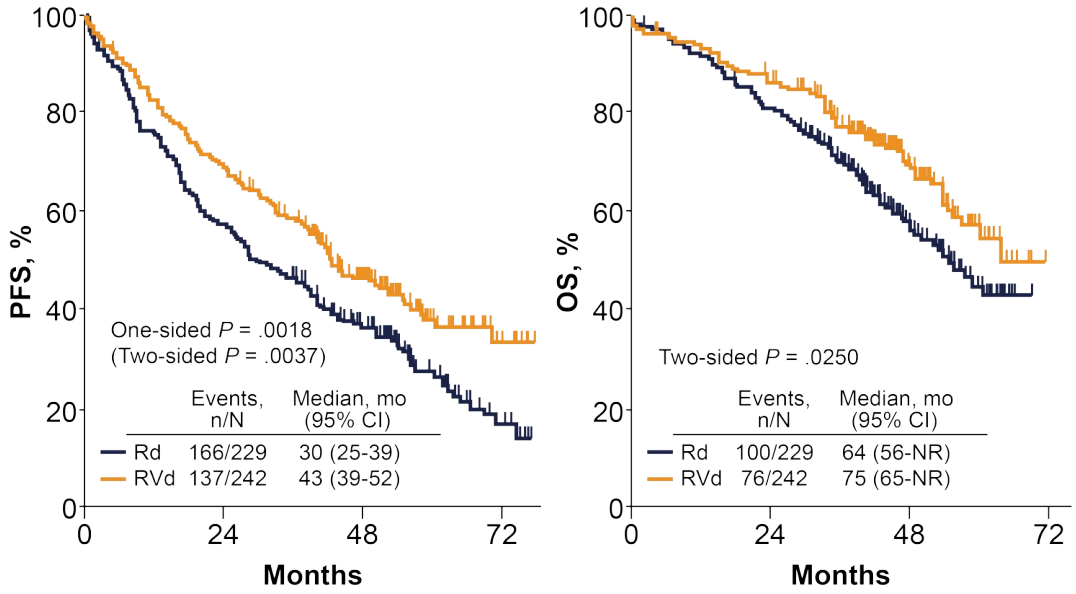
Memorial Sloan Kettering Cancer Center

Management Plan – Ongoing Process During Care



Memorial Sloan Kettering Cancer Center

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



Initial Therapy

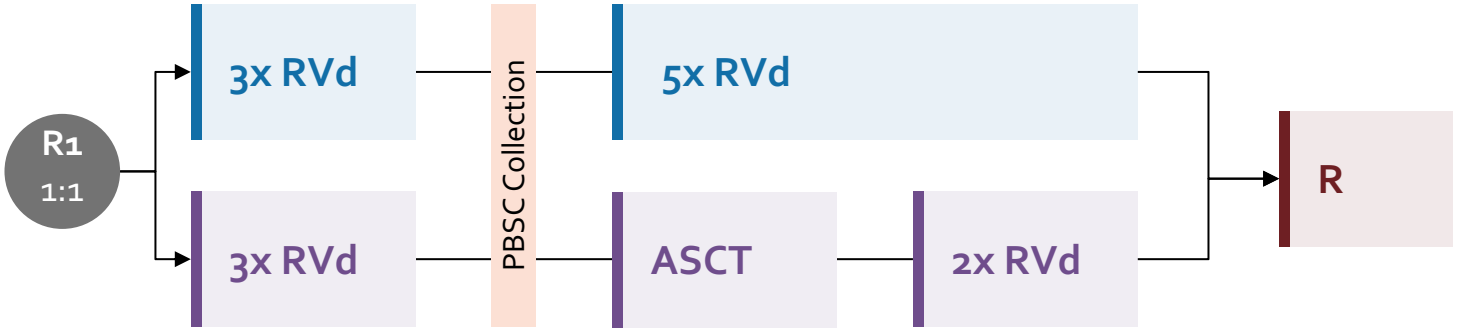
RVd for eight 21-d cycles vs Rd for six 28-d cycles in patients not intending to proceed to upfront transplant, followed by Rd in both arms (N = 525)

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

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

Memorial Sloan Kettering Cancer Center

IFM 2009 Study: Early vs Late ASCT



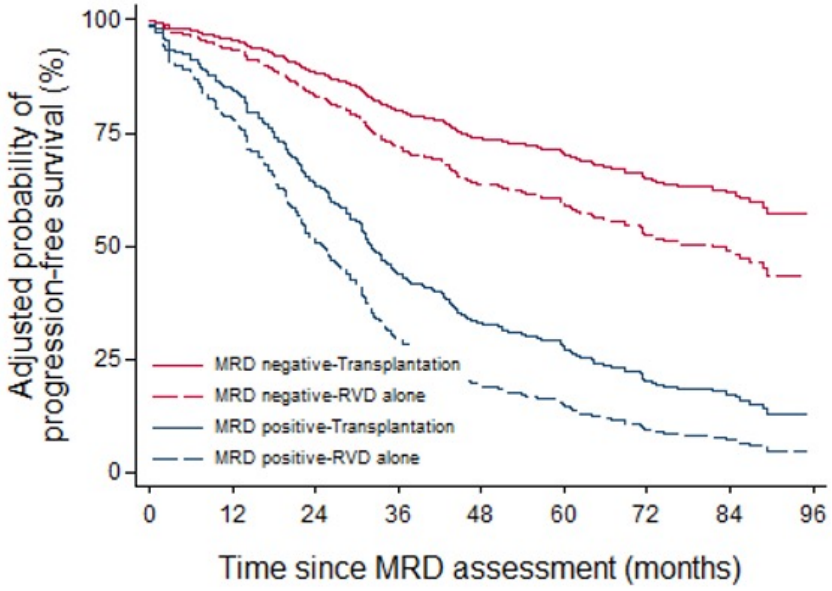
RVd 21-day Cycles
R: 25 mg d 1 – 14
V: 1.3 mg/m² d 1, 4, 8, 11
d: 20 mg d 1, 2, 4, 5, 8, 9, 11, 12

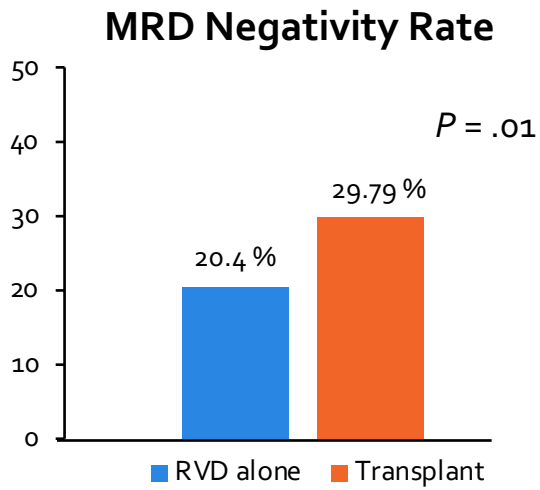
R Maintenance
R: 10-15 mg/d for 13 cycles

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

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

Superior PFS With ASCT vs RVd Alone





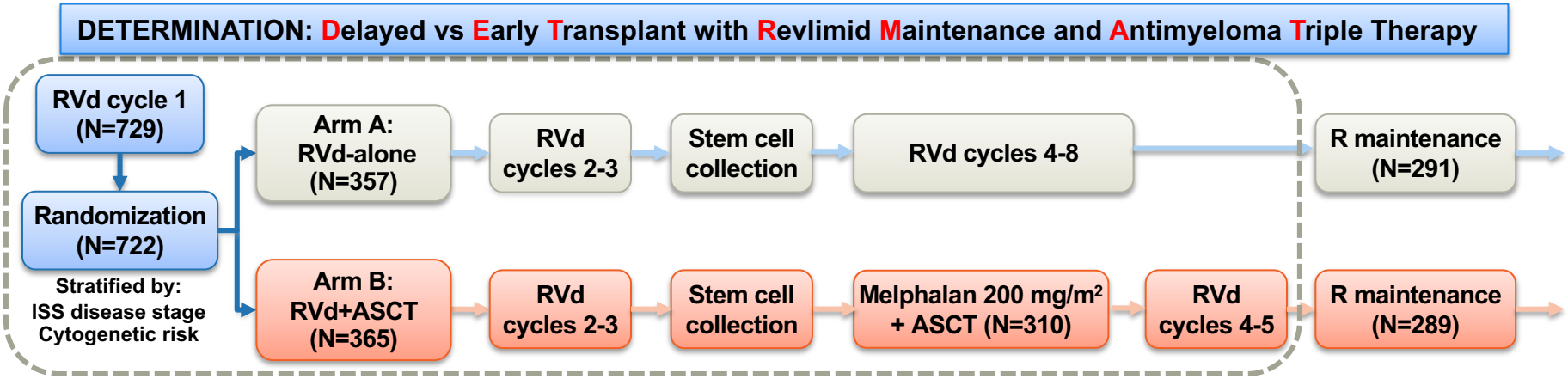
RVd + transplant was superior to RVd alone, even with undetectable MRD at 10^{-6}

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

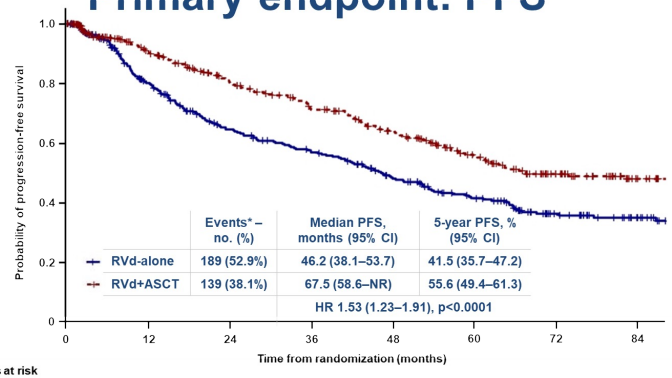
- d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

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

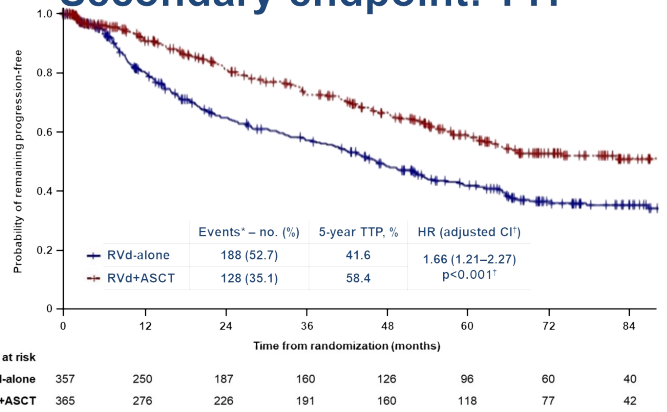
Memorial Sloan Kettering Cancer Center

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

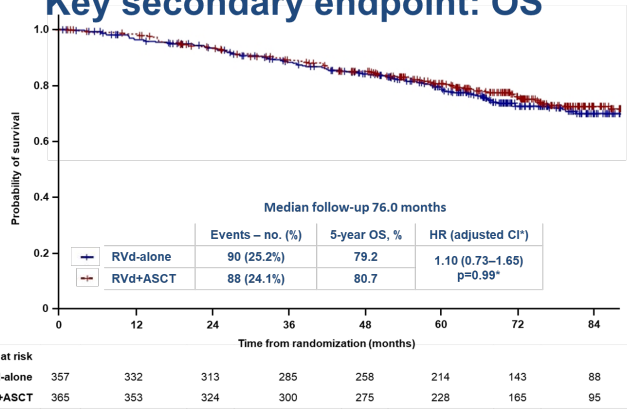
Primary endpoint: PFS



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

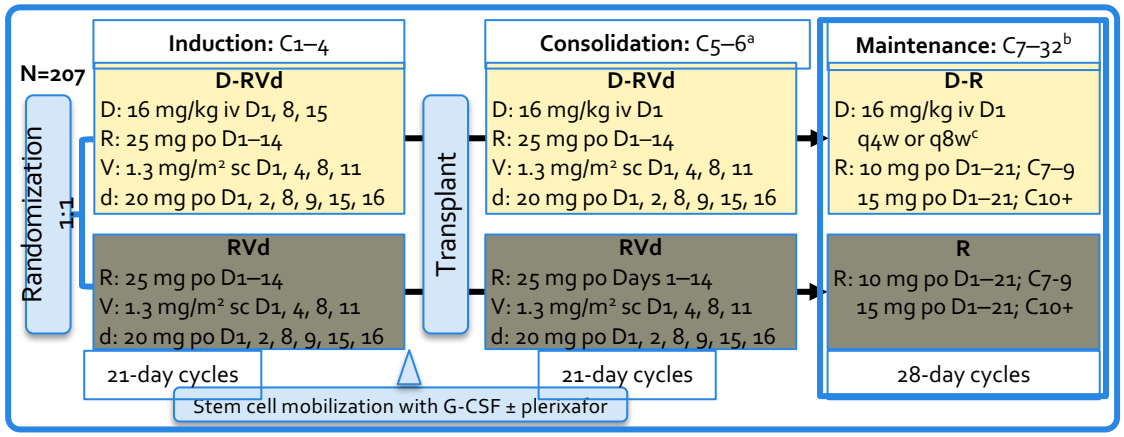
SPMs	RVd-alone (N=357)	RVd+ASCT (N=365)
Any, %	10.4	10.7
Any invasive SPM, %	5.3	6.8
Any hematologic SPM, %	2.5	3.6
ALL, n	7	3
AML/MDS, n	0	10
CLL/CML, n	2	0
Any solid tumor SPM, %	3.4	3.3
Any non-invasive solid tumor SPM, %	0	0.5
Any non-melanoma skin cancer, %	5.9	4.1

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

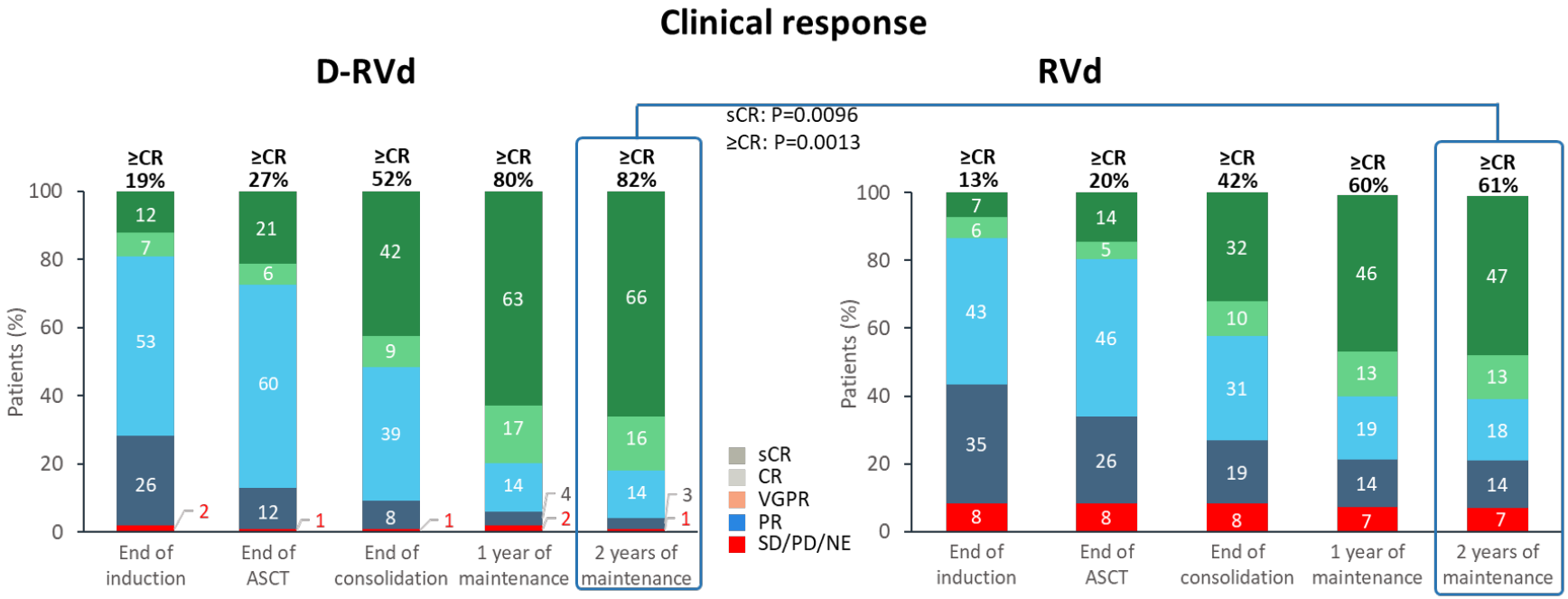
n (%)	D-RVd (n=104)	RVd (n=103)
Treated with maintenance therapy	90 (87)	70 (68)
Completed maintenance therapy	67 (64)	44 (43)
Discontinued treatment during maintenance therapy	21 (20)	21 (20)
Adverse event	8 (8)	7 (7)
Progressive disease	3 (3)	7 (7)
Patient withdrawal	2 (2)	4 (4)
Lost to follow-up	2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



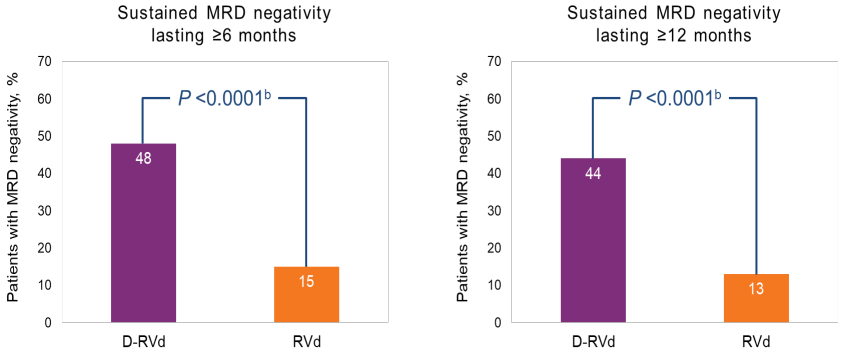
Laubach JP, et al. ASH 2021, Virtual Meeting. Abstract 79

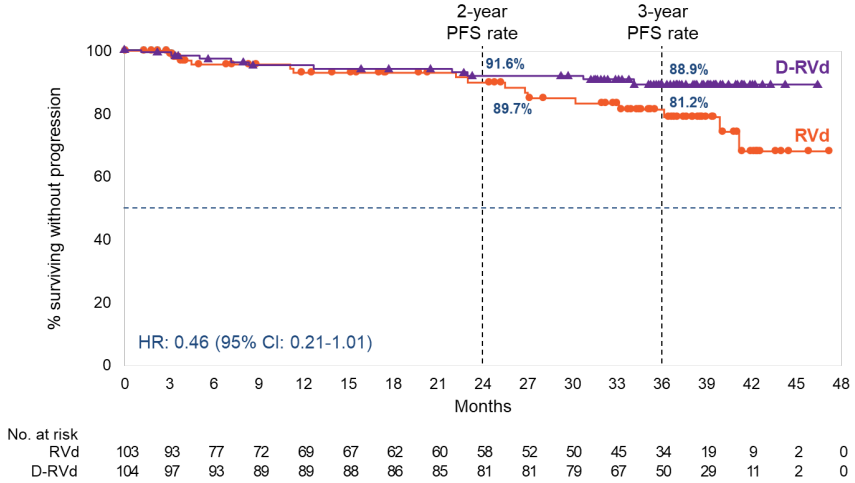
Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

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





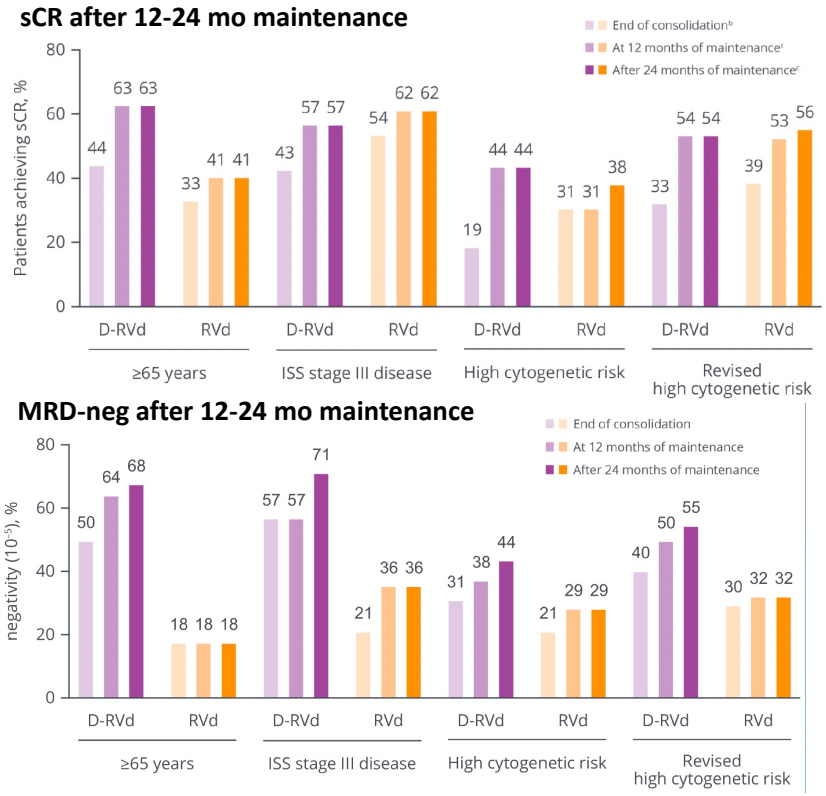
- Median follow-up: 38.6 months
- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR versus RVd/R
- The separation of the PFS curves begins beyond 1 year of maintenance and suggests a benefit of prolonged DR therapy

[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

Subgroup Analysis of GRIFFIN

- sCR rates were improved for D-RVd versus RVd in patients ≥65 years of age, and similar sCR rates between D-RVd and RVd were seen for those with ISS stage III disease, high cytogenetic risk.
- MRD-negativity rates were improved for D-RVd versus RVd in all subgroups, including patients with high-risk features

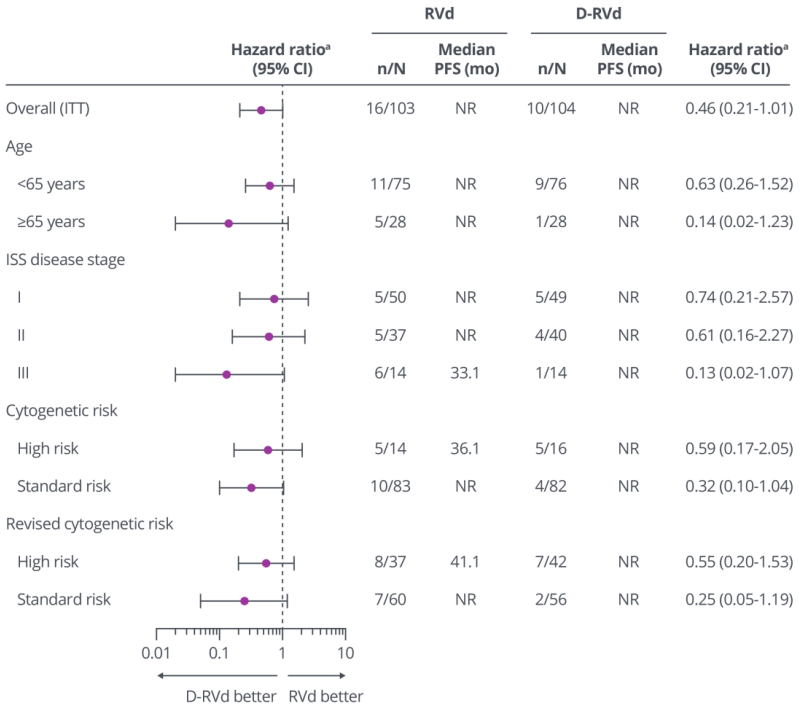


Anderson, et al. 2021 ASH Annual Meeting. Abstract 2723

Memorial Sloan Kettering Cancer Center

Subgroup Analysis of GRIFFIN

PFS after 24 mo maintenance

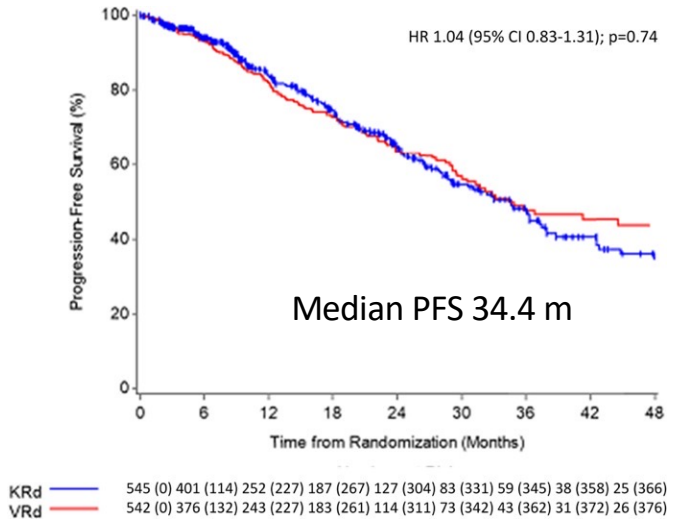


Anderson, et al. 2021 ASH Annual Meeting. Abstract 2723

Memorial Sloan Kettering Cancer Center

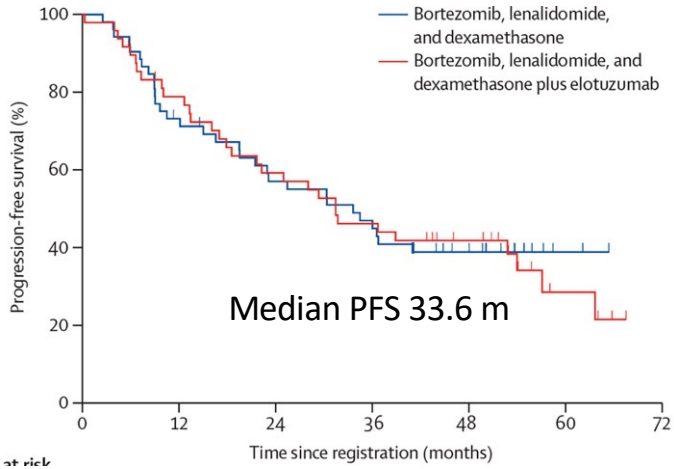
Impact of PI/IMiD Maintenance in High-Risk MM

Standard Risk



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

High Risk

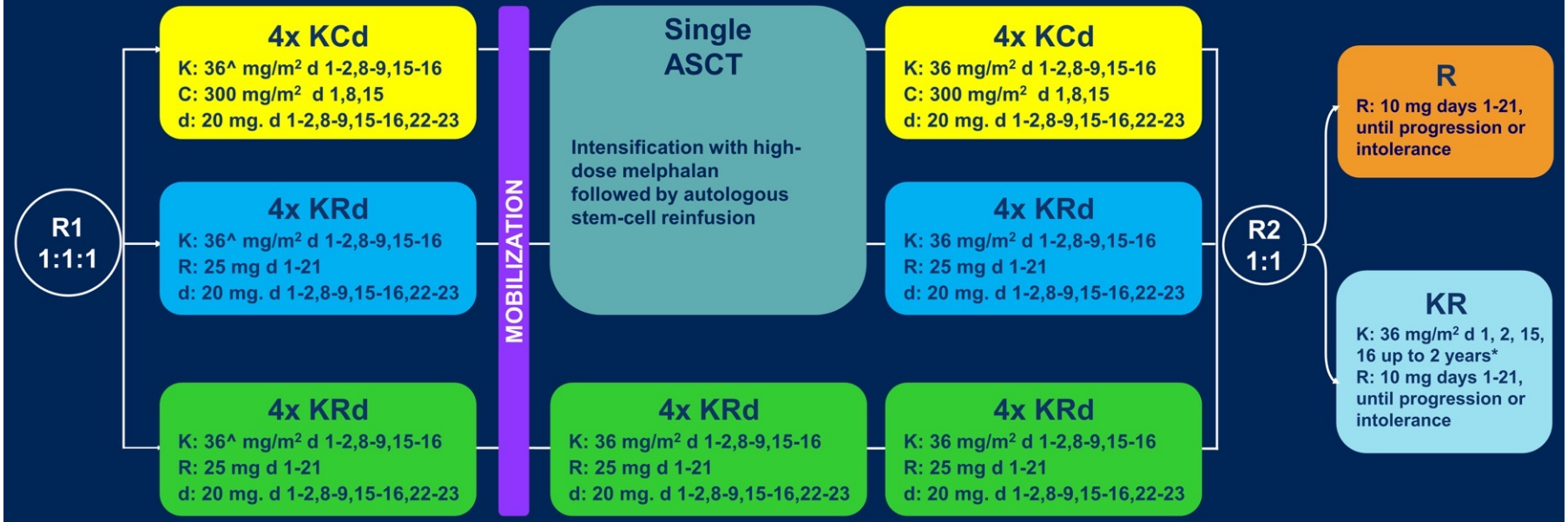


S1211: Elo VRd or VRd with VR maintenance
Usmani SZ et al Lancet Haematol 2021

Memorial Sloan Kettering Cancer Center

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

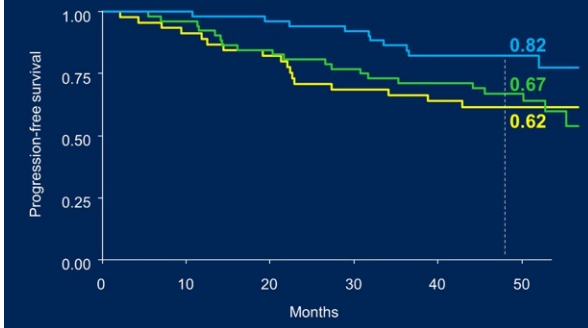
Memorial Sloan Kettering Cancer Center

Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

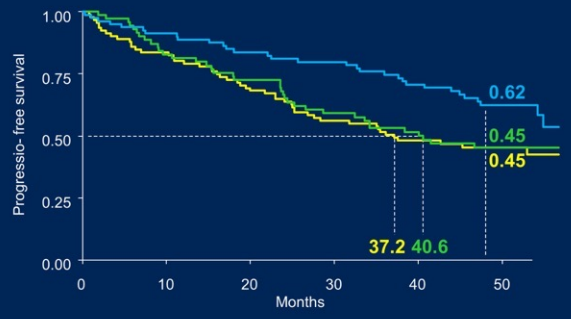
Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)



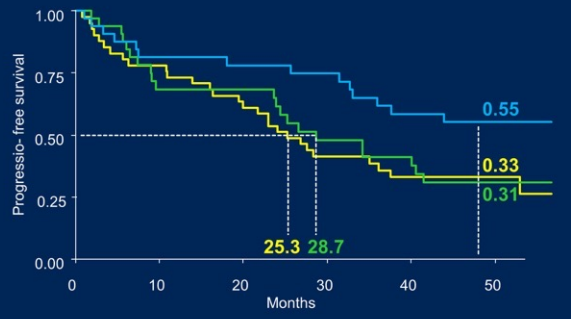
KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04
KRd_ASCT vs. KRd12: HR 0.46, p=0.04
KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

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 trasplantation; 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.

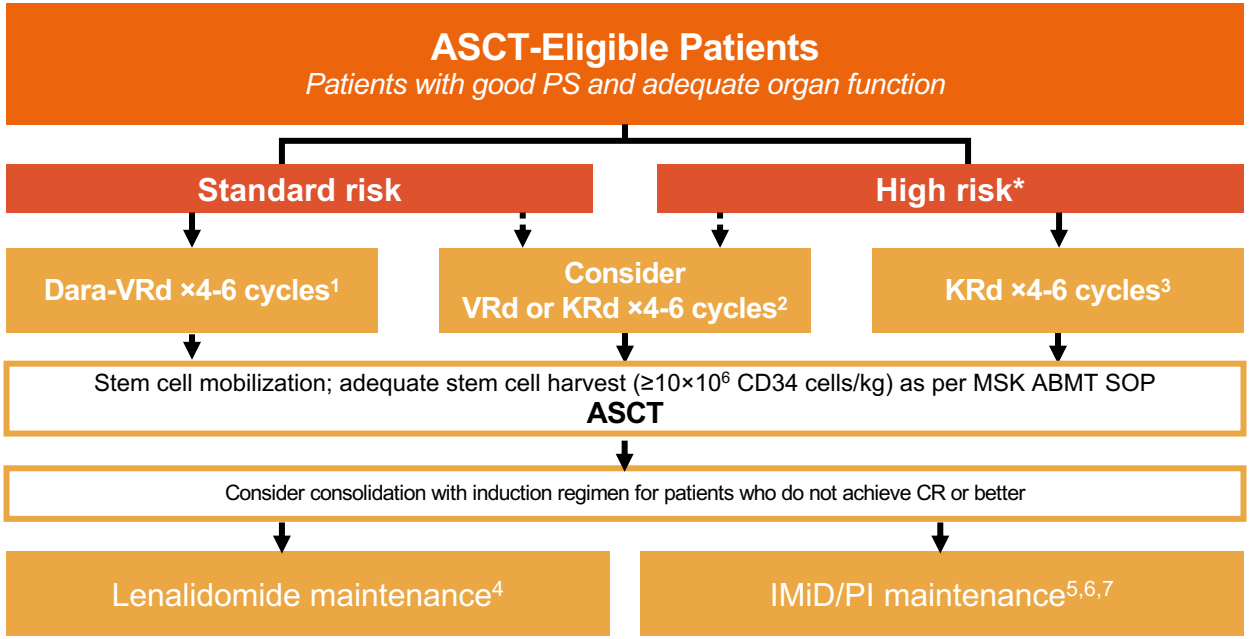
Presented By: Francesca Gay

2021 ASCO ANNUAL MEETING

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

Memorial Sloan Kettering Cancer Center

MSK Approach to Transplant Eligible NDMM

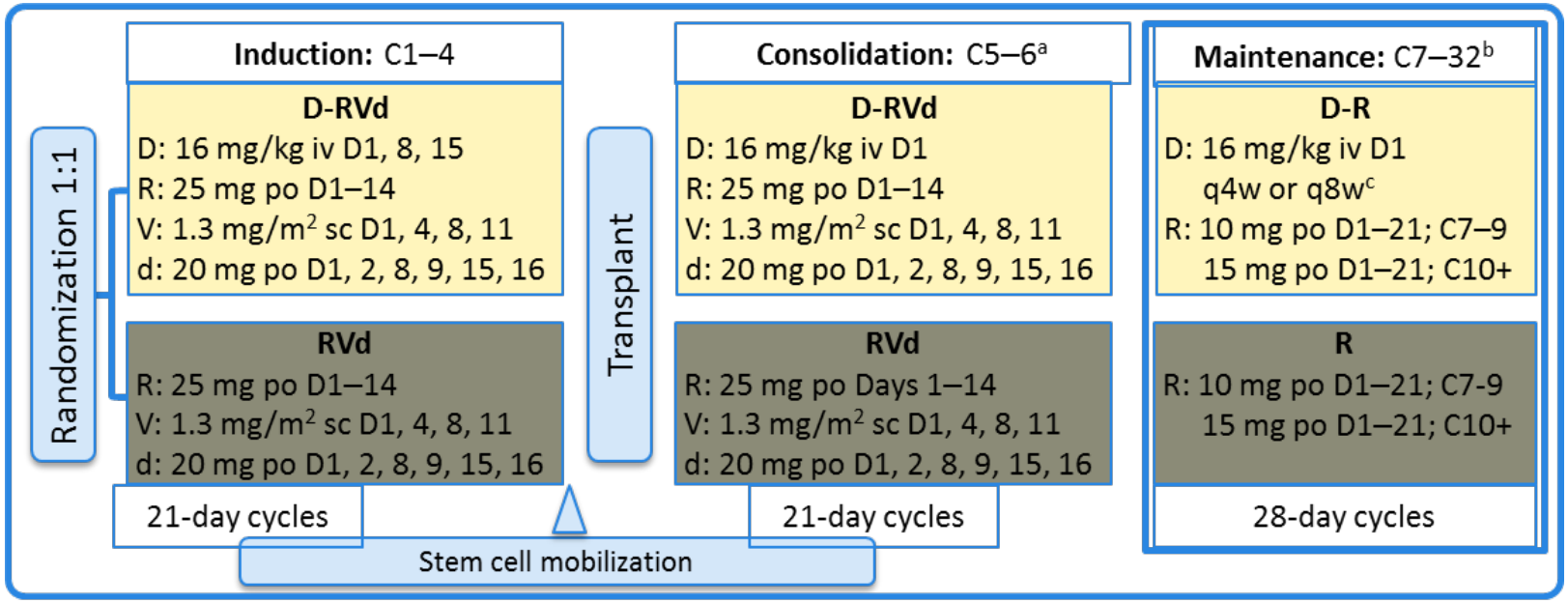


- ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; Tx, treatment.
- *By R-ISS staging (R-ISS II/III) and/or cytogenetics (t[4;14], t[14;16], or del[17p]), 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.

Memorial Sloan Kettering Cancer Center

PERSEUS: Study Design

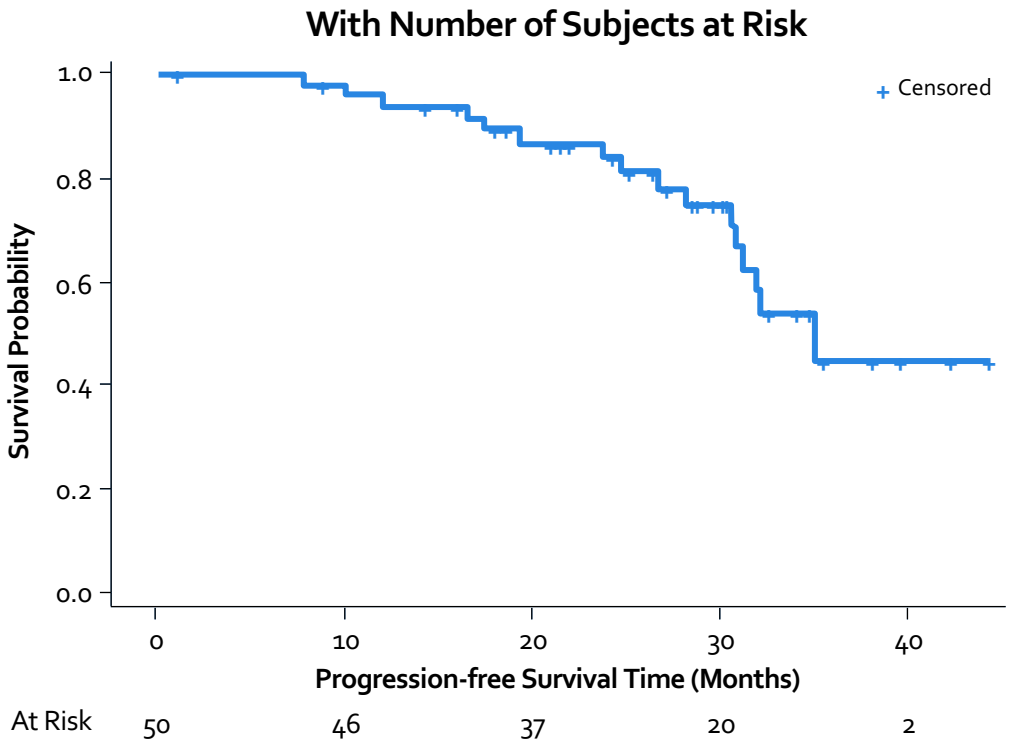
Phase 3 trial, n=390



Memorial Sloan Kettering Cancer Center

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



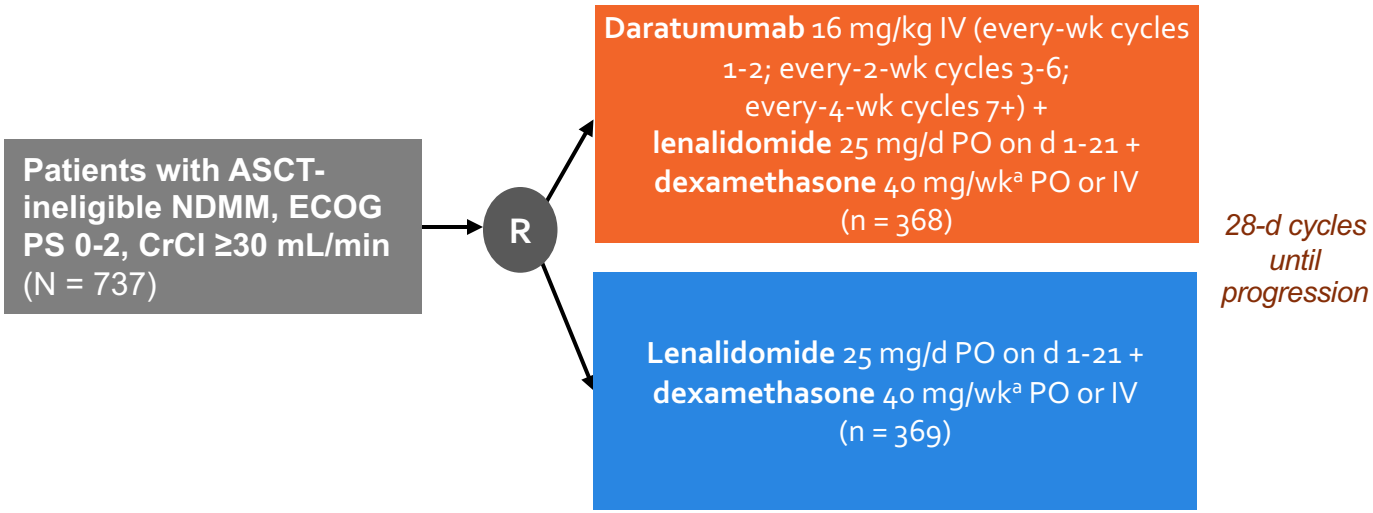
- PN, peripheral neuropathy.

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

Memorial Sloan Kettering Cancer Center

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.

Memorial Sloan Kettering Cancer Center

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)

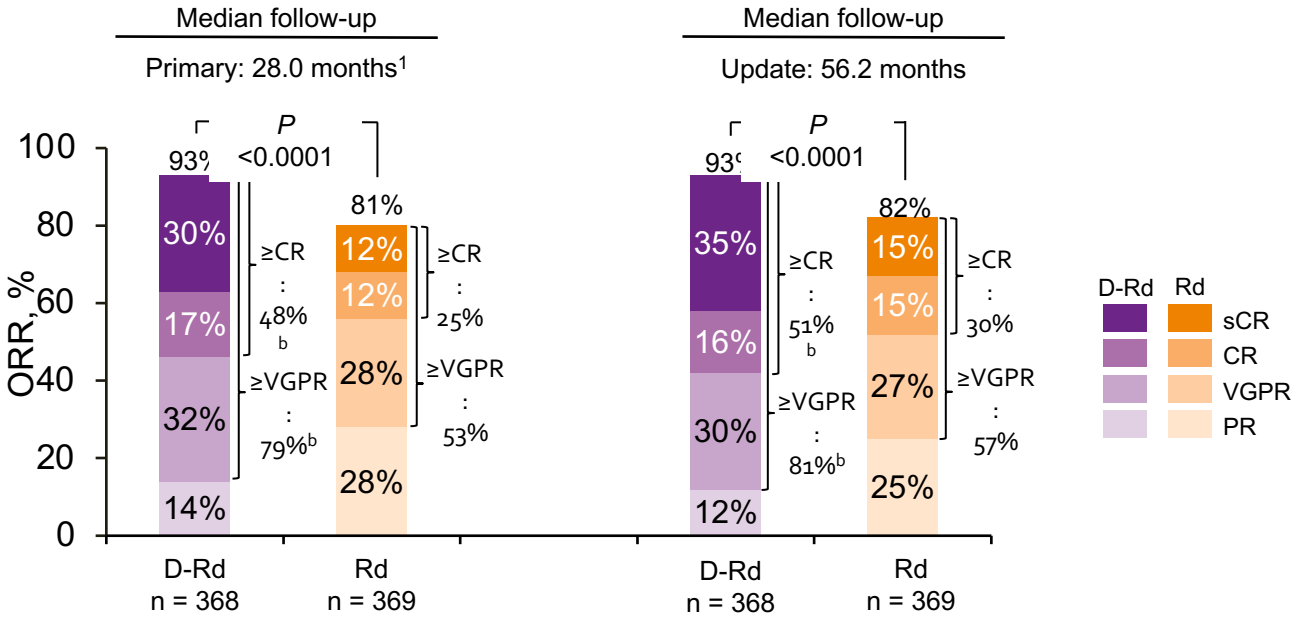
	D-Rd (n = 368)	Rd (n = 369)
Type of measurable disease, n (%)		
IgG	225 (61)	231 (63)
IgA	65 (18)	66 (18)
Other[d]	9 (2)	10 (3)
Detected in urine only	40 (11)	34 (9)
Detected as serum-free light chain only	29 (8)	28 (8)
Cytogenetic profile,[e] n/total n (%)		
Standard risk	271/319 (85)	279/323 (86)
High 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.
[a]ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]2 patients had an ECOG PS score >2 (1 patient each with an ECOG PS score of 3 and 4). [c]ISS stage is derived based on the combination of serum β_2-microglobulin and albumin; higher stages indicate more severe disease. [d]Includes IgD, IgE, IgM, and biclonal. [e]Cytogenetic 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.

Memorial Sloan Kettering Cancer Center

MAIA Phase III ORR[a]

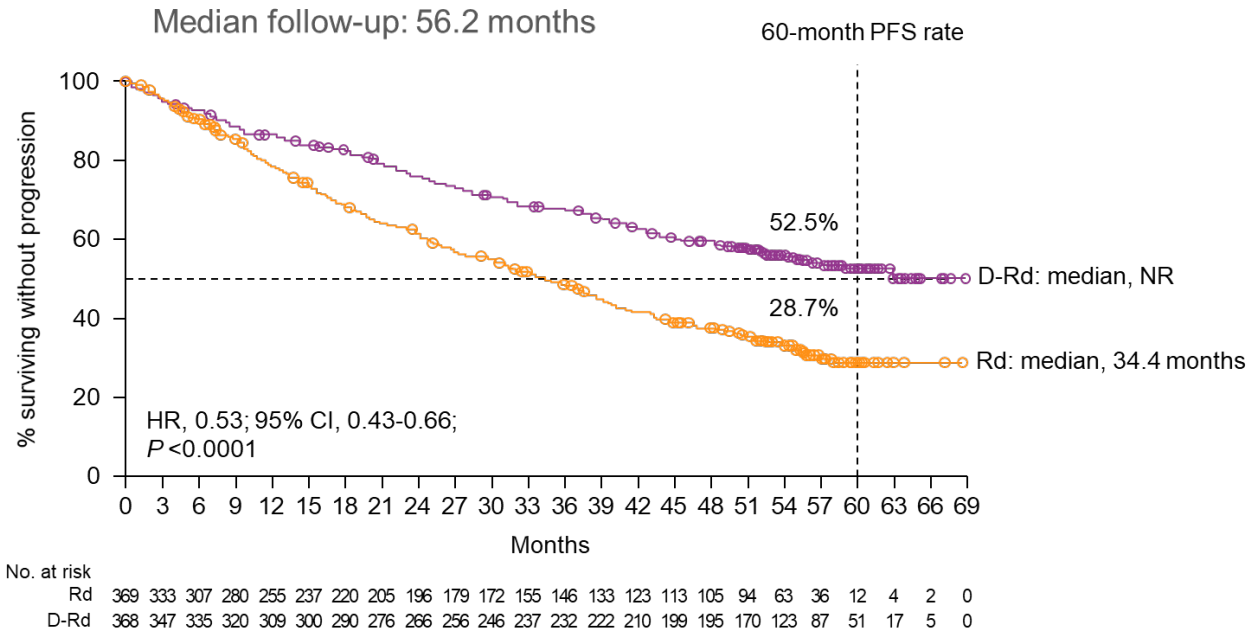


- **D-Rd induced deeper responses, with significantly higher rates of ≥CR and ≥VGPR, compared with Rd**
- **With >28 months of additional follow-up, responses deepened with continued daratumumab therapy**

VGPR, very good partial response; PR, partial response; OR, odds ratio.
[a]ITT population. [b]*P* <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.

Memorial Sloan Kettering Cancer Center

MAIA Phase III Updated PFS



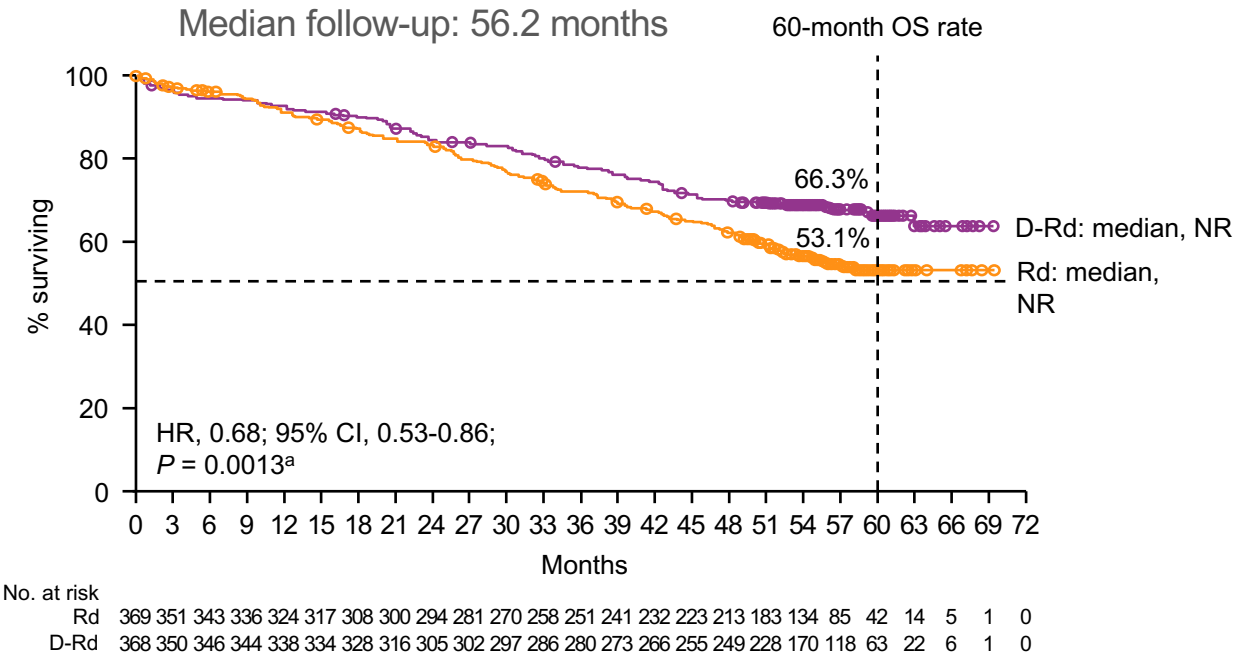
NR, not reached; CI, confidence interval.

- **D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd**
- **These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible**

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

Memorial Sloan Kettering Cancer Center

MAIA Phase III OS

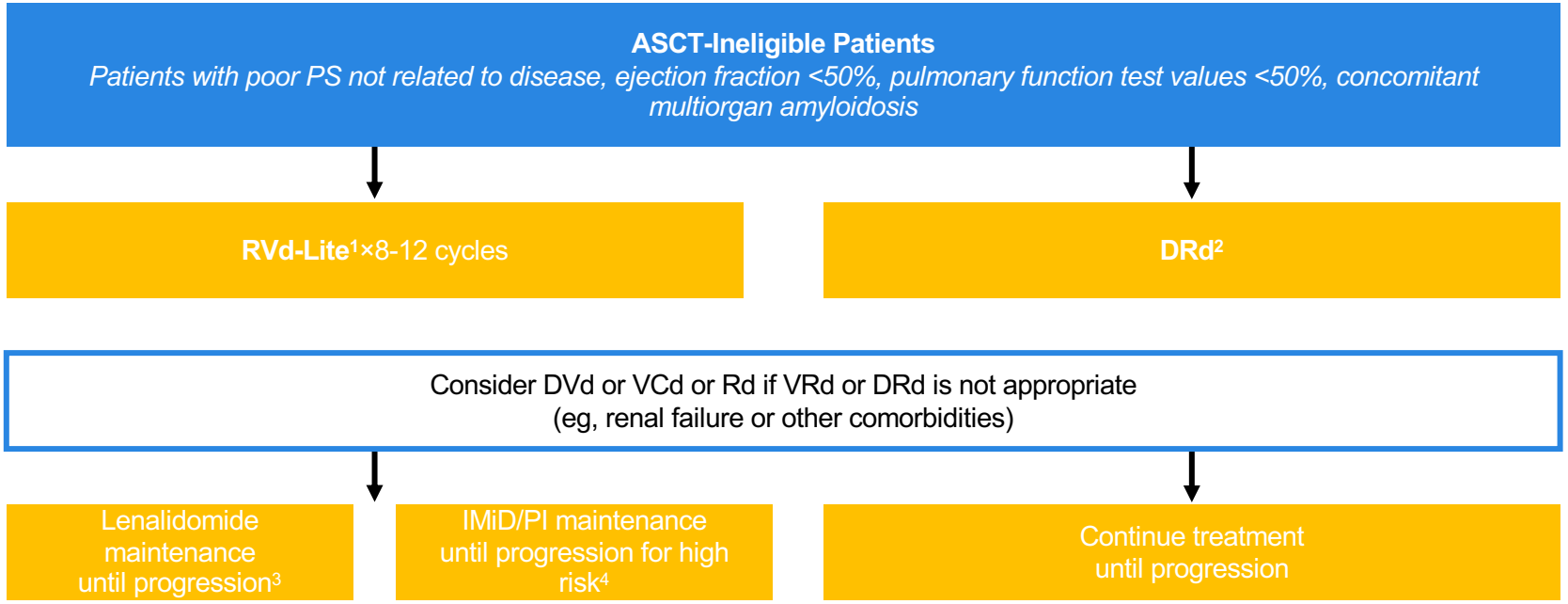


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

[a]*P* = 0.0013 is statistically significant, crossing the prespecified stopping boundary of *P* = 0.0414.

Memorial Sloan Kettering Cancer Center

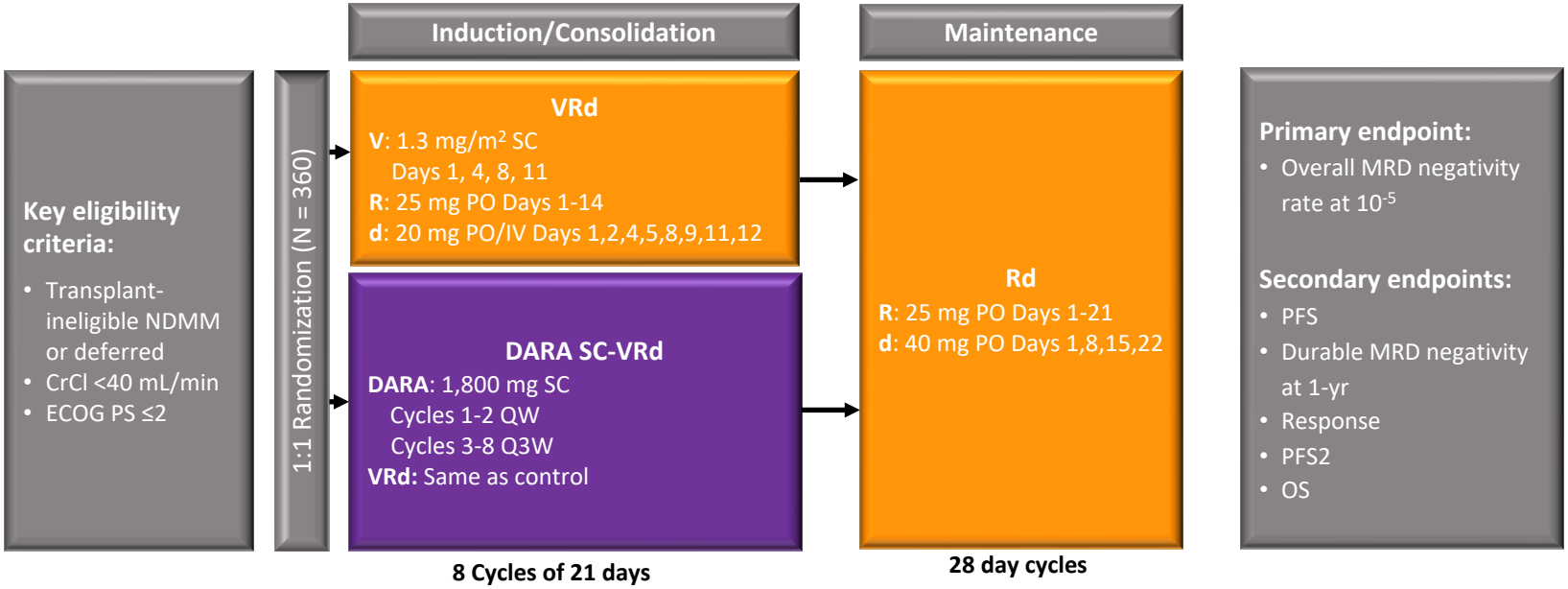
MSK Approach to Transplant Ineligible NDMM



- 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

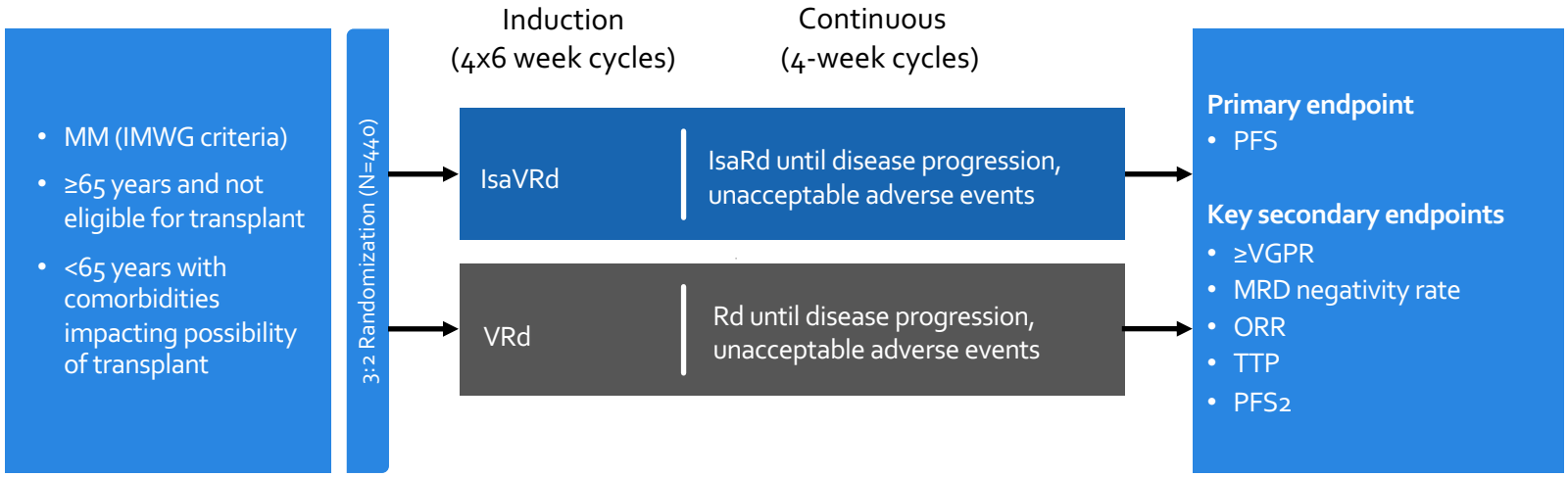
- **Phase 3 study of DARA-VRd versus VRd in transplant-ineligible NDMM**



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

IMROZ: Study Design

- **Phase 3 study of IsaVRd vs VRd in patients with transplant-ineligible NDMM**



Orlowski RZ, et al. Presented at ASCO Annual meeting. June 1-5, 2018. Chicago, IL. Abstract TPS8055.
ClinicalTrials.gov Identifier: NCT03319667. Accessed 7 July 2021.

Memorial Sloan Kettering Cancer Center

Key Questions Towards Curing Myeloma

- What is the molecular and immunobiology of disease evolution and progression in MM?
  - Can we recognize patients at precursor state and intervene early?
  - Can we pick different strategies for different disease biology and immune status?
- How to accurately assess sustained minimal residual disease (MRD) negativity?
  - Can we utilize novel imaging and novel peripheral blood assessments?
- Can MRD guide treatment time and treatment strategy?
  - Sustained MRD at which threshold, how far apart? Use the same for high-risk vs standard-risk disease?
- 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

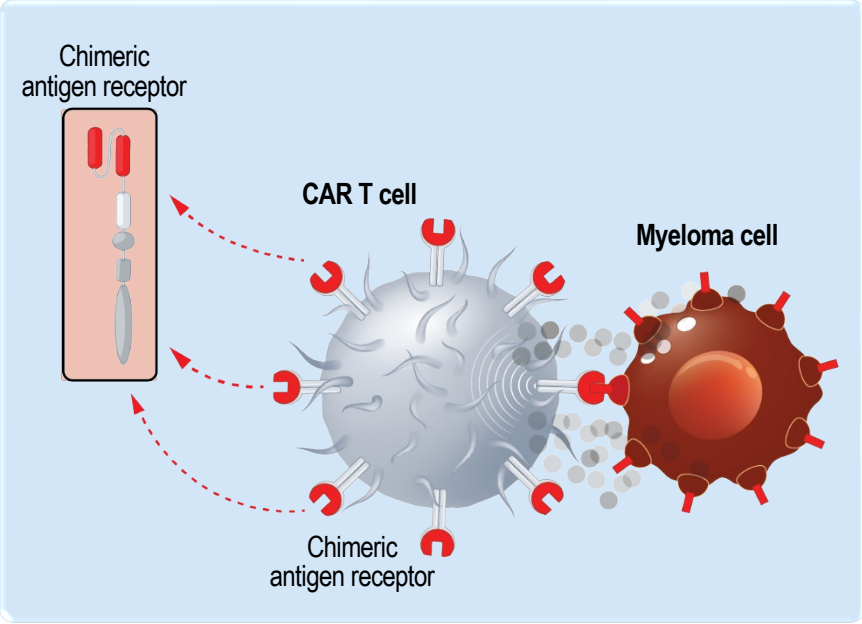
What is coming down the pike?

- Small Molecules
  - XPO1 inhibitors: Selinexor combinations
  - CelMods: Iberdomide, CC-480
  - BCL2/MCL1 Pathway: Venetoclax and its combinations, several MCL1 inhibitors
- Novel Antibody Drug conjugates
  - Belamaf combinations
- Bispecific Antibodies
- CARTs

Memorial Sloan Kettering Cancer Center

CAR T-Cell Therapy

- Genetically modified T cells designed to recognize specific proteins on MM cells
- CAR T cells are activated once in contact with the MM cell and can destroy the MM cell
- CAR T cells can persist for long periods of time in the body
- CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop "off-the-shelf" varieties



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

Memorial Sloan Kettering Cancer Center

BCMA CARTs: Summary

	CARTITUDE-1[1] Cilta-cel Phase 1/2	CRB-401[2] Ide-cel Phase 1	KarMMa[3] Ide-cel Phase 2	LUMMICAR-2[4] Zivo-Cel Phase 1b	PRIME[5] P-BCMA-101 Phase 1/2	GC012F[6] Dual CAR-T BCMA+CD19
Patients	97	62	128	20	55	19
Median prior regimens	6	6	6	5	8	5
Triple refractory, %	87.6%	69.4%	84.0%	85%	60%	95%
CAR-T dose	0.71×10^6 (range $0.5–0.95\times10^6$)	50, 150, 450 and 800 x 10^6	150, 300, 450 x10^6	1.5-1.8/2.5-3.0 x10^8	0.75-15 x10^6	1.0-3.0 x10^5
ORR	97.9%	75.8%	50%/69%/82.0%	94.0%	67%[b]	94.7%
CR/sCR	80.4%	38.7%	25%/29%/39%	28%	NR	84.2%
PFS	66%@ 18m	8.8m	12m @450mil			
CRS, all grades	94.8%	75.8%	50%/76%/96%	77%/83%[a]	17%	95%
CRS, grade 3/4	4%	6.5%	0/7%/6%	0%	0%	11%
Neurotoxicity, all grades	20.6%	35.5%	0/17%/20%	15%/17%[a]	3.8%	0%
Neurotoxicity, grade 3/4	10.3%	1.6%	0/1%/6%	8%/0[a]	3.8%	0%

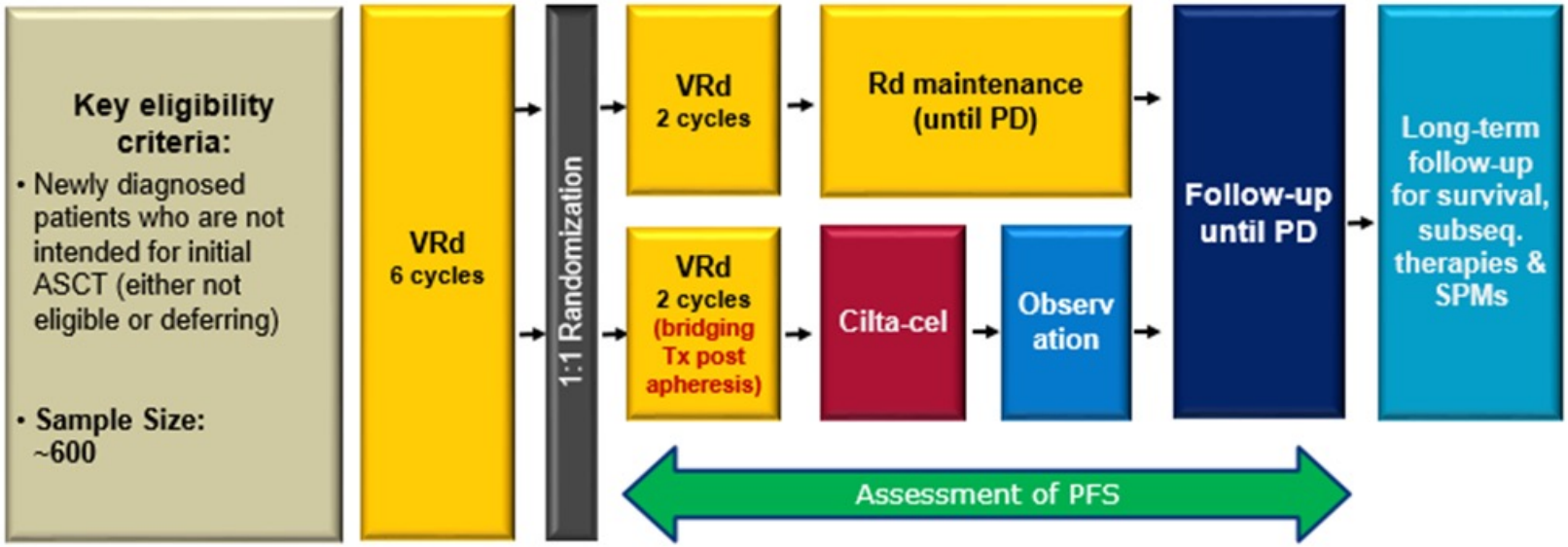
[a]1.5-1.8/2.5-3.0 x10^8 dose, [b]0.75x10^6 dose

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; NR, not reported

1. Usmani et al., ASCO 2021: Abstract 8005; 2. Lin et al., ASH 2020: Abstract 131;
3. Anderson et al., ASCO 2021: Abstract 130; 4. Kumar et al., ASH 2020: Abstract 133;
5. Costello et al., ASH 2020: Abstract 134; 6. Jiang et al., ASCO 2021: Abstract 8014

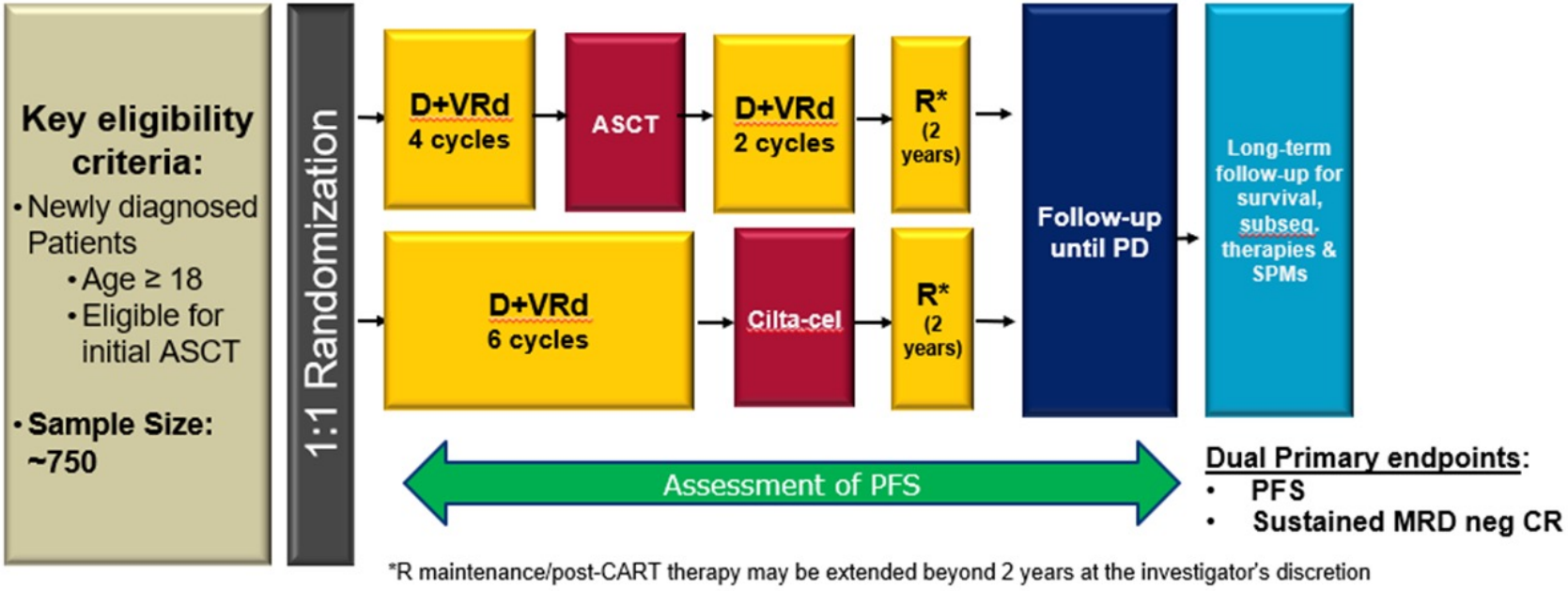
Memorial Sloan Kettering Cancer Center

CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant



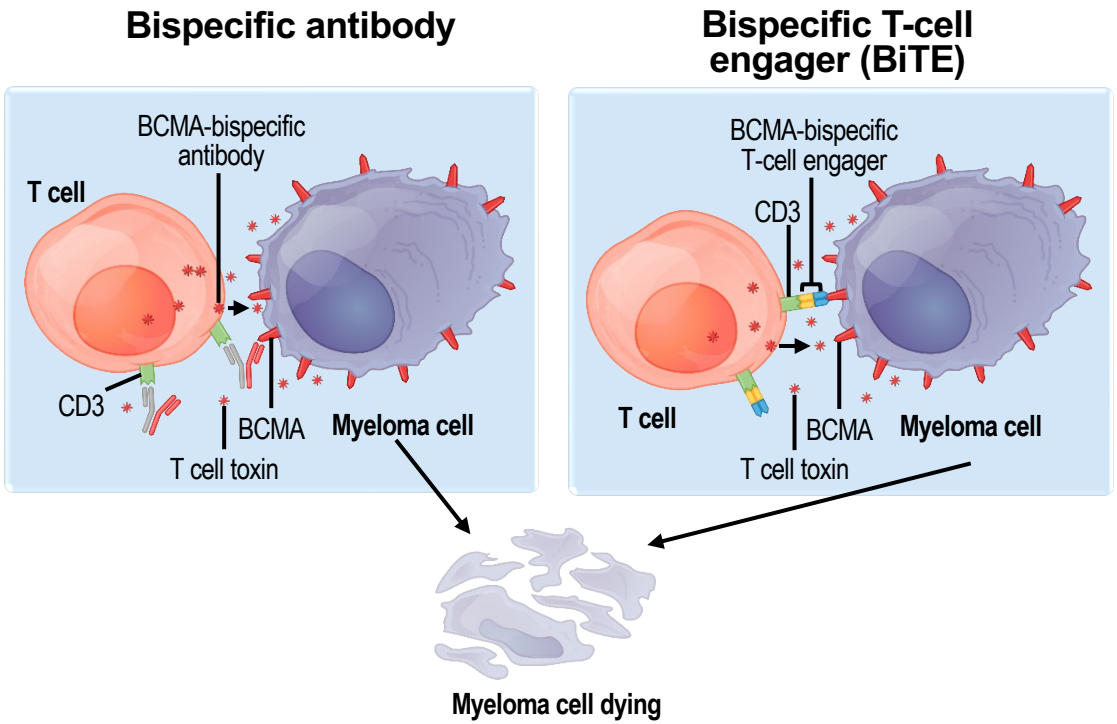
Memorial Sloan Kettering Cancer Center

CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible



Memorial Sloan Kettering Cancer Center

Bispecific antibodies and Bispecific T-Cell Engagers (BiTEs)



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

Memorial Sloan Kettering Cancer Center

BCMA Bispecific Antibodies (ASH 2021 Updates)

	Teclistamab[1]	Elranatamab[2]	TNB-383B[3]	REGN5458[4]
Schedule	Weekly SC	Weekly SC or Q2W SC	IV q3W	Weekly IV
Patients	165	55	118	73
Median prior lines	5	6	5	5
Triple Class and Penta Refractory	78% and 30%	91% and NA	61% and NA	89% and 38%
Prior BCMA	No	22%	No	No
CRS, All (Gr 3/4)	72% (0.6%)	87% (0%)	54% (3%)	38% (0%)
ICANS, All (Gr 3/4)	3% (0%)	NA	2% (NA)	4% (0%)
ORR at higher doses	62%	69% 70% in prior BCMA	60%	75%
CR at higher doses	29%	Not reported	20%	16%

1.Moreau et al. Abstract #896; 2.Sebag et al. Abstract#895; 3. Kumar et al. Abstract #900; 4. Zonder et al. Abstract #160 (ASH 2021)

Memorial Sloan Kettering Cancer Center

Non-BCMA Bispecific Antibodies

	Talquetamab[1]	Cevostamab[2]
Target	GPRC5D	FcRH5
Schedule	Weekly & Q2W SC	Q3 week IV
Patients	55	161
Median prior lines	5-6	6
Prior BCMA	**22%**	**34%**
Triple Class and Penta Refractory	76% and 21%	85% and 68%
CRS, All (Gr 3/4)	75% (2%)	81% (1%)
ICANS, All (Gr 3/4)	NA	14% (0.6%)
ORR and CR at higher doses	**69%**	**57%**
CR at higher doses	**16%**	**8%**
Other notable AEs	**Skin, nail, taste changes**	

1. Krishnan et al. Abstract # 158; 2. Trudel et al. Abstract #157 (ASH 2021)

Memorial Sloan Kettering Cancer Center

Bispecific Antibody Combinations

	Talquetamab+ Daratumumab[1]	Teclistamab + Daratumumab[2]
Target	GPRC5D + CD38	BCMA + CD38
Schedule	Weekly & Q2W SC	Weekly & Q2W SC
Patients	29	37
Median prior lines	6	5
Prior BCMA	**55%**	**19%**
CD38 refractory	**66%**	**60%**
Triple Class and Penta Refractory	52% and 31%	54% and 19%
CRS, All (Gr 3/4)	55% (0%)	65% (0%)
ICANS, All (Gr 3/4)	3% (3%)	3% (0%)
ORR at higher doses	**81%**	**82%**
CR at higher doses	**19%**	**27%**

1. Chari et al. Abstract #161; 2. Rodriguez-Otero et al. Abstract #1647.

Memorial Sloan Kettering Cancer Center

What Will It Take For T-Cell Redirection To Beat ASCT?

	ASCT	CART	Bispecifics Ab
Data			
Cost	$$	$$$$	$$$
Manufacturing concerns	No	Yes	No
Available Globally	Yes		
Non-relapse mortality	Low		
Long-term safety data	Yes	No	No

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

Memorial Sloan Kettering Cancer Center

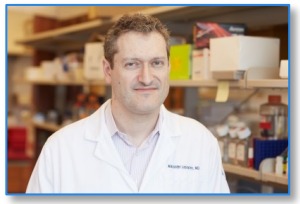
MSKCC Myeloma Service

Saad Z. Usmani (Chief)
High-Risk Disease
Biology/Trials
Bispecific Antibodies
CAR T Cells
Checkpoint Inhibitors
Developmental Therapeutics

Sham Mailankody
MM
Immunotherapy
CAR T Cells

Malin Hultcrantz
MM Precursor Disease
Antibody drug conjugates
Genetics/MRD

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



Alex Lesokhin
MM Immunotherapy
Bispecific Antibodies
Checkpoints Inhibitors
Neoantigens
Microbiota

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

Neha Korde
NDMM Clinical Trials
MRD Directed therapy
Supportive Care

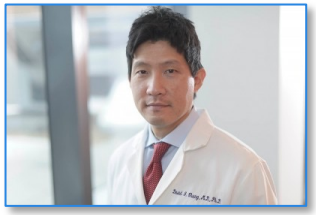
Carlyn Tan
MM Precursor diseases
Supportive Care
Bone Health

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

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

Memorial Sloan Kettering Cancer Center

Q&A Session