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Managing Newly Diagnosed Multiple Myeloma in 2024

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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.

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NDMM: Principles of Therapy

- 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.
  - MRD 10^{-5} >> MRD 10^{-6} >> Sustained MRD 10^{-6}
- Optimize induction, consolidation and maintenance based on:
  - Disease biology (what kind?).
  - Disease burden (how much?).
  - Patient characteristics (PS, co-morbidities, frailty).
  - Patient preference.
- Never under-treat, put your best foot forward!
  - Especially true for high risk NDMM (HR-NDMM)
- Do not forget supportive care measures: bone health, infection prevention, pain management, physical therapy and rehabilitation, mental health.

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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 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]

- R-ISS III
- R-ISS II with 1q21+, Del17p, t(14;16), t(14;20)
- Circulating PCs ≥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. 3. D'Agostino et al. *J Clin Oncol* 2022 ;40(29):3406-3418; 4; Davies F et al. Blood Cancer Discovery 2022

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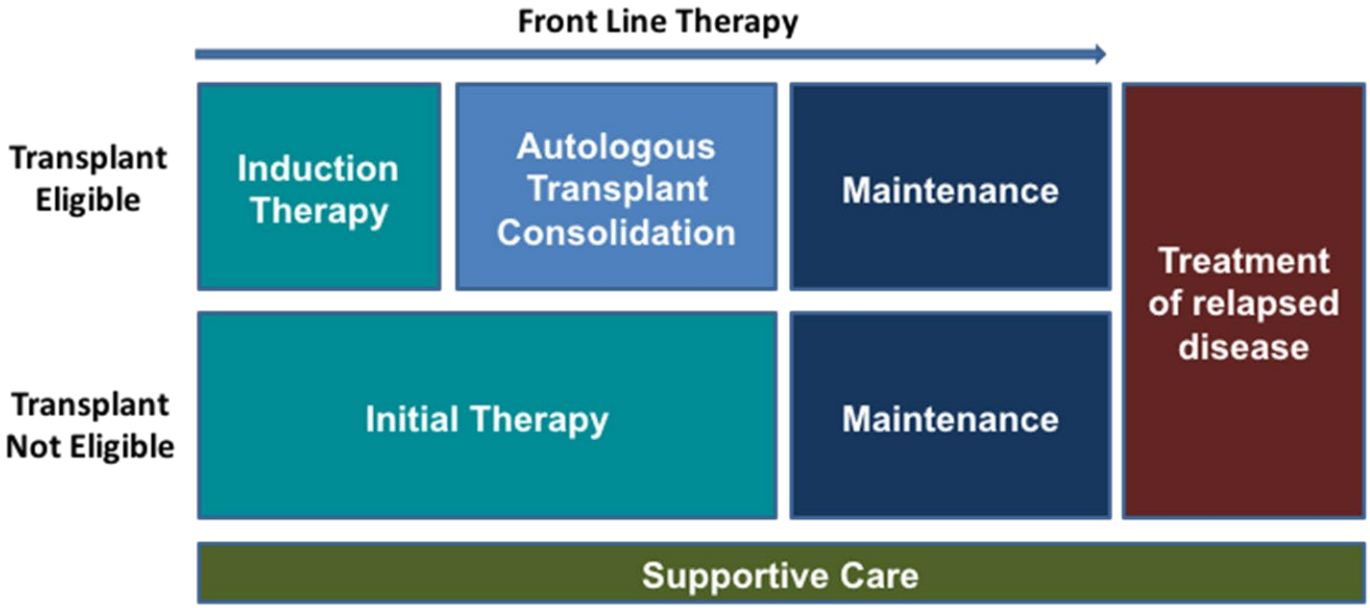
Treatment Paradigm For Newly Diagnosed Multiple Myeloma



Standard-Risk NDMM OS: ~ 13 years
High-Risk NDMM OS: ~ 7 years

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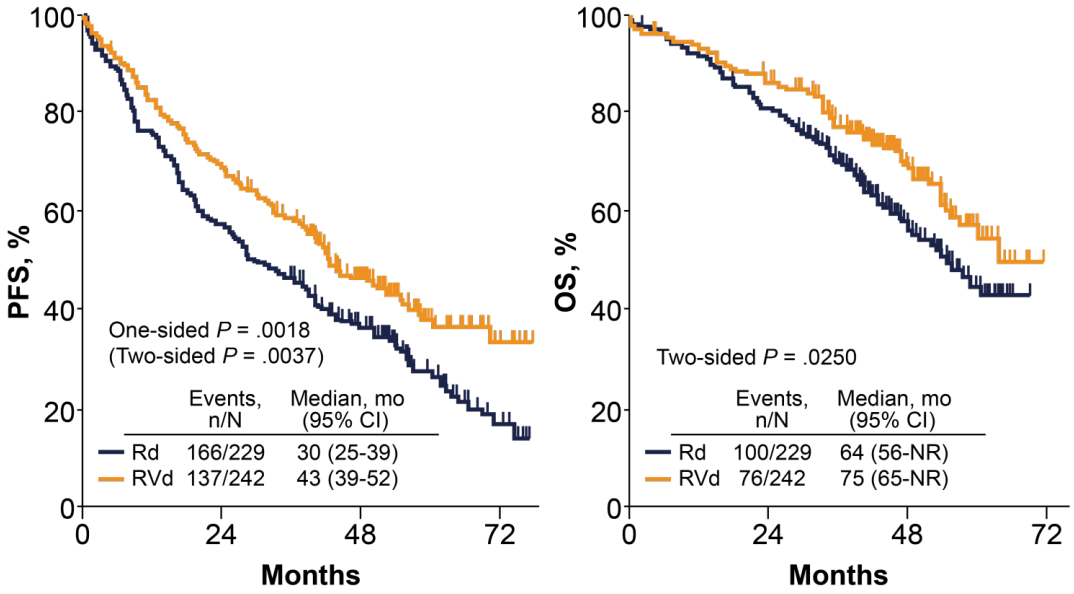
SWOG S0777: RVd Versus Rd in Patients Without Immediate Intent for ASCT[1]



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.

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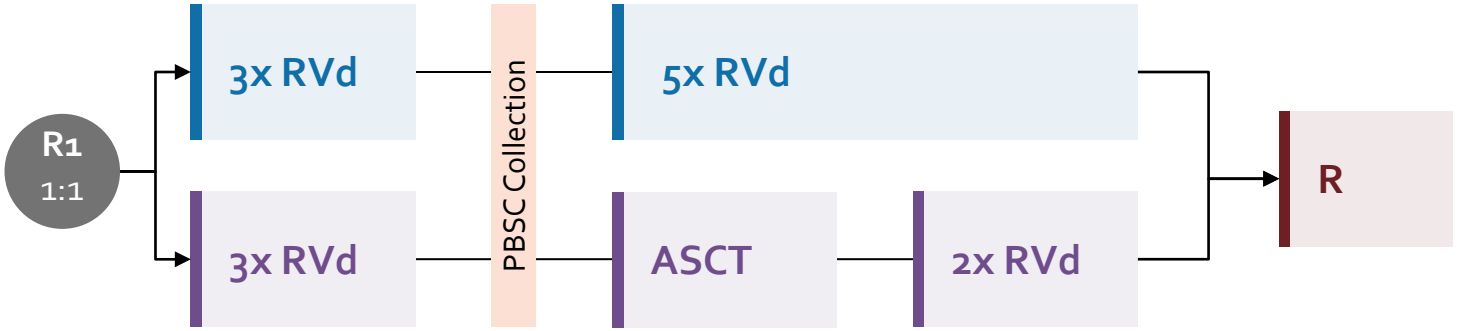
IFM 2009 Study: Early vs Late ASCT



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.

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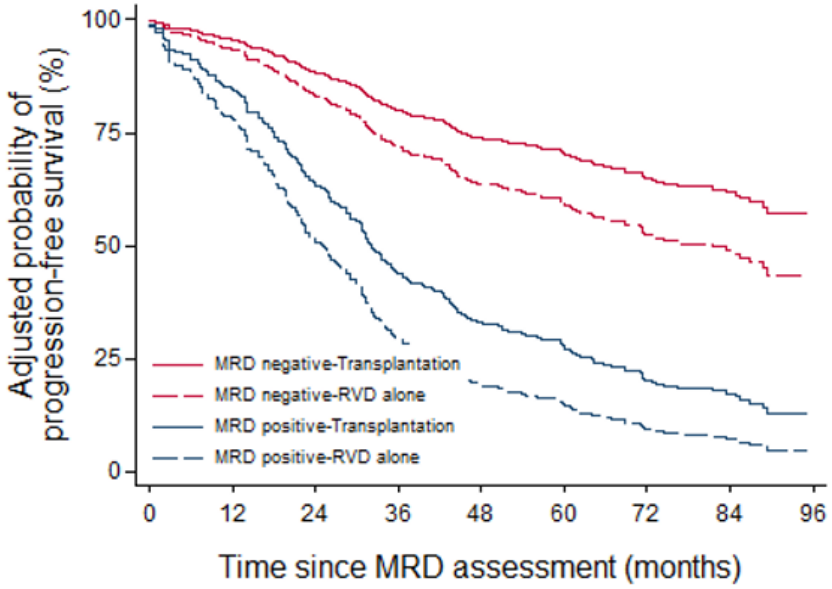
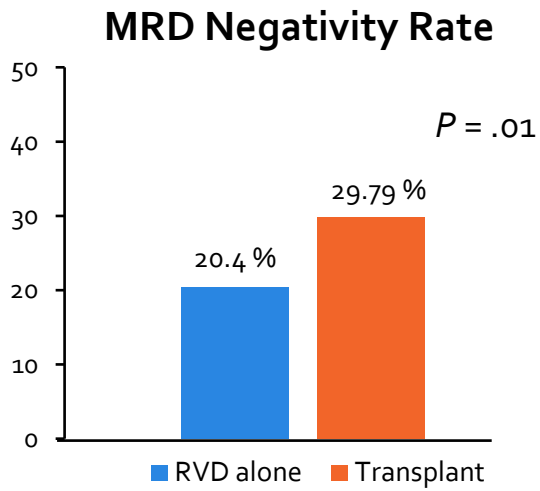
Superior PFS With ASCT vs RVd Alone





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.

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

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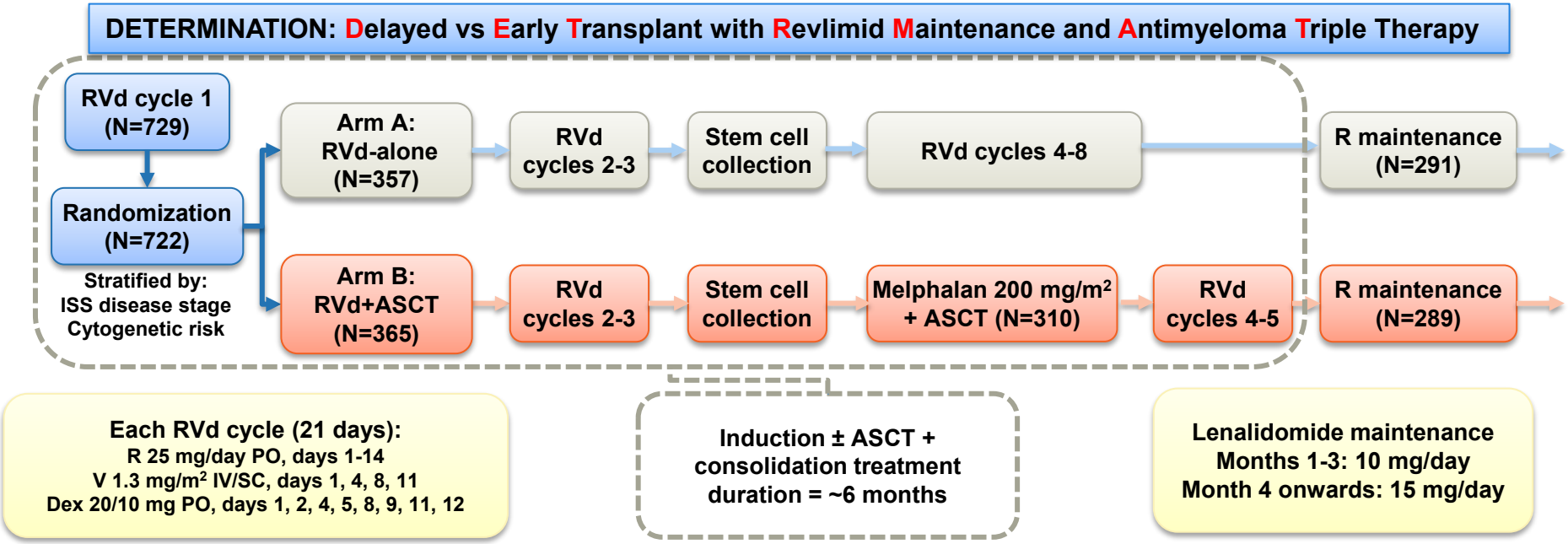
DETERMINATION: study design and patient disposition



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

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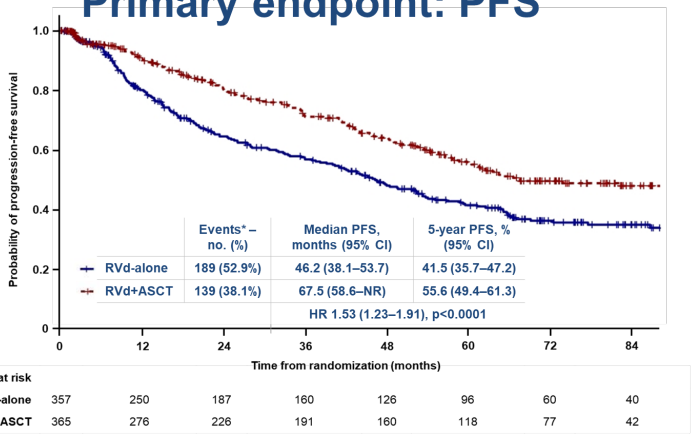
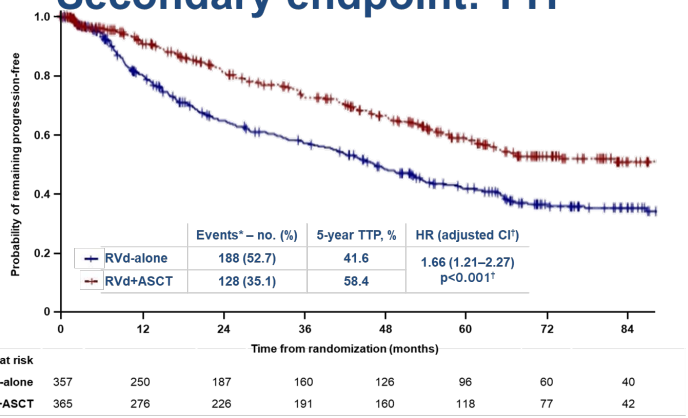
DETERMINATION: Endpoint Readouts
(Median follow-up 70 months)

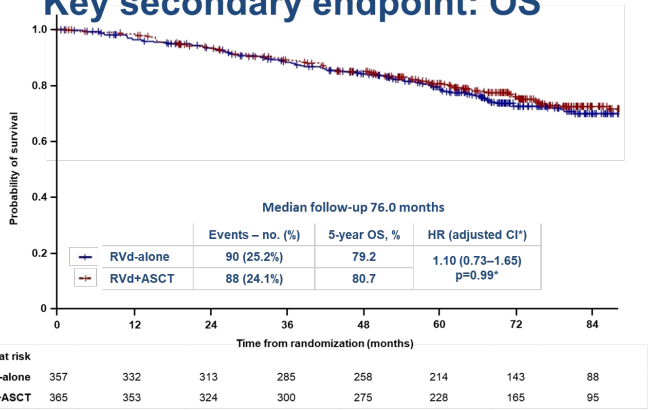
Primary endpoint: PFS



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

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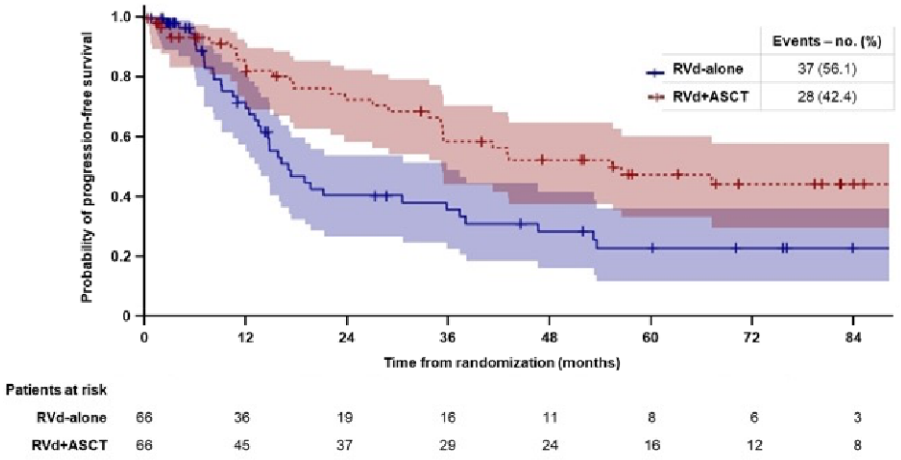
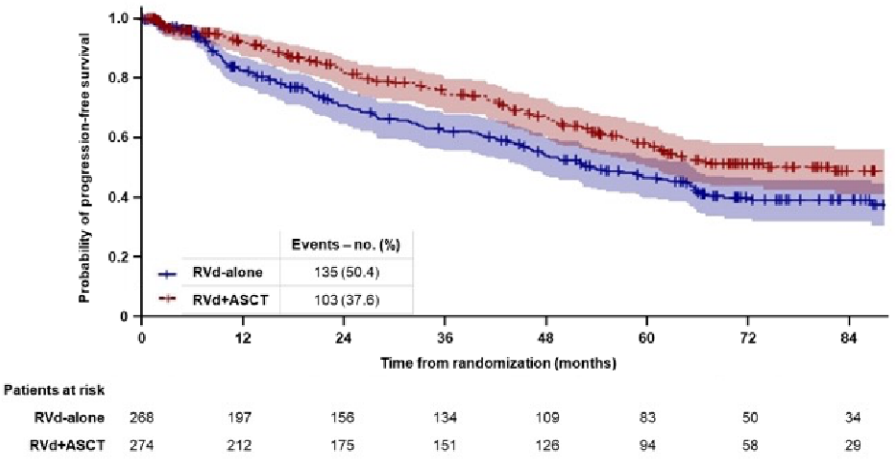
DETERMINATION Trial: PFS by Risk





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

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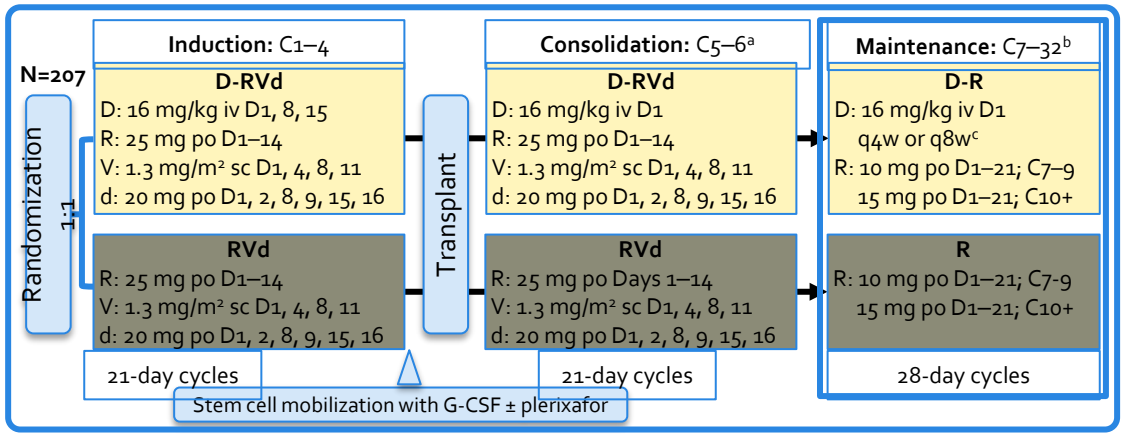
GRIFFIN: Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Eligible NDMM – 24 Months of Maintenance

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

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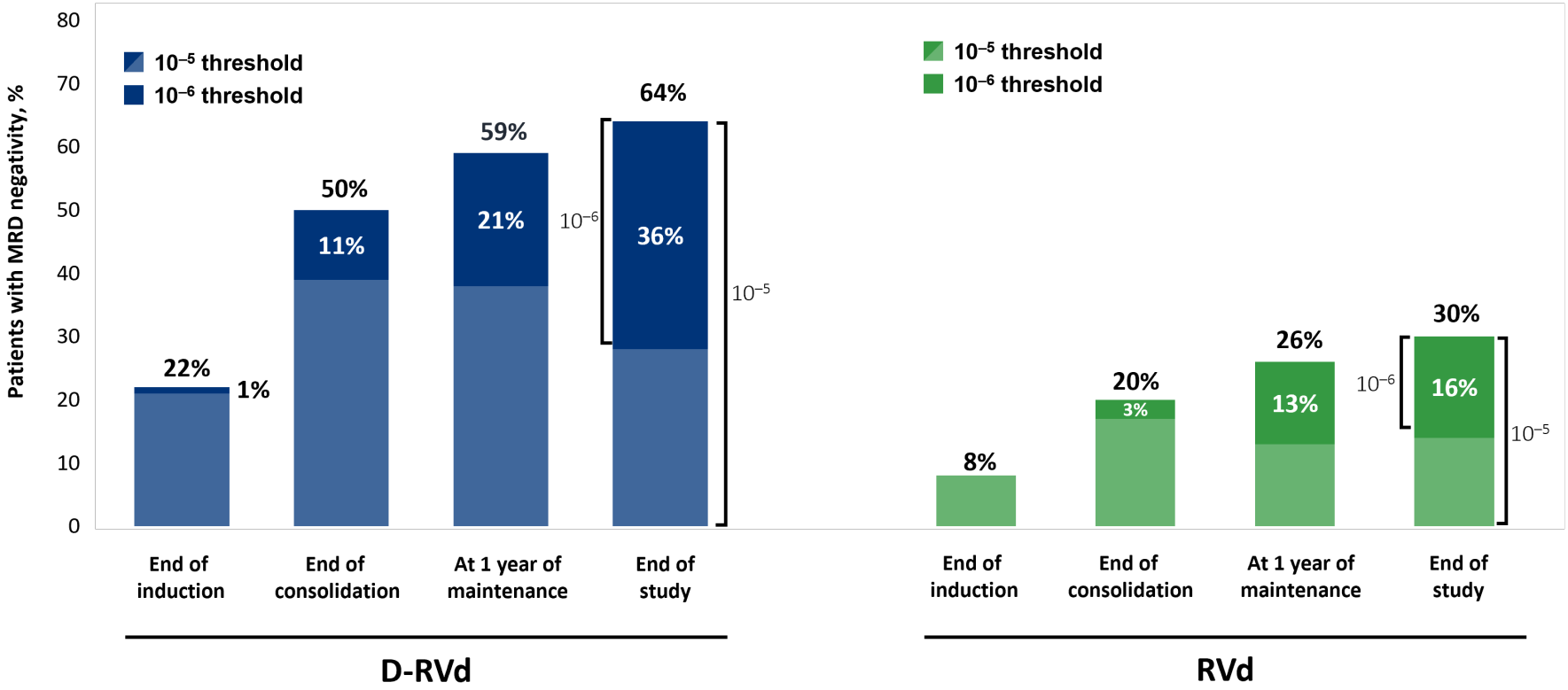
GRIFFIN: Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Eligible NDMM – 24 Months of Maintenance

RVd ± Daratumumab x 6 cycles (4 pre- and 2 post ASCT) → ASCT → R ± Daratumumab maintenance x 2 years → optional R maintenance



Voorhees PM et al. Lancet Haematology 2023.

MRD assessed in the ITT population

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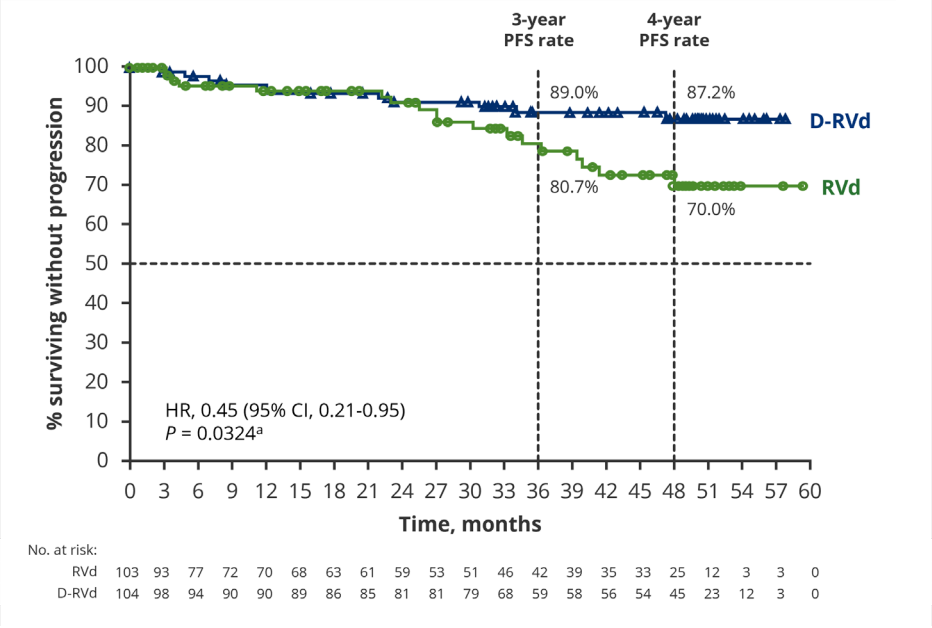
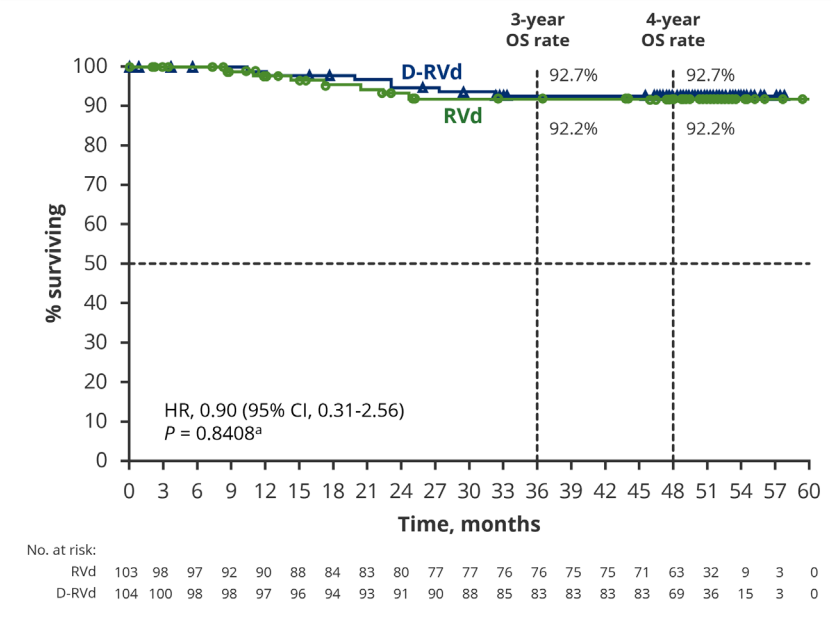
GRIFFIN: Longitudinal Outcomes





Voorhees PM et al. Lancet Haematology 2023.

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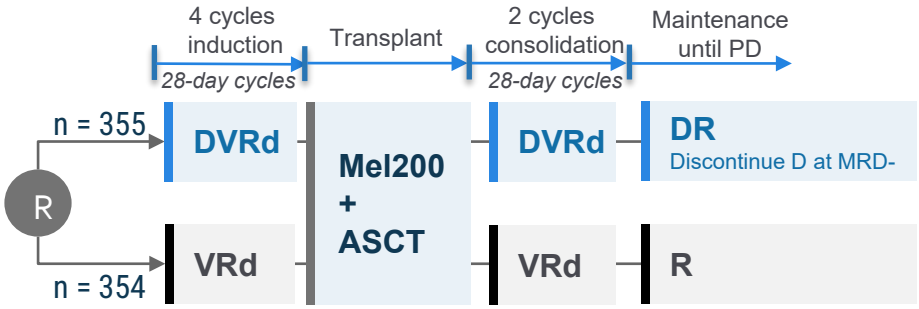
PERSEUS: *DVRd vs VRd in Transplant-Eligible NDMM*

Eligibility

- Transplant-eligible NDMM
- Age 18 – 70
- ECOG PS 0 – 2



Induction/Consolidation Schedule
D: 1800 mg SC days 1, 8, 15, 22 in cycles 1-2, days 1, 15 in cycles 3-6
V: 1.3 mg/m² days 1, 4, 8, 11
R: 25 mg PO days 1 – 21
d: 40 mg PO/IV days 1-4, 9-12

Key Baseline Characteristics	DVRd n = 355	VRd n = 354
Median age (range), y	61 (32 – 70)	59 (31 – 70)
High risk cytogenetics, n (%)	76 (21.4)	78 (22.0)
Extramedullary disease, n (%)	15 (4.2)	16 (4.5)
ISS stage, n (%)		
I	186 (52.4)	178 (50.4)
II	114 (32.1)	125 (35.4)
III	55 (15.5)	50 (14.2)

Primary endpoint: PFS

Key secondary endpoints: CR rate, MRD, OS

- ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; DR, daratumumab and lenalidomide; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IV, intravenous; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; PS, performance status; OS, overall survival; PO, by mouth; R, lenalidomide; SC, subcutaneous; VRd, bortezomib, lenalidomide, and dexamethasone.

Sonneveld P, et al. NEJM 2023

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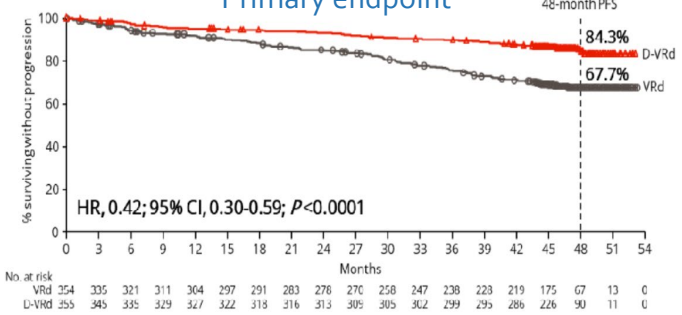
PERSEUS: *PFS and OS*

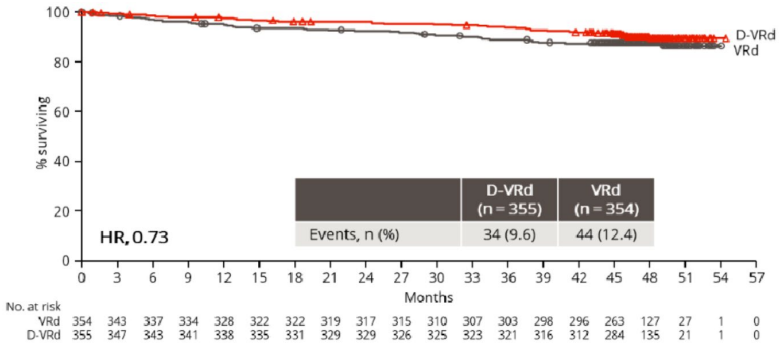
Median follow-up 47.5 mo

PFS

Primary endpoint



OS



Sonneveld P, et al. NEJM 2023

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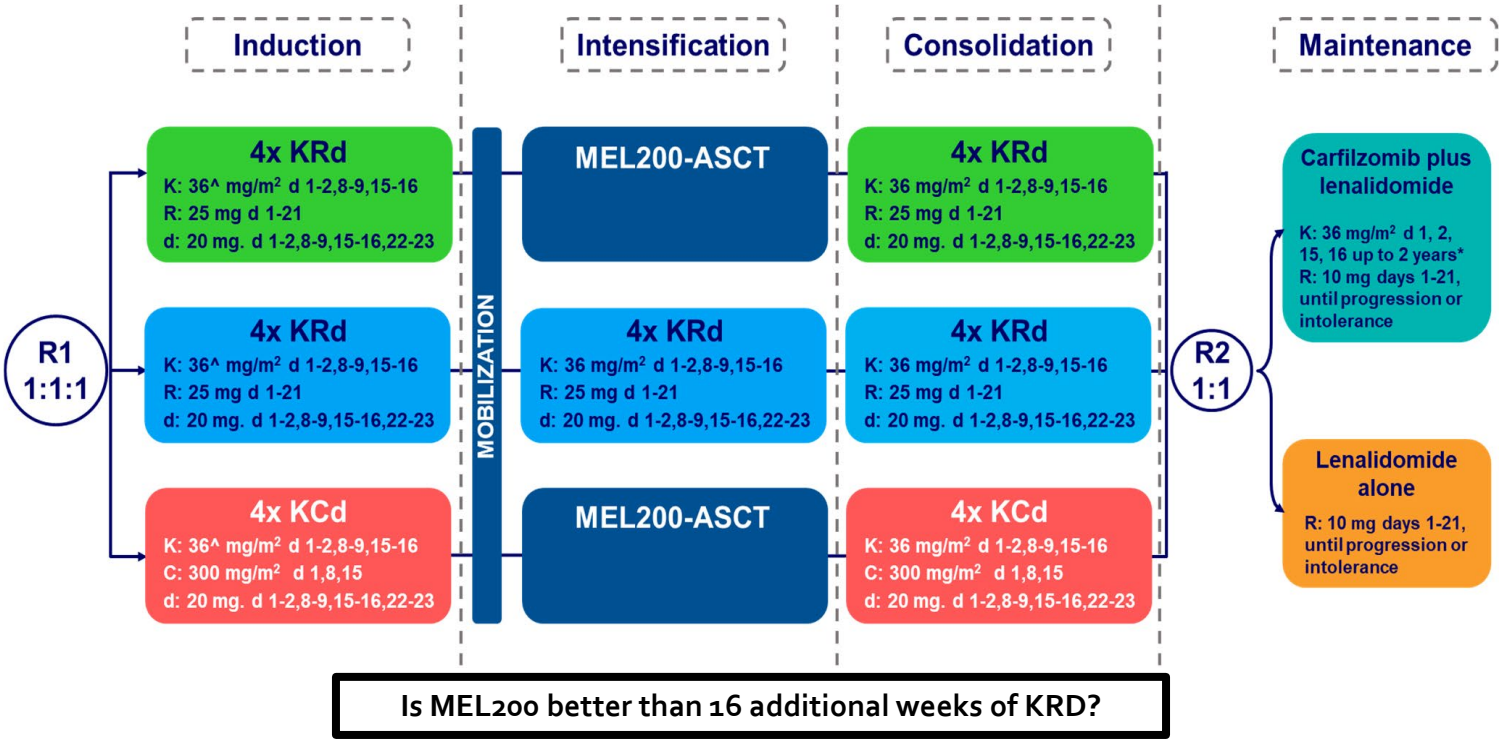
The FORTE Trial

Multicenter, Randomized (1:1), Open-Label, Phase 2 Study



FORTE. Updated November 3, 2022. https://classic.clinicaltrials.gov/ct2/show/NCT02203643

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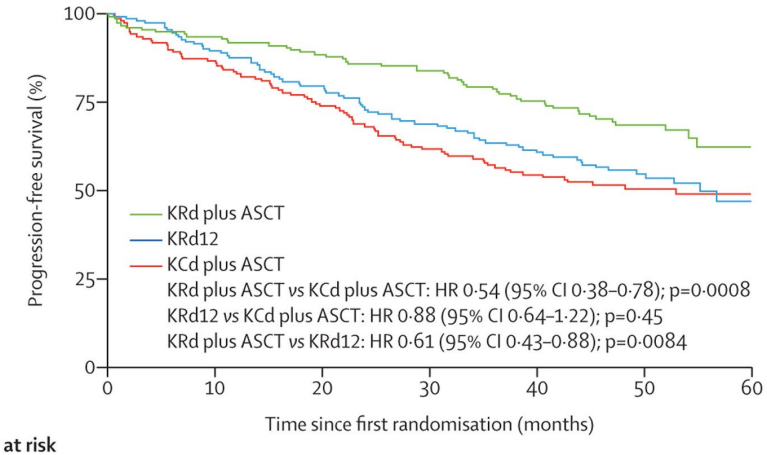
FORTE: Depth of Response and PFS

Progression-Free Survival



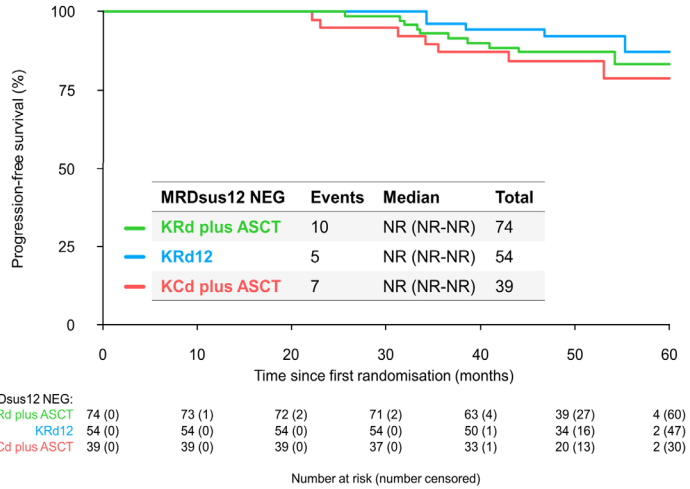
Number at risk (number censored)							
KRd plus ASCT	158 (0)	147 (1)	137 (3)	129 (4)	111 (9)	61 (51)	5 (103)
KRd12	157 (0)	135 (6)	120 (6)	103 (7)	90 (9)	51 (39)	5 (81)
KCd plus ASCT	159 (0)	137 (1)	115 (3)	94 (5)	80 (8)	46 (37)	6 (76)

The quality of MRD negativity was superior in the KRd → ASCT arm

MRD Negativity		
Treatment Arm	**Pre-Maintenance**	**Sustained 1 Year**
KRd → ASCT	62%	47%[†]
KRd 12	58%	35%
KCd → ASCT	43%	25%

[†] OR KRd → ASCT vs KRd 12: 1.69 (95% CI 1.07 – 2.66, *P* = .024).

Progression-Free Survival With Sustained MRD Negativity



MRDsus12 NEG:							
KRd plus ASCT	74 (0)	73 (1)	72 (2)	71 (2)	63 (4)	39 (27)	4 (60)
KRd12	54 (0)	54 (0)	54 (0)	54 (0)	50 (1)	34 (16)	2 (47)
KCd plus ASCT	39 (0)	39 (0)	39 (0)	37 (0)	33 (1)	20 (13)	2 (30)

Number at risk (number censored)

Gay F et al. *Lancet Oncol*. 2021;22(12):1705-1720.

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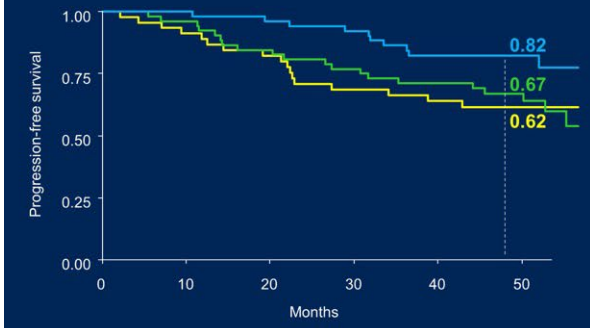
Progression-free survival: Random 1

KRd_ASCT vs. KRd12 vs. KCd_ASCT

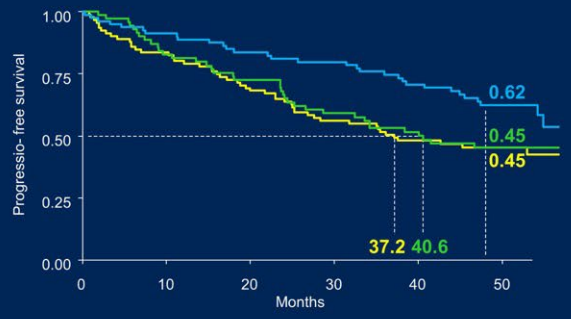
Median follow-up from Random 1: 51 months (IQR 46-55)

Standard risk (N=153)



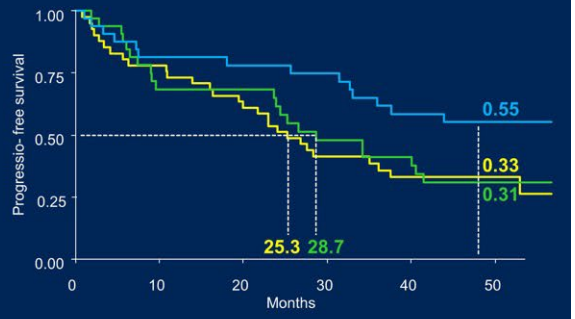
KRd_ASCT vs. KCd_ASCT: HR 0.44, p=0.04
KRd_ASCT vs. KRd12: HR 0.46, p=0.04
KRd12 vs. KCd_ASCT : HR 0.96, p=0.9

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 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

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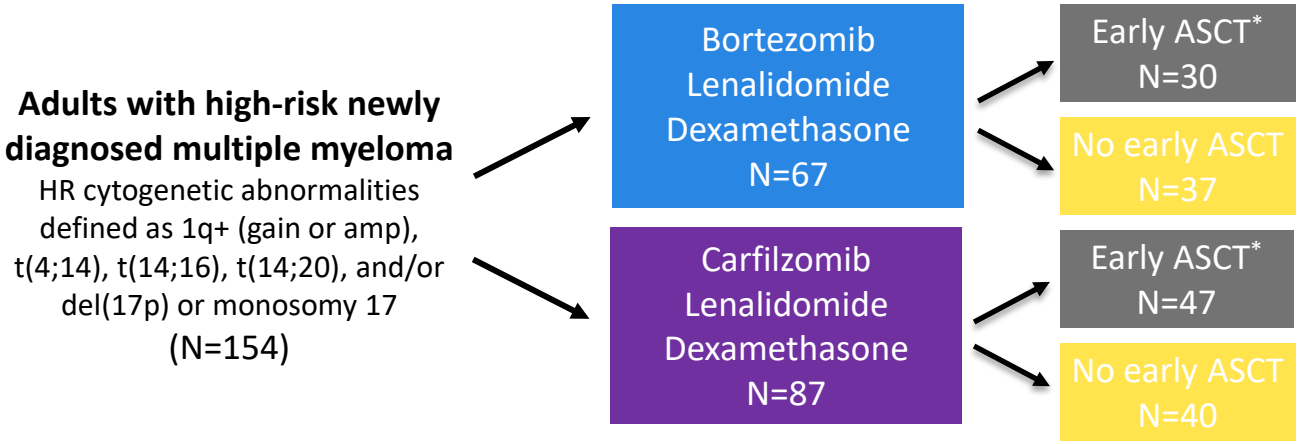
Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Bortezomib, Lenalidomide, and Dexamethasone (VRd) as Induction Therapy in Newly Diagnosed HR-NDMM

- **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**



Primary endpoint:
Progression Free Survival
Secondary endpoints:
- Overall response rate
- MRD negativity rate
- Event Free Survival
- Overall Survival

*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

Tan C et al, ASH 2022

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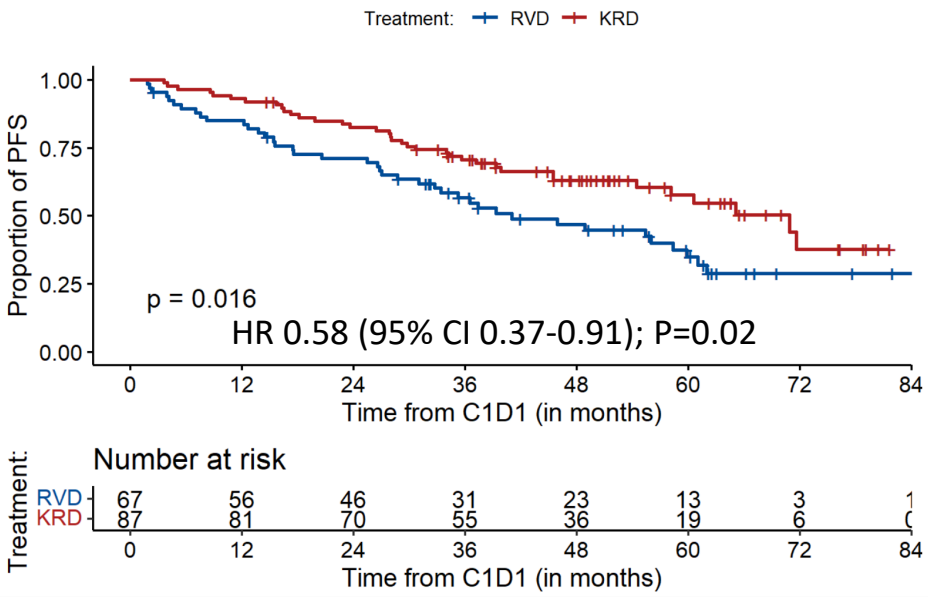
Progression Free Survival



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 KRd 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

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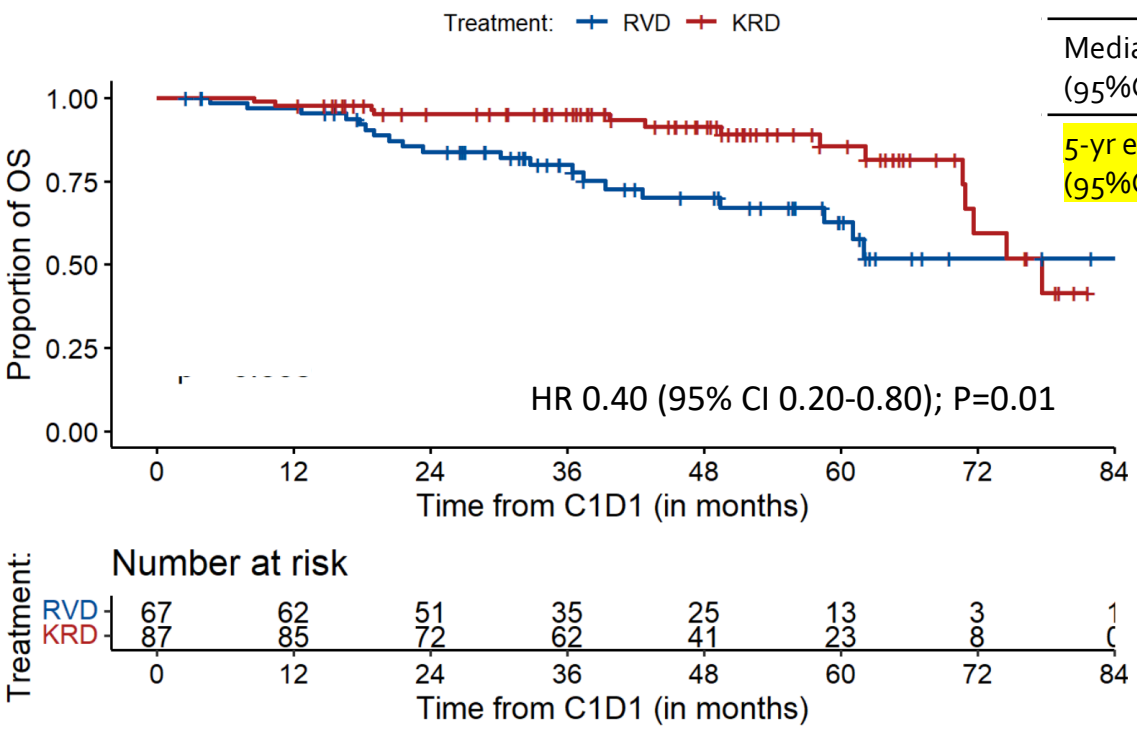
Overall Survival



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

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Daratumumab-KRd for NDMM

Study/Phase	Patient Characteristics	Responses	PFS data	Safety (Grade ¾)
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

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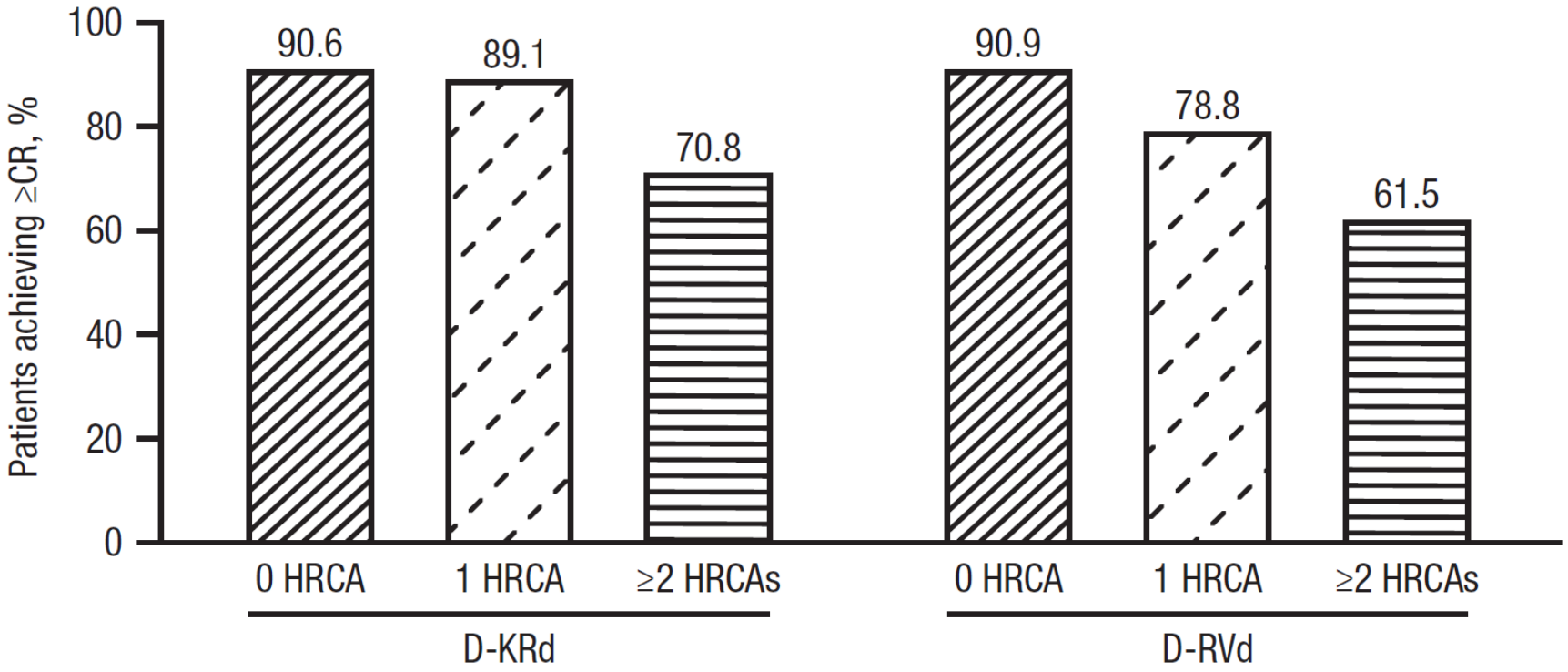
Rates of ≥CR (best response on study) by cytogenetic risk status* in MASTER and GRIFFIN trials



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

In press

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MRD negativity by cytogenetic risk status* among patients who received D-KRd in MASTER and D-RVd in GRIFFIN

	D-KRd			D-RVd		
	0 HRCA	1 HRCA	≥2 HRCAs	0 HRCA	1 HRCA	≥2 HRCAs
MRD negative						
Evaluable population	n = 50†	n = 44†	n = 24†	n = 67‡	n = 34‡	n = 13‡
10^{-5} sensitivity, %	80.0	86.4	83.3	76.1	55.9	61.5
10^{-6} sensitivity, %	68.0	79.5	66.7	44.8	26.5	15.4
In patients achieving ≥CR	n = 45	n = 39	n = 17	n = 60	n = 26	n = 8
10^{-5} sensitivity, %	84.4	89.7	94.1	74.6	52.9	53.8
Durable MRD negativity lasting ≥12 months						
Evaluable population	n = 50†	n = 44†	n = 24†	n = 67‡	n = 34‡	n = 13‡
10^{-5} sensitivity, %	64.0	72.7	50.0	53.7	38.2	30.8

MRD minimal residual disease, D-KRd daratumumab plus carfilzomib/lenalidomide/dexamethasone, D-RVd daratumumab plus lenalidomide/bortezomib/dexamethasone, HRCA high-risk cytogenetic abnormality, CR complete response, NA not available.

*HRCAs include any of the following genetic abnormalities: del(17p), t(4;14), t(14;16), t(14;20), and gain/amp(1q21) (≥3 copies of chromosome 1q21). Patients were grouped into categories: standard risk (0 HRCA), high risk (1 HRCA), or ultra-high risk (≥2 HRCAs).

†For MASTER, data are for all enrolled patients with available MRD data.

‡For GRIFFIN, the D-RVd group included patients from the randomized phase (n = 104) and the safety run-in phase (n = 16). Patients were grouped by HRCA: 0 HRCA (n = 67), 1 HRCA (n = 34), or ≥2 HRCAs (n = 13). 6 patients were not evaluable for cytogenetic abnormalities.

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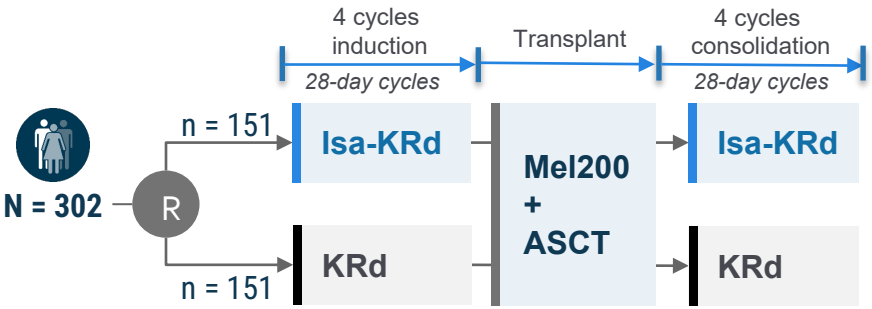
IsKia

Isa-KRd vs KRd in Transplant-Eligible NDMM

Eligibility

- Transplant-eligible NDMM
- Age < 70y



Induction/Consolidation Schedule
Isa: 10 mg/kg IV days 1, 8, 15, 22 in cycle 1,
10 mg/kg IV days 1,15 in cycles 2 – 4
K: 20/56 IV mg/m² days 1, 8, 15
R: 25 mg PO days 1 – 21
d: 40 mg PO days 1, 8, 15, 22

Primary endpoint: rate of post-consolidation MRD-negativity in ITT population

Key secondary endpoints: post-induction MRD-negativity, PFS

Key Baseline Characteristics	Isa-KRd n = 151	KRd n = 151
Median age (range), y	61 (55 – 66)	60 (54 – 63)
High risk by IMWG[a]	25 (18)	26 (19)
# of HRCA[b], n (%)		
0	78 (56)	75 (54)
1	49 (35)	49 (35)
2 or more	13 (9)	15 (11)
Missing	11	12
R-ISS stage, n (%)		
I	50 (35)	48 (34)
II	82 (58)	85 (59)
III	10 (7)	10 (7)
R2-ISS stage, n (%)		
I	34 (24)	35 (25)
II	45 (32)	47 (34)
III	52 (37)	51 (37)
IV	8 (6)	6 (4)

- a. del(17p), t(4;14), and/or t(14;16); b. del(17p), t(4;14), t(14;16), gain or amp(1q).
- Isa, isatuximab; KRd, carfilzomib, lenalidomide, and dexamethasone; R-ISS, Revised International Staging System; Mel200, melphalan 200 mg.

Gay F, et al. Blood. 2023;142(Suppl 1): Plenary Abstract 4.

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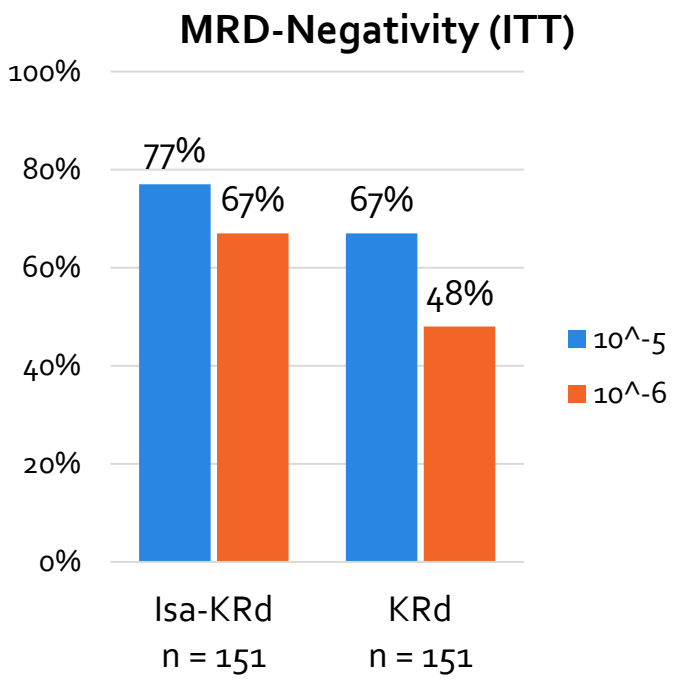
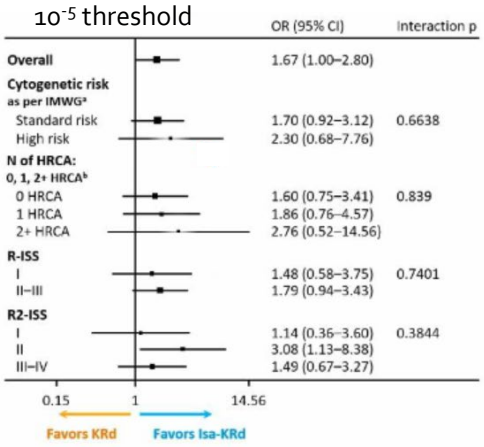
IsKia: Responses

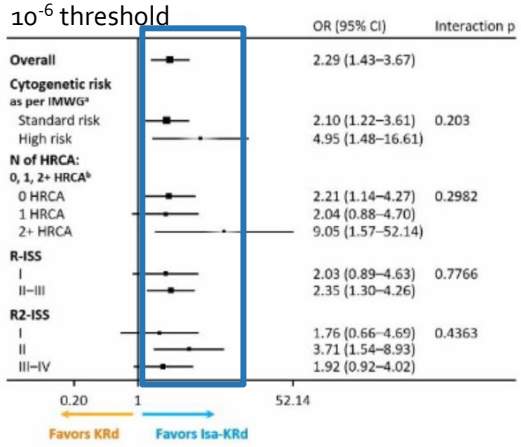
Post-consolidation MRD-Negativity in ITT population
Primary endpoint



- Gay F, et al. Blood. 2023;142(Suppl 1): Plenary Abstract 4.

MRD advantage with Isa-KRd retained across all subgroups
Subgroup analysis





MRD-Negativity by HRCA	10-5		10-6	
	Isa-KRd	KRd	Isa-KRd	KRd
0 HRCA	79%	72%	65%	48%
1 HRCA	78%	65%	69%	53%
2+ HRCA	**77%**	**53%**	**77%**	**27%**

Gay F, et al. Blood. 2023;142(Suppl 1): Plenary Abstract 4.

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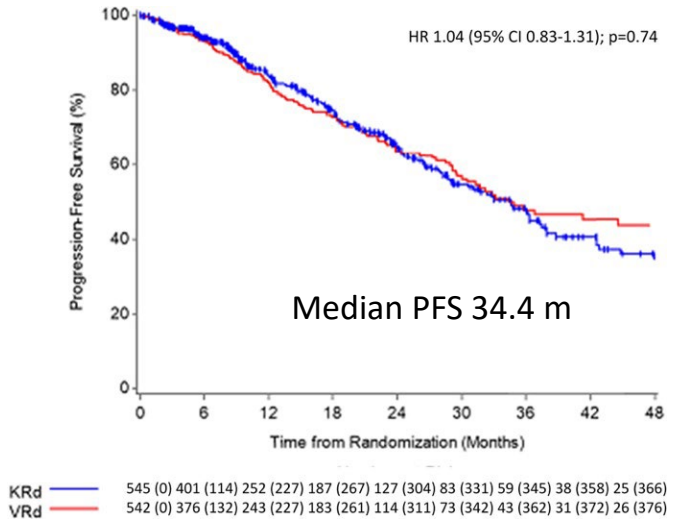
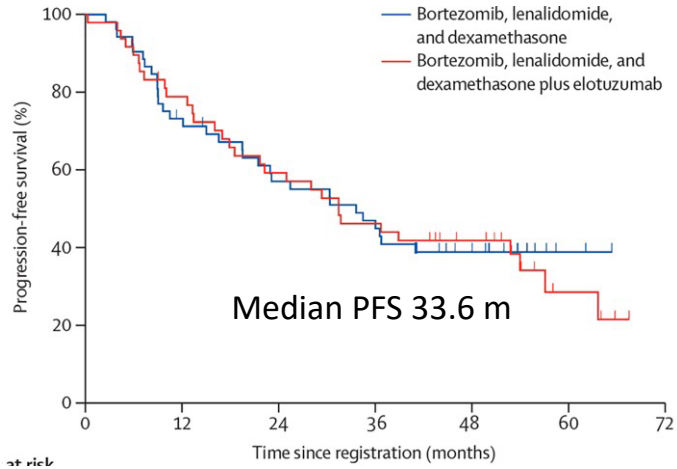
Impact of PI/IMiD Maintenance in High-Risk MM

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

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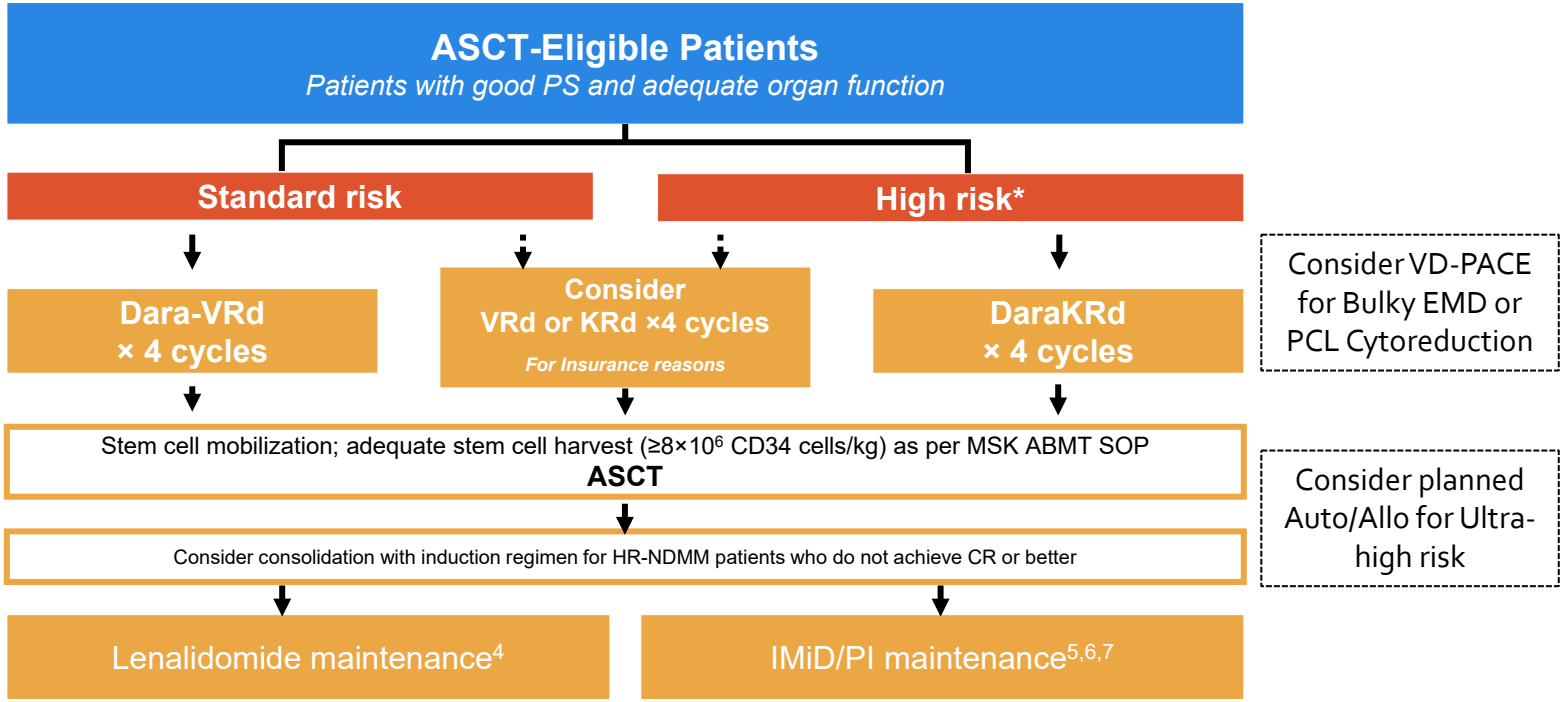
MSK Approach to Transplant Eligible NDMM



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.

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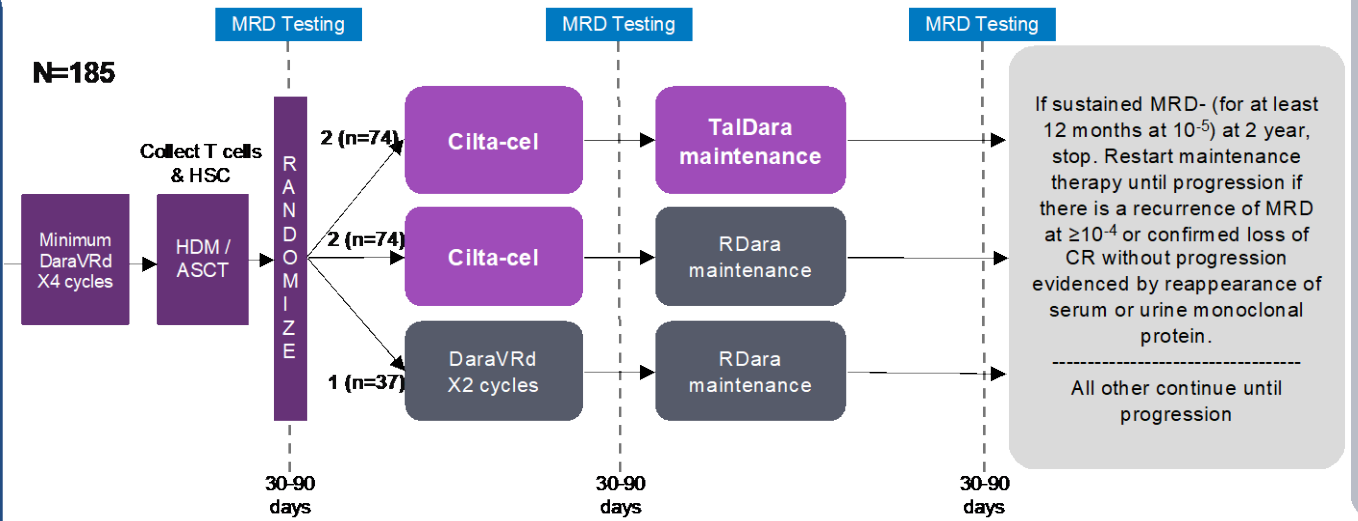
TRIUMpH Trial: Phase 3 BMT-CTN Study in HR-NDMM *(In Development)*

Patient Selection
- Revised ISS-3
- Revised ISS-2 with:
  - FISH for t(4;14), t(14;16), t(14;20), Del17p, ≥3 copies of chr 1q21
  - Genomic: GEP70hI, SKY92hI, biallelic TP53 deletion, c-Myc rear / mut
  - Imaging: >3 FDG avid bone lesions on PET-CT
- Extra-medullary disease at diagnosis
- Circulating plasma cells >5% at diagnosis



Primary Endpoint:
- PFS

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

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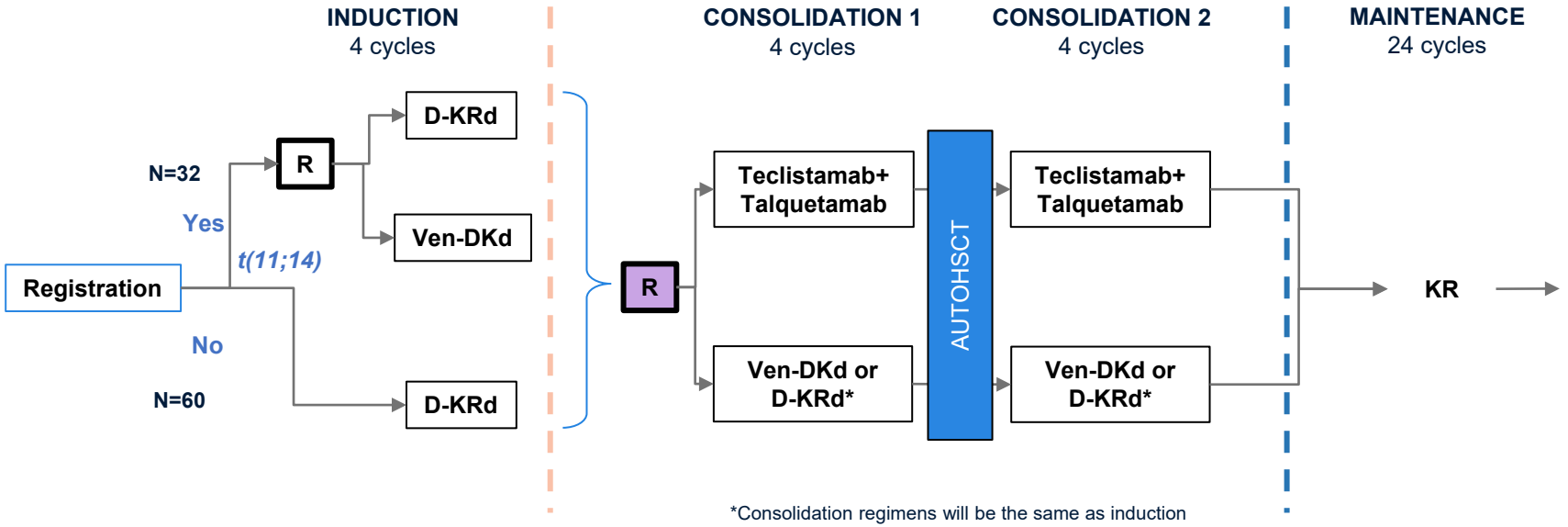
A062104: Phase 2 trial investigating quadruplet induction followed by novel consolidation for Primary Plasma Cell Leukemia

Primary endpoint:
- Rate of MRD negativity (10^{-5}) for t(11;14) patients post-induction

Key secondary endpoints:
- Rate of MRD negativity post-consolidation pooled across *all* patients
- Overall survival



*Consolidation regimens will be the same as induction

Stratified on t(11;14) status and induction regimen
t(11;14) with D-KRd vs.
t(11;14) with Ven-DKd vs.
non-t(11;14) with D-KRd

KRd, carfilzomib-lenalidomide-dexamethasone

Alliance for Clinical Trials in Oncology

SWOG CANCER RESEARCH NETWORK

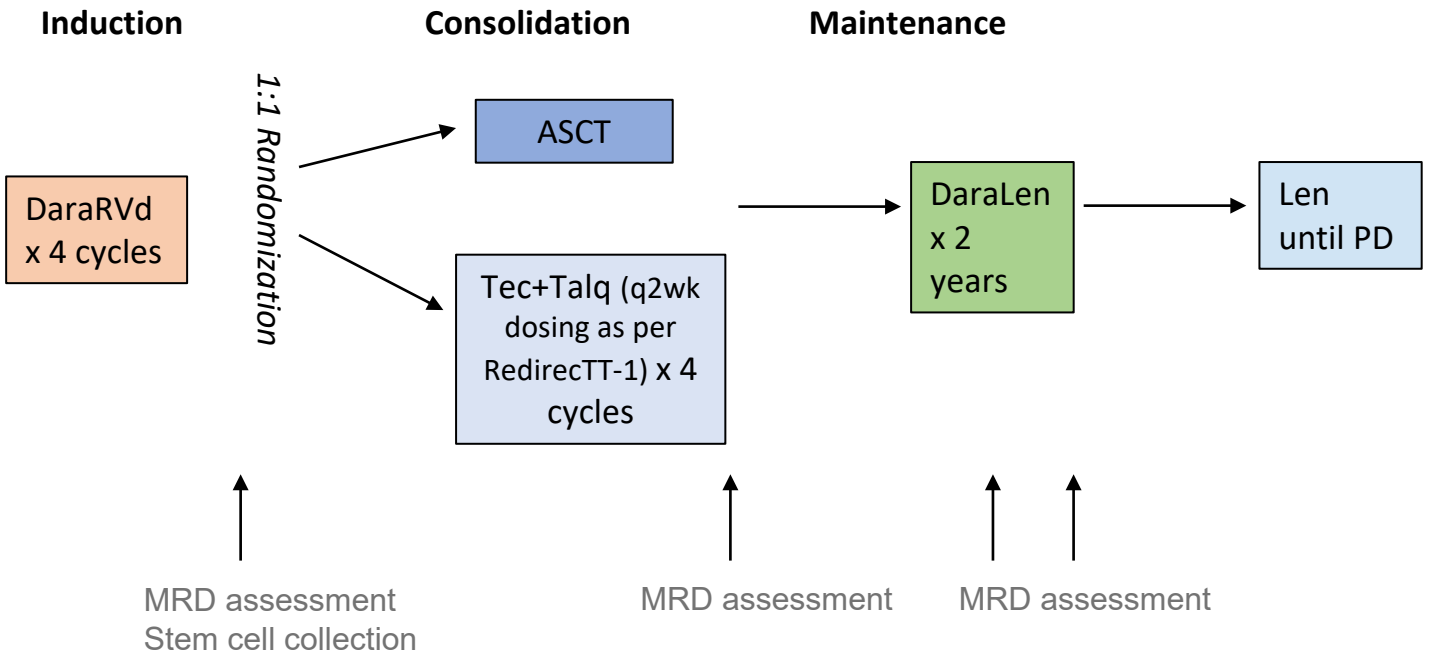
Memorial Sloan Kettering Cancer Center

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network

NCI Community Oncology Research Program

Newly diagnosed, standard risk concept



- **<u>Co-primary endpoints</u>: PFS (non-inferiority with planned superiority assessment) and cumulative incidence of severe infections**
- Key secondary endpoints: OS, MRD-neg post consolidation, sustained MRD negativity after 2 yrs of maintenance
- QOL/PRO endpoint as correlative/exploratory endpoint: incorporate into design as an integrated biomarker with separate hypotheses, power statements and analysis plans

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

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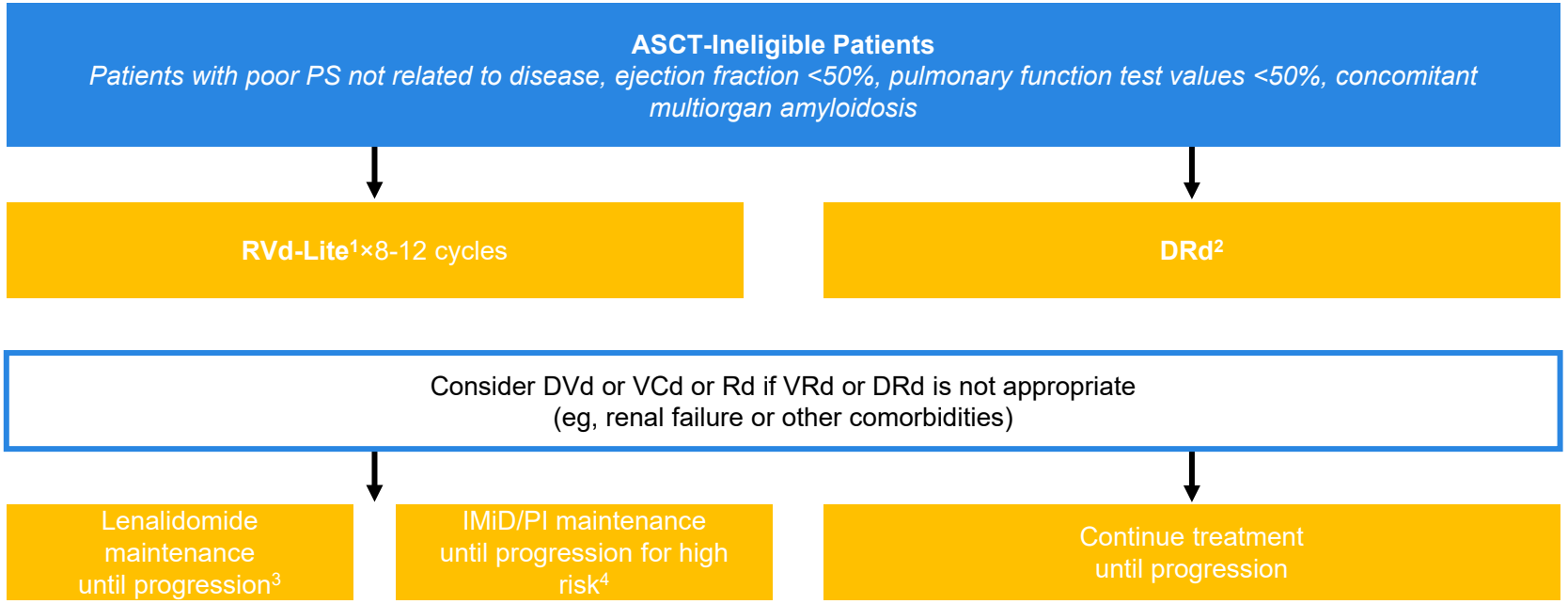
MSK Approach to Transplant Ineligible NDMM



- 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.

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

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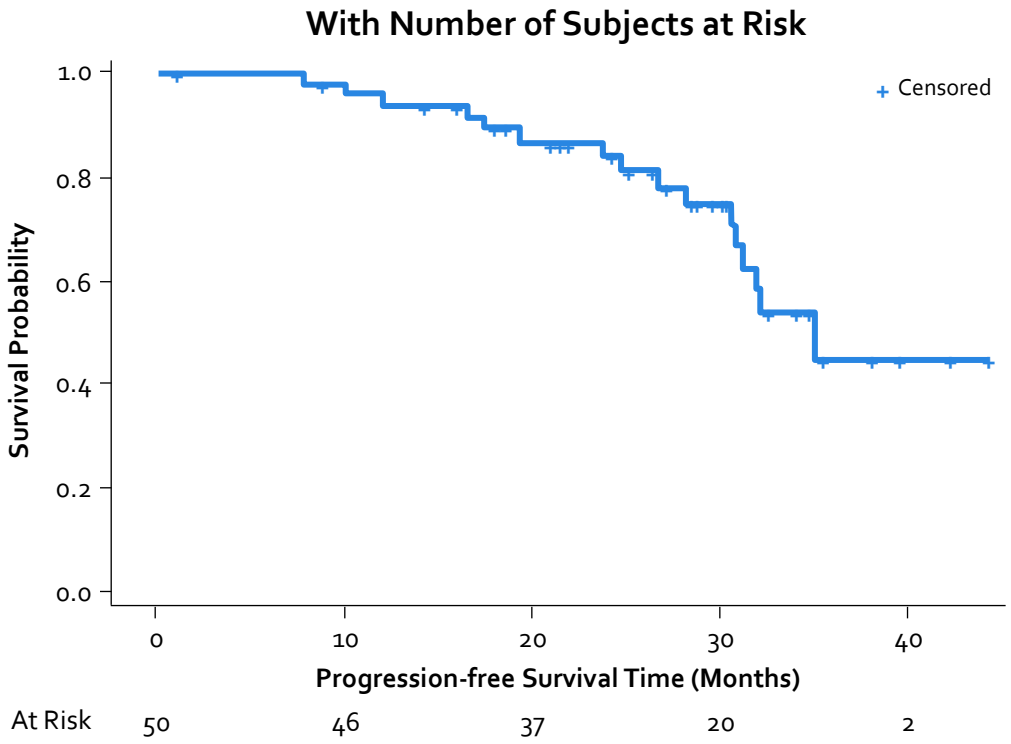
RVd-Lite

- 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.

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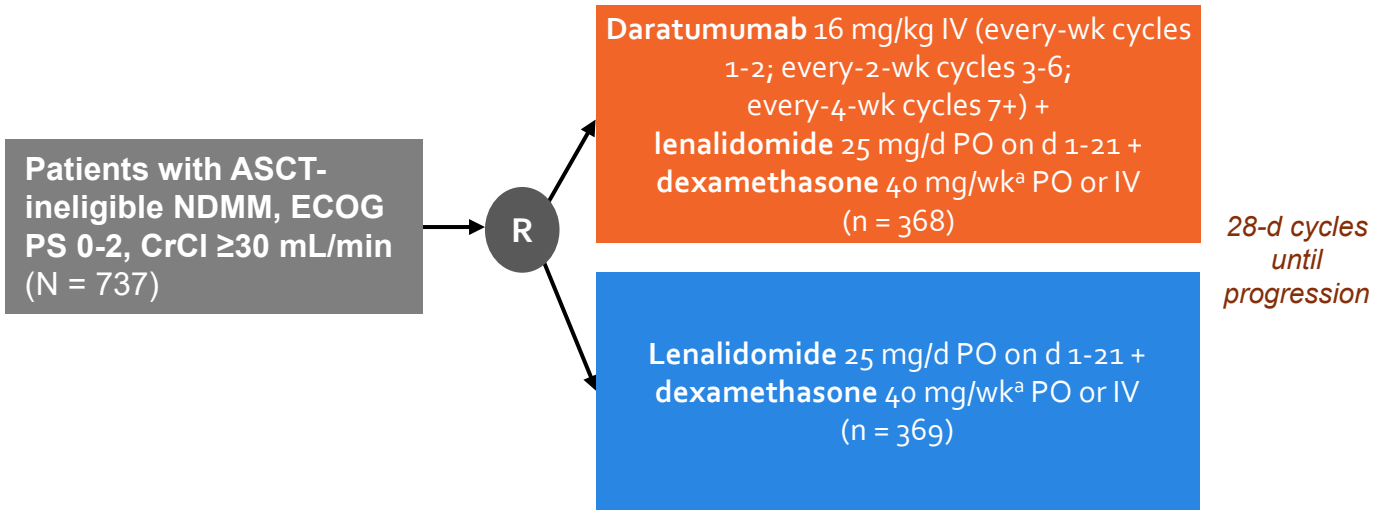
Phase 3 MAIA Study: Daratumumab Plus Rd in NDMM

- 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.

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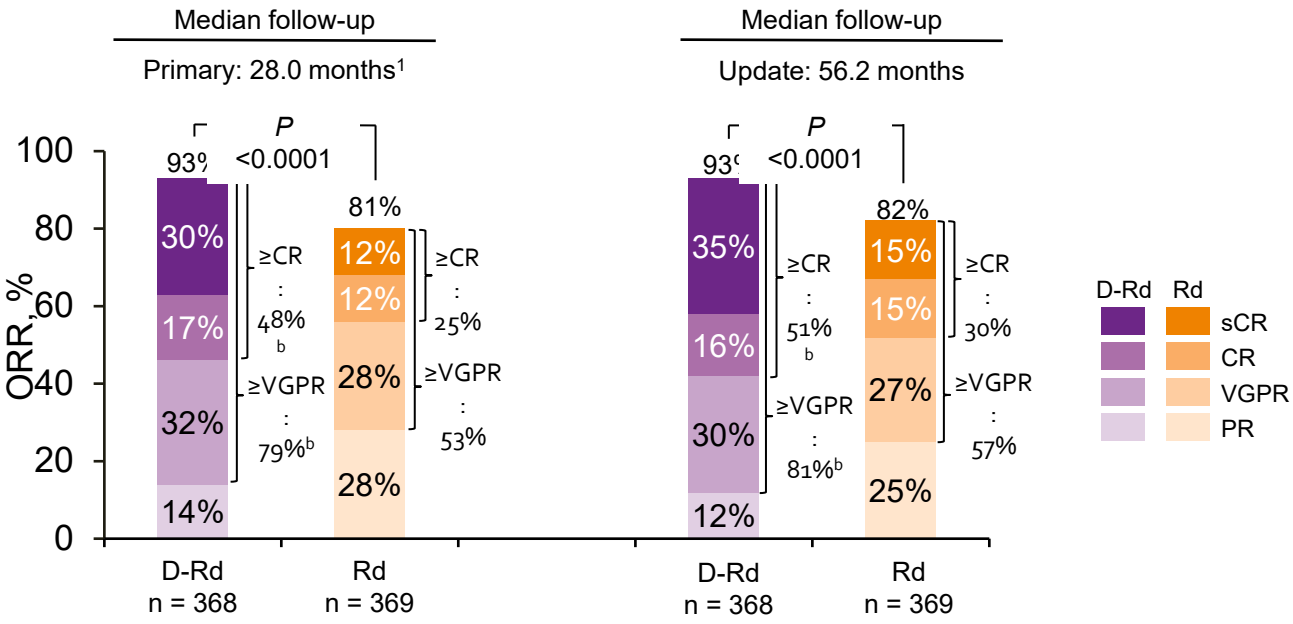
MAIA Phase III ORR[a]



- **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.

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

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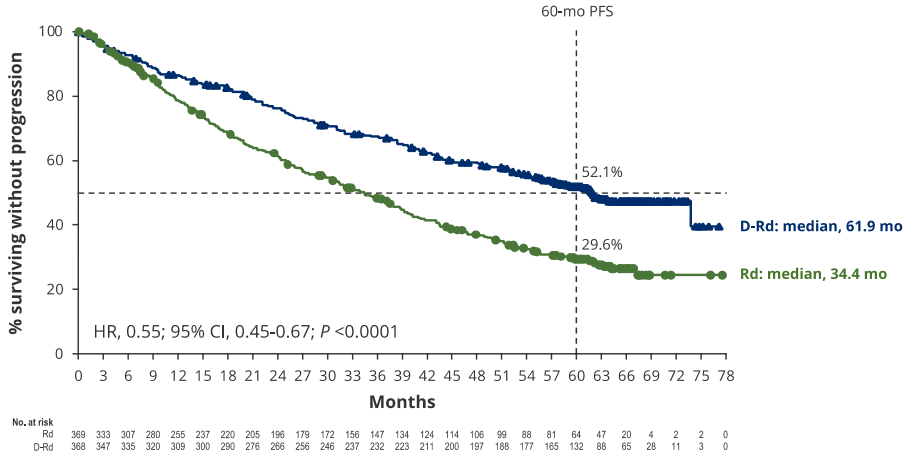
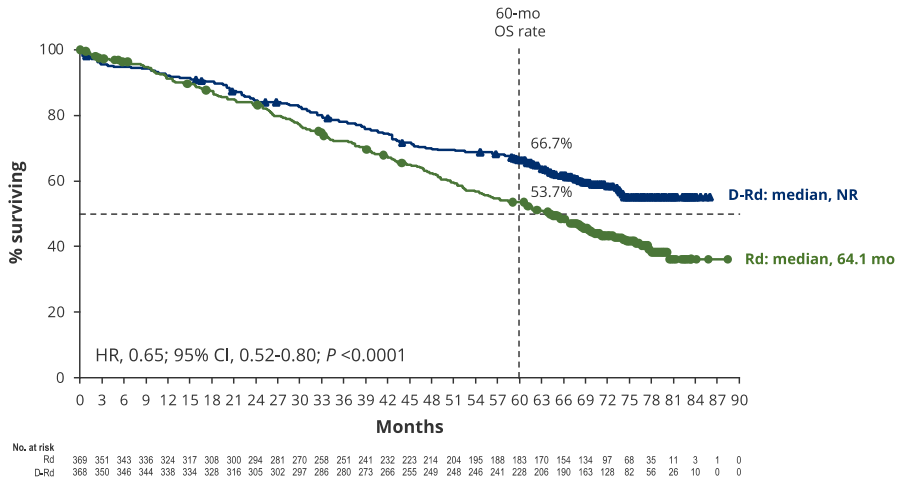
MAIA Phase III Updated PFS/OS





Kumar S et al, EHA 2023

NR, not reached; CI, confidence interval.

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

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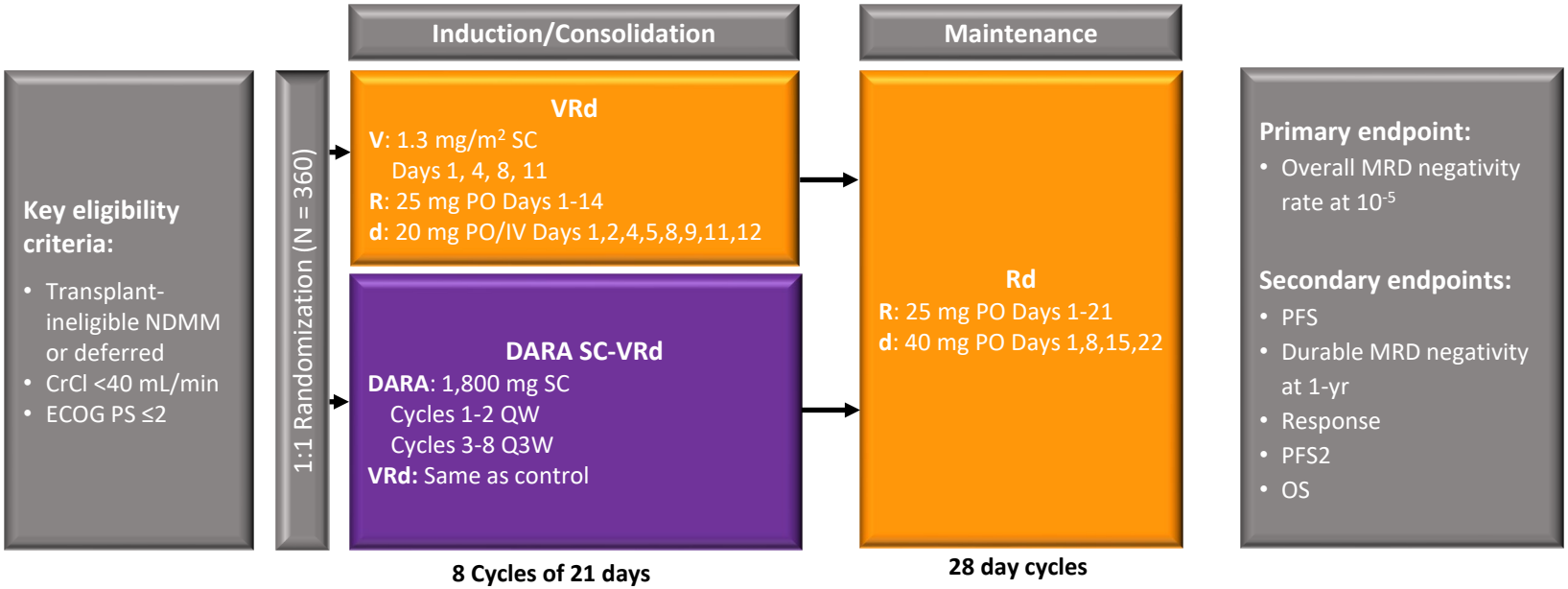
CEPHEUS: Study Design

- **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

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

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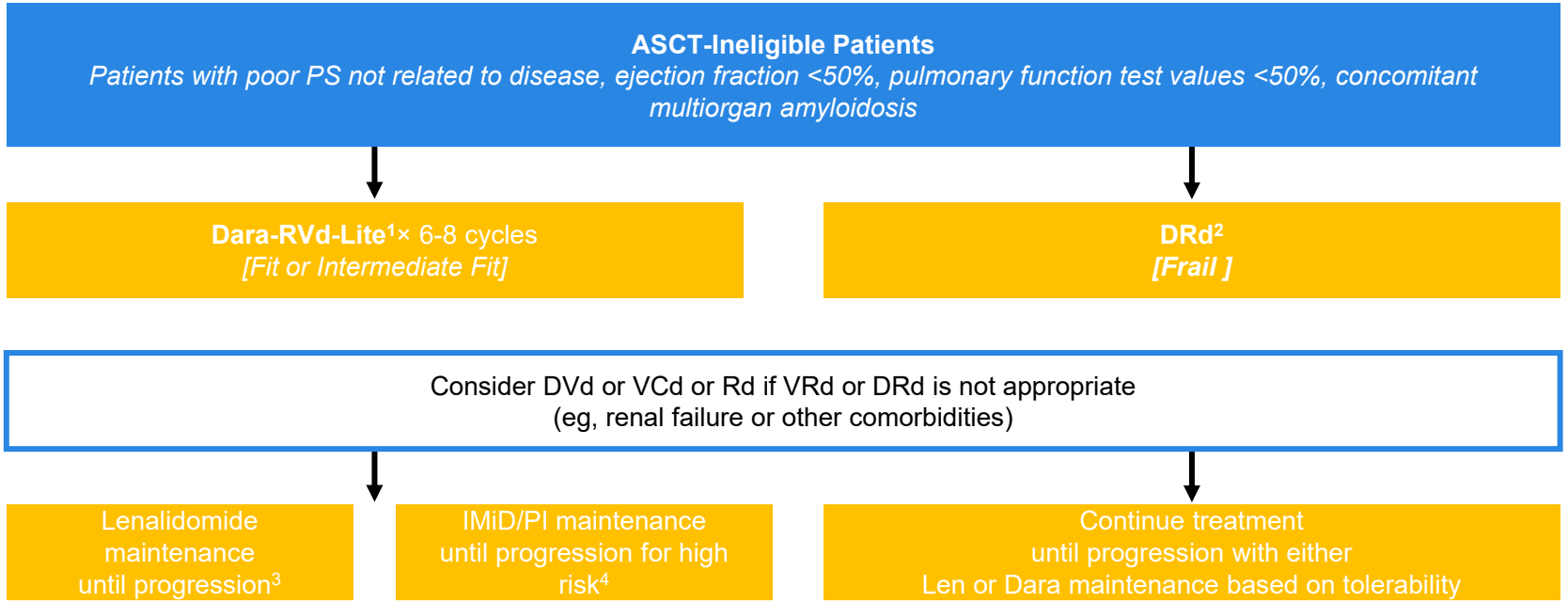
MSK Approach to Transplant Ineligible NDMM (? 2024)



- 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.

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Conclusions

- 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.
- Anti-CD38 monoclonal antibody-based quadruplet induction provide better depth of response, translating in to better PFS (GRIFFIN, CASSIOPEIA, ? GMMG-HD7).
- Future strategies may incorporate BsAb or biomarker directed small molecules into induction.
- Never under-treat, put your best foot forward!
  - Especially true for high risk NDMM (HR-NDMM)

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MSKCC Myeloma Team – It Takes a Village!

Physicians:
- Parastoo Dahi (ABMT)
- Sergio Giralt (Deputy Chair, DHM)
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- David Chung (ABMT)
- Hani Hassoun
- Malin Hultcrantz
- Neha Korde (Clinical Director)
- Heather Landau (ABMT)
- Kylee Maclachlan
- Sham Mailankody (Research Director)
- Dhwani Patel
- Sridevi Rajeeve
- Michael Scordo (ABMT)
- Gunjan Shah (ABMT)
- Urvi Shah
- Carlyn Tan
- Saad Z. Usmani (Chief)

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- Katie Jones
- Justina Kiernan (BER)
- Lori Lang (WES)
- Katelyn Kelly-Johnson (CMK)
- Jennifer Rielly
- Ashley Steinberger
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- Mackenzie Galvin
- Anna Howard
- Kyla Lafond
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- Bianca Gonzalez
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- Selena Hamid
- Roger Huang
- Meredith Hyland
- Mosammed Kabir
- Emily Lei
- Guljar Nahar
- Alexis Nwakwo
- Garrett Preusz
- Anna Przemielewska
- Raisa Rahman
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- Jeannen Santos
- Tala Shekarkhand
- Felicia Slaton
- Clare Sullivan
- Kristina Vinzon-Baltazar

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- Xavier Ayala
- Elhaji Ba
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- Odali Espinal
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- Daniel Maldonado
- Krystal Soto

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- Shaneeza Imran
- Gladys Acosta