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NEWLY DIAGNOSED MULTIPLE MYELOMA: BALANCING EFFICACY WITH TOXICITY

2026 FLASCO Clinical Oncology Series: Malignant Hematology

Precision Approaches in the Modern Era

August 29, 2026

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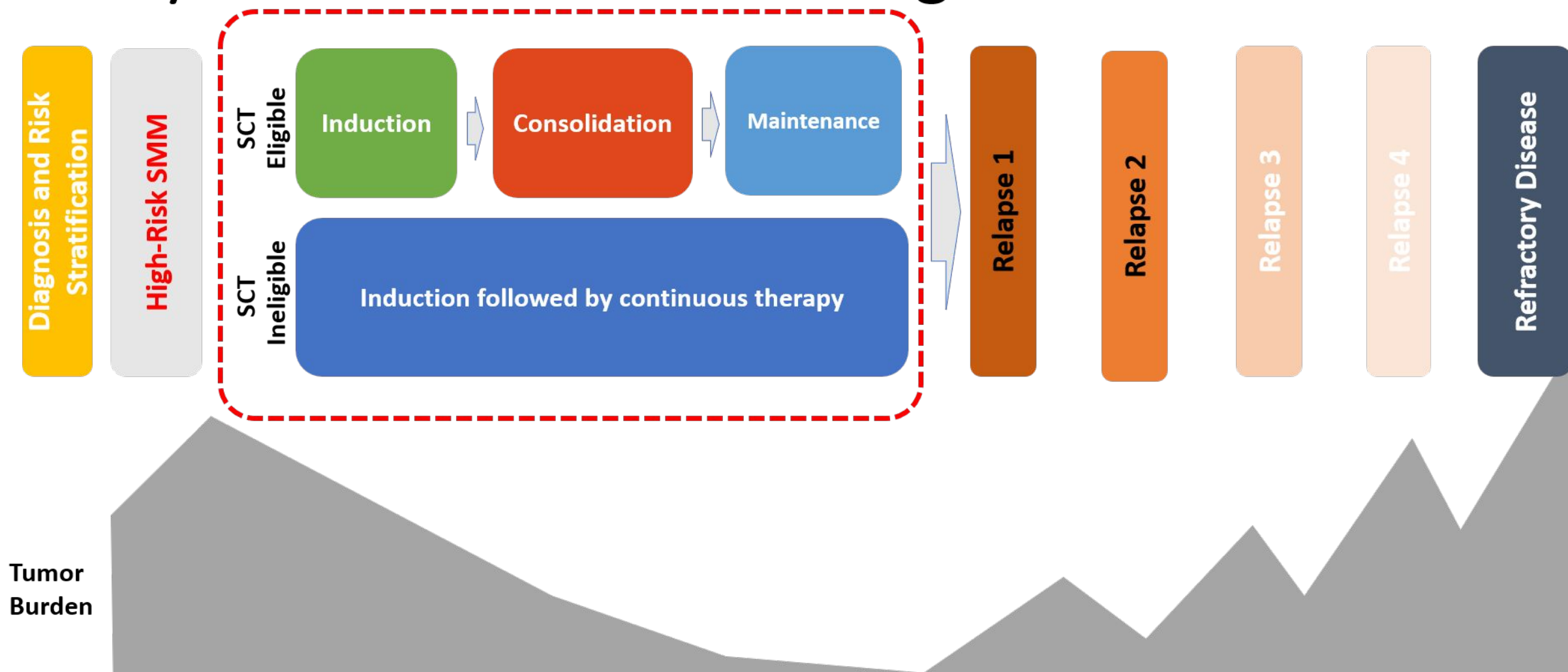
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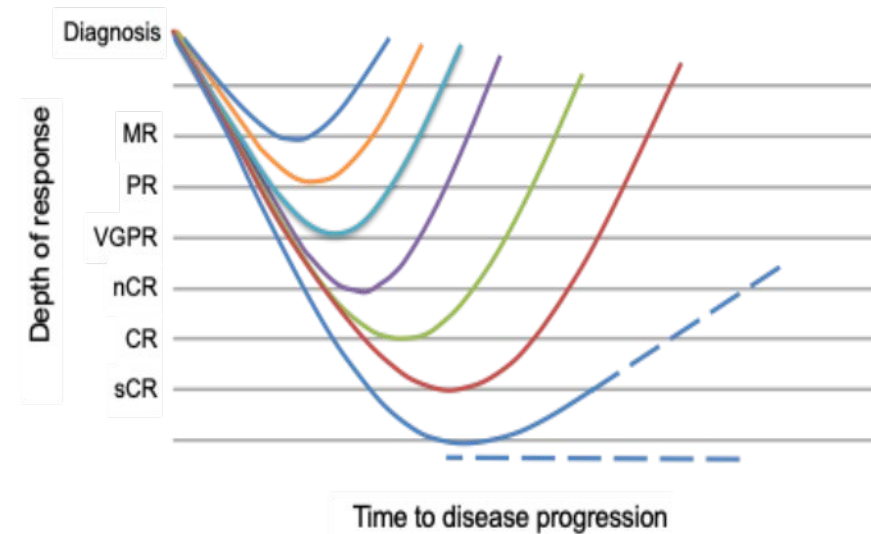
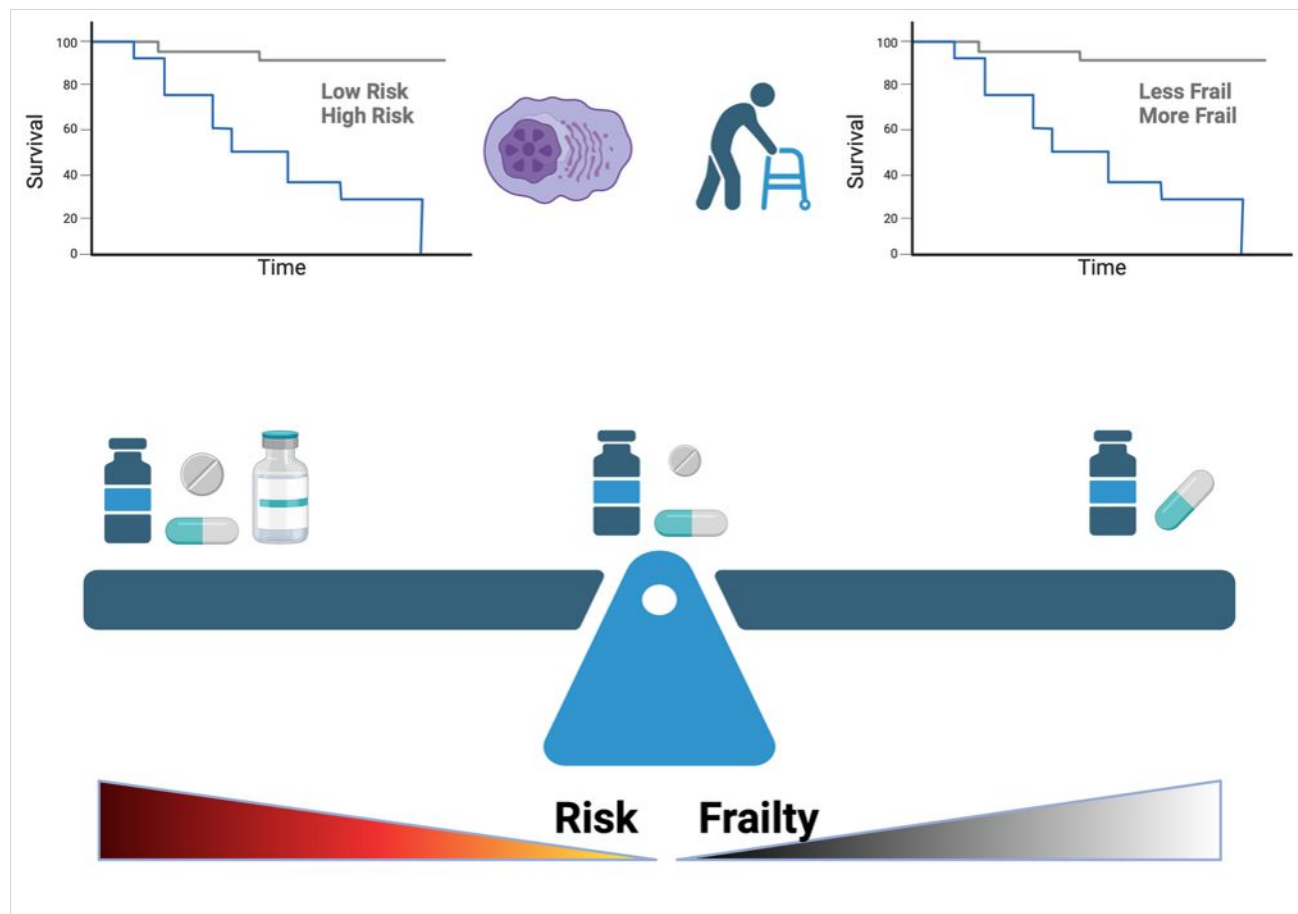
OBJECTIVES

- **To discuss management of newly-diagnosed multiple myeloma in the context of:**
 - Triplets vs. Quadruplets: For what patient?
 - Tolerability: Supportive care
 - Role and timing of autologous transplant
 - Role of MRD and MRD-guided strategies; No transplant? Stop maintenance?
 - Future outlook: incorporation of T-cell redirecting immunotherapies in the front-line setting

Myeloma Treatment Paradigm



What drives the treatment decisions?



IMS-IMWG 2024 CONSENSUS HRMM DEFINITION

Criteria for HRMM
Del(17p) ^a and/or TP53 mutation ^b
One of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32)
Monoallelic del(1p32) along with +1q, or biallelic del(1p32)
High β 2M (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL)

^aCCF $\geq$ 20%, by analyses conducted on CD138-positive/purified cells.

^bAssessed using an NGS-based method.

+1q, gain (3 copies) or amplification ($\geq$ 4 copies) of the long arm of chromosome 1;

CCF, cancer clonal fraction; HRMM, high-risk multiple myeloma; NGS, next-generation sequencing.

GOALS OF THERAPY

- Induce a deep and durable remission (ideally MRD negative)
- Improve myeloma symptoms
- Improve and maintain quality of life
- Minimize side effects
- Prevent or reverse organ damage
- Prolong survival



TRIPLETS VS. QUADRUPLETS

QUADRUPLETS VS. TRIPLETS IN NEWLY DIAGNOSED TRANSPLANT ELIGIBLE PATIENTS

Trial	Quadruplet	Triplet	ORR	MRD- after induction*	MRD- Day ~100 post-ASCT*	PFS
GRIFFIN ¹ (Phase II)	D-VRd	VRd	99% vs 91%	22% vs 14%	51% vs 20%	48-mo PFS 84.3% vs 67.7%; HR 0.45
PERSEUS ² (Phase III)	D-VRd	VRd	99.6% vs 98.4%	~76% vs 48%†	75.2% vs 47.5%	HR 0.42; 4-yr PFS 84.3% vs 67.7%
CASSIOPEIA ³ (Phase III)	D-VTd	VTd	92.6% vs 89.9%	64% vs 44%	64% vs 44%‡	83.7 mo vs. 52.8 mo; HR 0.61
GMMG-HD7 ⁴ (Phase III)	Isa-VRd	VRd	90.8% vs 87.7%	50.1% vs 35.6%	66.2% vs 47.7%	3-yr PFS 83% vs 75%; HR 0.70

*MRD assessed by next-generation flow or sequencing at 10⁻⁵ sensitivity (slight assay differences exist between studies).
†PERSEUS publications primarily emphasize MRD negativity after transplant and before maintenance; the 75.2% vs 47.5% figure is the landmark post-consolidation/pre-maintenance assessment.
‡CASSIOPEIA reported MRD after consolidation (following transplant), which corresponds approximately to the Day +100 assessment used in North American studies.

- In transplant eligible patients, **quadruplets are superior to triplets** and result in superior MRD negativity rates both after induction and transplant and result in superior progression free survival

¹Voorhees PM, et al. Lancet Haematol. 2023 Oct;10(10):e825-e837.
²Sonneveld P, et al. N Engl J Med. 2024 Jan 25;390(4):301-31
³Moreau P, et al. Lancet Oncol. 2024 Aug;25(8):1003-101
⁴Mai EK, et al. J Clin Oncol. 2025 Apr 10;43(11):1279-1288.

QUADRUPLETS VS. TRIPLETS IN NEWLY DIAGNOSED TRANSPLANT INELIGIBLE PATIENTS

Trial	Population	Quadruplet	Control	ORR	MRD Negativity (10 ⁻⁵)	PFS
IMROZ ¹ (Phase III)	Transplant-ineligible NDMM (≤80 yrs)	Isa-VRd → Isa-Rd	VRd → Rd	91% vs 92%	55.5% vs 40.9%	60 mo PFS 63.2% vs. 45.2%; HR 0.60
CEPHEUS ² (Phase III)	Transplant-ineligible or transplant-deferred NDMM	D-VRd → D-Rd	VRd → Rd	95.9% vs 90.9%	60.9% vs 39.4%	54 mo PFS 68.1% vs. 49.5%; HR 0.57
BENEFIT ³ (Phase III)	Transplant-ineligible NDMM (≤80 yrs)	Isa-VRd	Isa-Rd	≈93% vs 86%	53% vs 26% (18-month landmark)	Not mature/reported

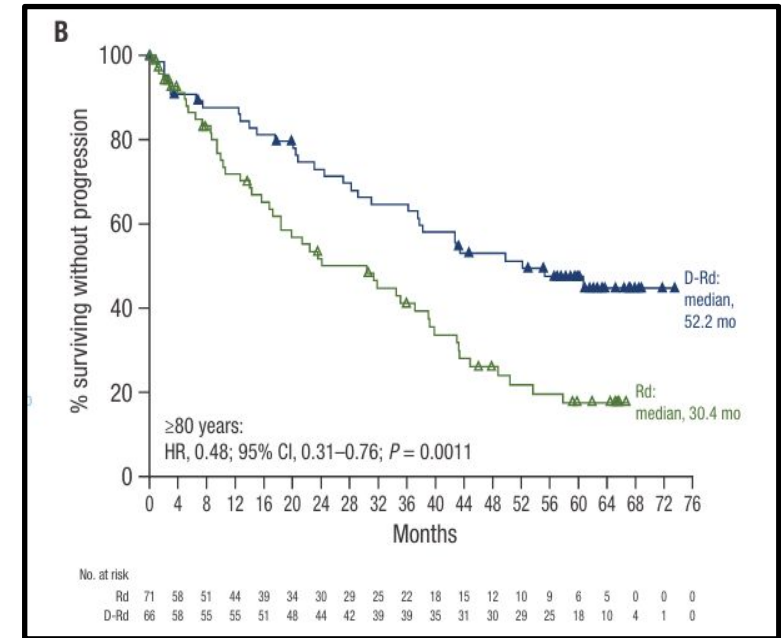
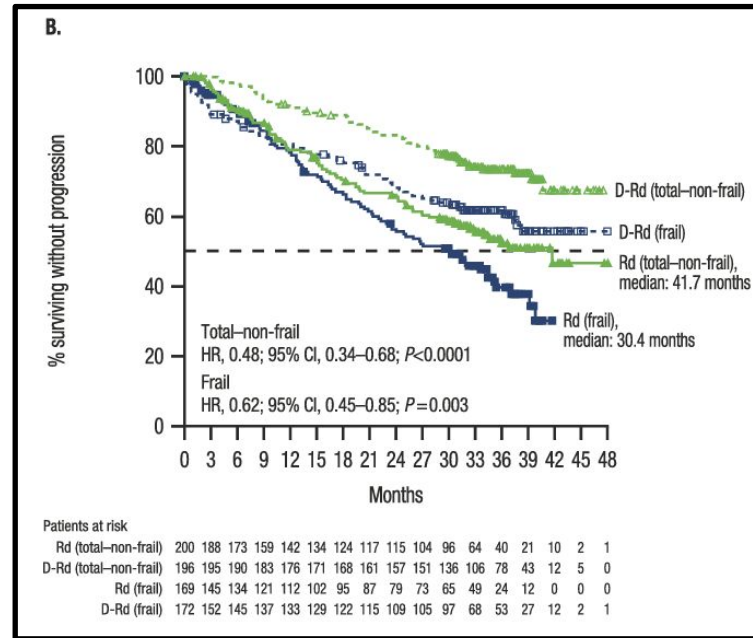
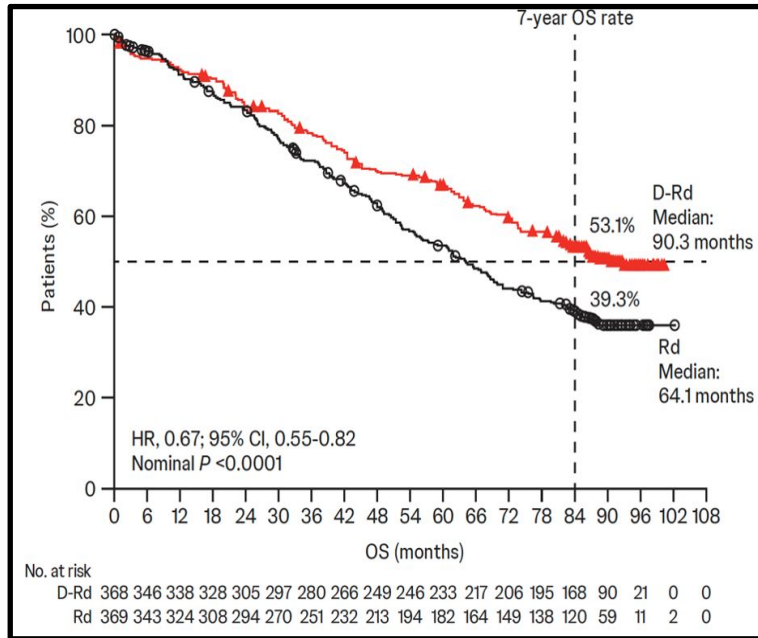
- In transplant ineligible patients ≤80 years of age, **quadruplets are superior to triplets** and result in superior MRD negativity rates and progression free survival

¹Facon T, et al. N Engl J Med. 2024 Oct 31;391(17):1597-1609

²Usmani SZ, et al. Nat Med. 2025 Apr;31(4):1195-1202

³Leleu X, et al. Nat Med. 2024 Aug;30(8):2235-2241

TRIPLET VS. DOUBLET DARA-RD VS. RD

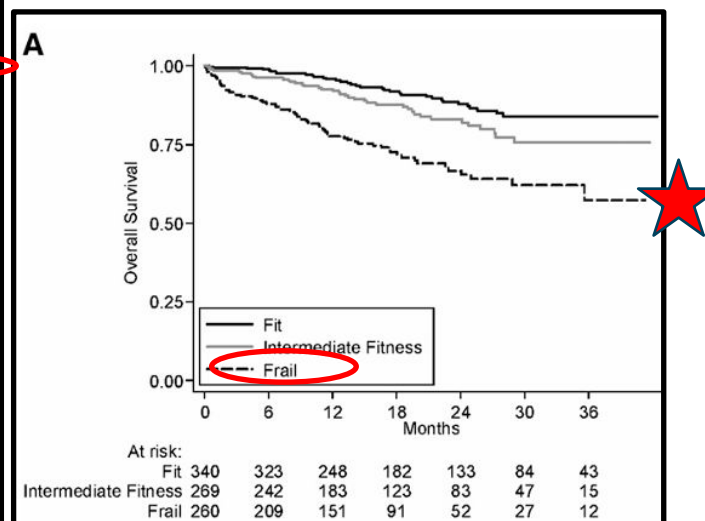


- MAIA trial evaluated patients ≥ 80 years of age, DRd superior to Rd
- Frail patients did worse than non-frail but frail did better with DRd than Rd (simplified frailty score ≥ 2)
- MAIA trial did not use IMWG Frailty Index, used the simplified IMWG frailty score (age, CCI, ECOG)

WHAT ABOUT FRAIL PATIENTS?

IMWG Frailty Score is the Gold Standard Frailty Assessment¹

	HR (95% CI)	P	Score
Age, y			
≤75	1	—	0
76-80	1.13 (0.76-1.69)	.549	1
≥80	2.40 (1.56-3.71)	<.001	2
ADL			
>4	1	—	0
≤4	1.67 (1.08-2.56)	.020	1
IADL			
>5	1	—	0
≤5	1.43 (0.96-2.14)	.078	1
CCI			
≤1	1	—	0
≥2	1.37 (0.92-2.05)	.125	1
ISS			
I	1	—	—
II	2.37 (1.38-4.09)	.002	—
III	3.21 (1.85-5.58)	<.001	—
Chromosome abnormalities			
Favorable	1	—	—
Unfavorable	1.79 (1.23-2.60)	.002	—
Missing	1.13 (0.69-1.83)	.036	—
Therapy			
Proteasome inhibitors	1	—	—
Lenalidomide	0.74 (0.50-1.11)	.142	—



- IMROZ, CEPHEUS, and BENEFIT trials excluded patients ≥80 years of age
- IMWG frailty score ≥2 (frail) was exclusion criteria in the CEPHEUS and BENEFIT trials
- In IMROZ trial, 26% of patients treated with Isa-VRd had sIMWG frailty score ≥2 and those patients had superior MRD- and PFS with Isa-VRD vs. VRd²
- **Data on quadruplets in frail patients and patients ≥80 is limited**

Table 3. Additive total score and related rate of OS and PFS at 3 years

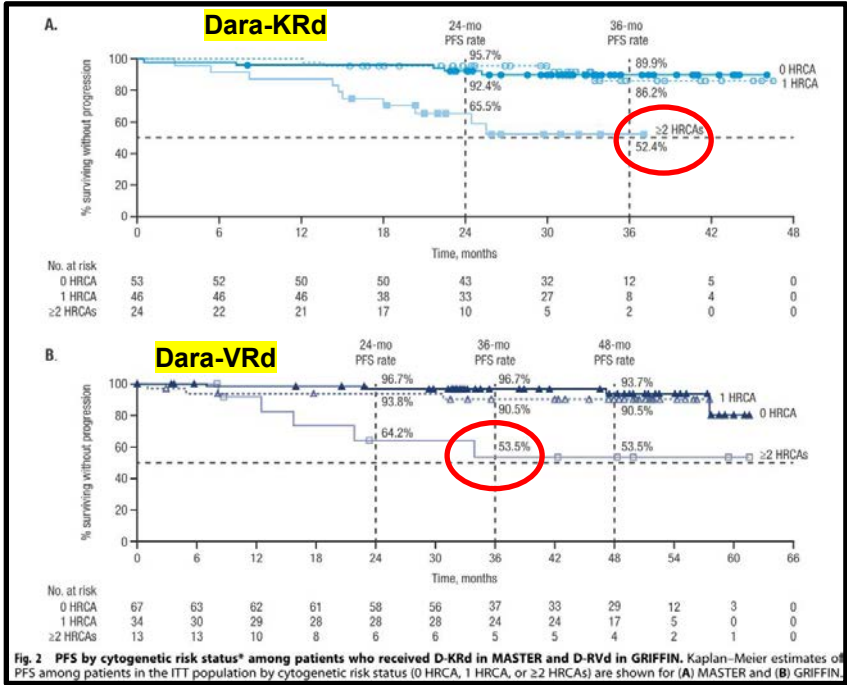
Additive total score	Patient status	No. of patients (%)	% (95% CI)		Cumulative incidence at 12 mo, %	
			OS	PFS	Treatment discontinuation	Grade 3-4 nonhematologic AEs
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate-fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34

¹Palumbo A, et al. Blood. 2015 Mar 26;125(13):2068-74.

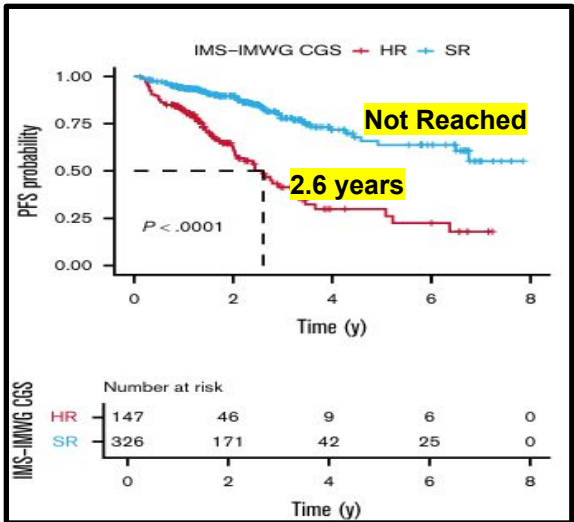
²Manier S, et al. Haematologica. 2025 Sep 1;110(9):2139-2150.

PFS using Quadruplets (DVRd/DKRd) in NDMM with ≥2 HR Cytogenetic Abnormalities¹

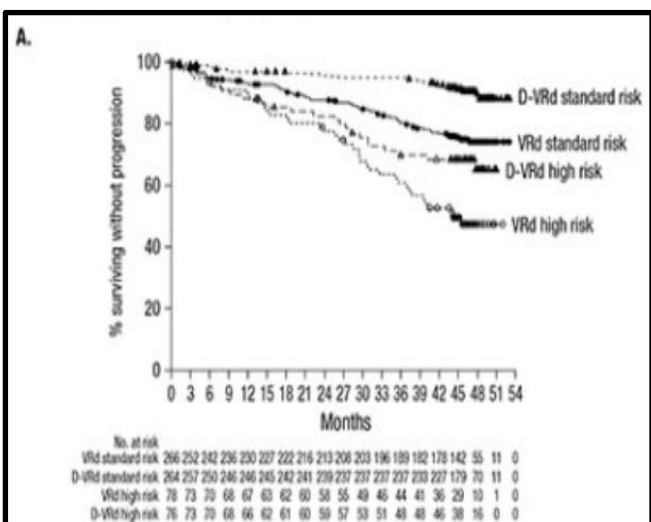
WHAT ABOUT HIGH-RISK PATIENTS?



PFS using Quadruplets (DVRd/DKRd) in NDMM with High Risk Cyto based on IMS-IMWG CGS²



PFS of DVRd vs. VRd in PERSEUS trial in NDMM based on Cytogenetic Risk³



- Quadruplets improve PFS in high risk NDMM patients compared to triplets
- Patients with high-risk multiple myeloma based on the IMS-IMWG 2025 Consensus Criteria, have inferior outcomes, even in the era of quadruplets
- MRD- rates are less durable/sustained in patients with high-risk disease compared to patients with standard risk disease
- Novel strategies are needed in high risk NDMM patients

¹Callander, NS, et al. Blood Cancer J. 14, 69 (2024).

²MacLachlan KH, et al. Blood Adv. 2026 Apr 28;10(8):2616-2625

³Dimopoulos MA, et al. Presented at the 2024 International Myeloma Society Annual Meeting; September 25-28, 2024; Rio De Janeiro, Brazil. Abstract OA-48.

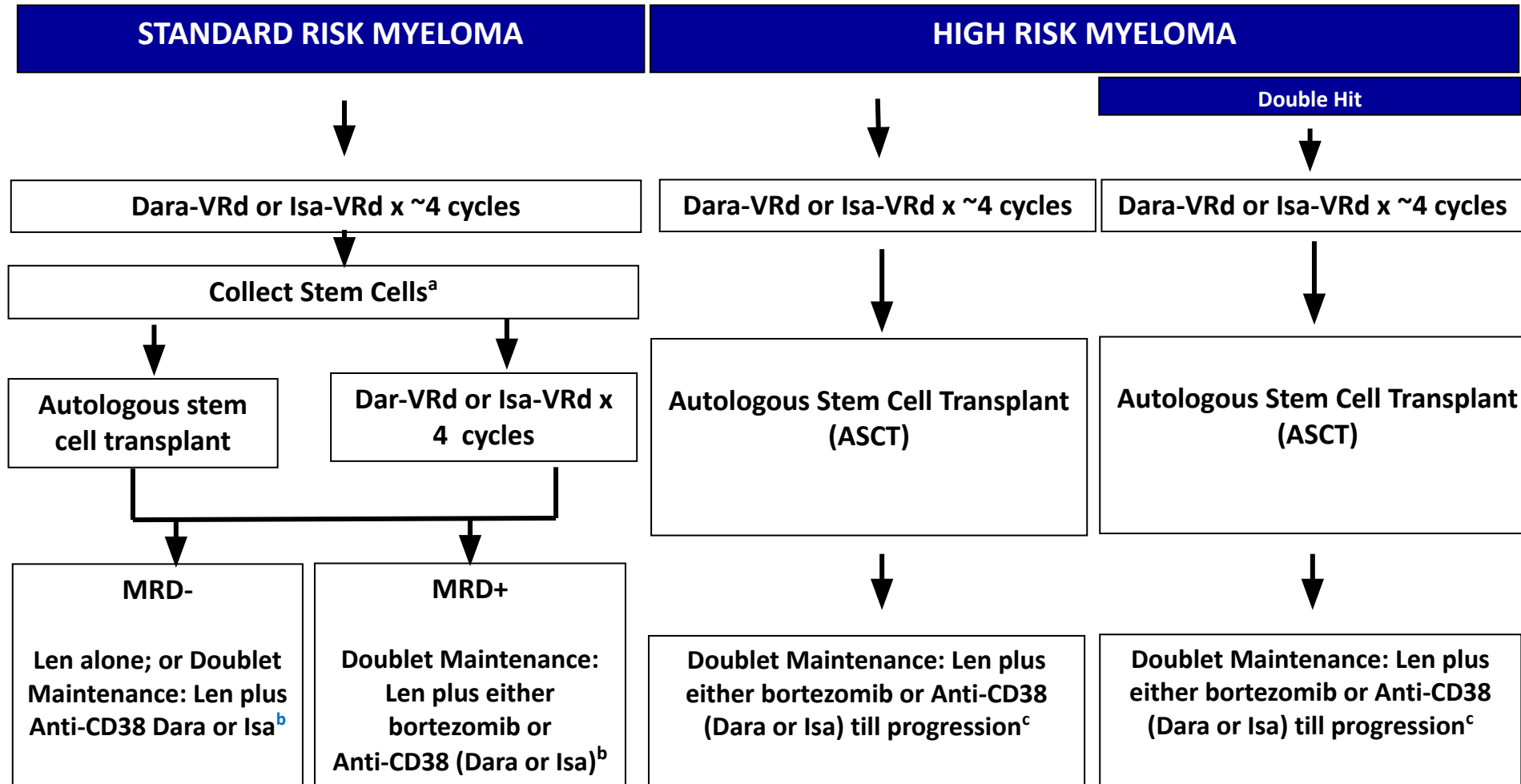
DARATUMUMAB/ISATUXIMAB-VRD VS. DARATUMUMAB/ISATUXIMAB-KRD

Trial	Regimen	ORR after induction	MRD negativity after induction	PFS	
CASSIOPEIA	Dara-VTd	92.6%	34.6% (10^{-5})	6-year PFS 72% (overall study)	Bortezomib-Containing Quadruplets
GRIFFIN	Dara-VRd	98%	21.2% (10^{-5})	4-year PFS 87.2%	
PERSEUS	Dara-VRd	~97%	~48% (10^{-5}) after induction	4-year PFS 84.3%	
GMMG-HD7	Isa-VRd	~90%	50.1% (10^{-5})	3-year PFS 83%	
BENEFIT	Isa-VRd (transplant-ineligible)	~90–95%*	Not yet mature	PFS immature	
IMROZ	Isa-VRd (transplant-ineligible)	~90%*	MRD assessed later (not induction)	5-year PFS 63.2%	
CEPHEUS	Dara-VRd (transplant-ineligible)	~95%	~61% (10^{-5})	4.5-year PFS 68.1%	Carfilzomib-Containing Quadruplets
MASTER	Dara-KRd	97%	~42–45% after induction	2-year PFS 87%	
MANHATTAN	Dara-KRd (no transplant)	100%	71% (10^{-5}) after 8 cycles	1-year PFS 98%	
ISKIA	Isa-KRd	~97%	~50% after induction	PFS immature	
MIDAS	Isa-KRd	~97–98%	~65% (10^{-5}) after induction	PFS immature	
ADVANCE	Dara-KRd	~95–100%	~55–60%	PFS immature	

- No prospective study compares quadruplet therapy with bortezomib vs. carfilzomib
- MRD- rates appear higher with carfilzomib-based quadruplets
- Consider carfilzomib-based quadruplet in patients with contraindication to bortezomib (i.e. peripheral neuropathy)

mSMART – Off-Study

Transplant Eligible



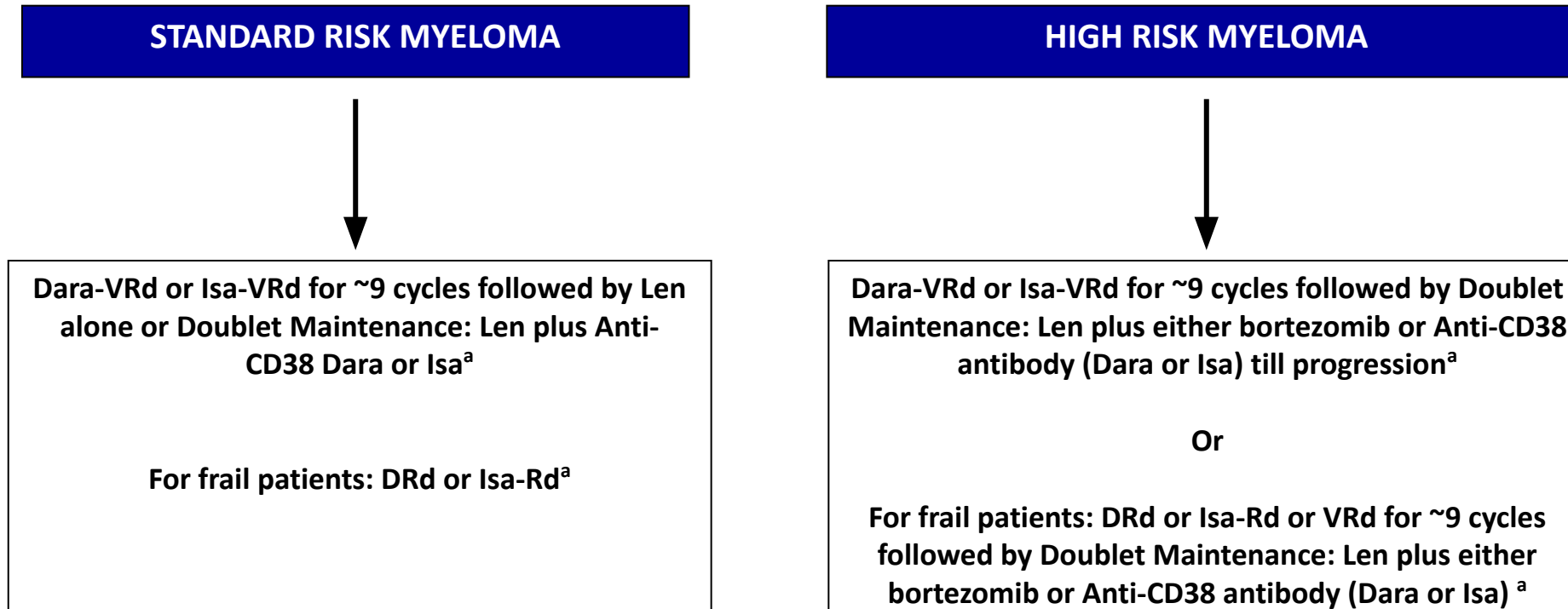
^a If age >65 or > 4 cycles of induction therapy, consider mobilization with G-CSF plus cytoxan or plerixafor; ^b Duration usually until progression based on tolerance; Discontinued Anti-CD38 if MRD- for 2 years; ^c In patients with ≥grade 2 neuropathy at baseline, and in whom bortezomib needs to be dose reduced or discontinued due to neuropathy, consider carfilzomib instead.
 Dara-VRd, Daratumumab, bortezomib, lenalidomide, dexamethasone; Isa-VRd, Isatuximab, bortezomib, lenalidomide, dexamethasone; Dara, daratumumab; isa, isatuximab

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376.

v23 //last reviewed Oct 2025

mSMART – Off-Study

Transplant Ineligible



^aDuration usually until progression based on tolerance; Discontinue Anti-CD38 if MRD- for 2 years

Dara-VRd, Daratumumab, bortezomib, lenalidomide, dexamethasone; Isa-VRd, Isatuximab, bortezomib, lenalidomide, dexamethasone; VRd, Bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; Isa-Rd, isatuximab, lenalidomide, dexamethasone; dara, daratumumab; isa, isatuximab

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376.

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TOLERABILITY: SUPPORTIVE CARE

INCREASED ADVERSE EVENTS WITH QUADRUPLETS VS. TRIPLETS

Adverse event	Quadruplet regimen impact vs triplet	Typical difference observed	Mechanistic rationale
Infections (overall)	↑ More common with quadruplets	Absolute increase ~5–15% depending on trial	Added immunosuppression from anti-CD38 therapy (NK-cell depletion, hypogammaglobulinemia) plus deeper responses
Grade ≥3 infections	↑ Increased	Usually modest increase (~2–8% absolute)	Impaired humoral immunity and cellular immune dysfunction
Upper respiratory tract infections	↑ Increased	Among most consistently increased AEs	Anti-CD38-associated immune depletion
Pneumonia	↑ Increased	More frequent and occasionally higher grade	Increased susceptibility to bacterial and viral infections
COVID-19 infections	↑ Increased in contemporary trials	Higher incidence in anti-CD38 arms	Impaired antibody responses and immune recovery

Table 3. Most Common Adverse Events (Safety Population).^{*} PERSEUS TRIAL¹

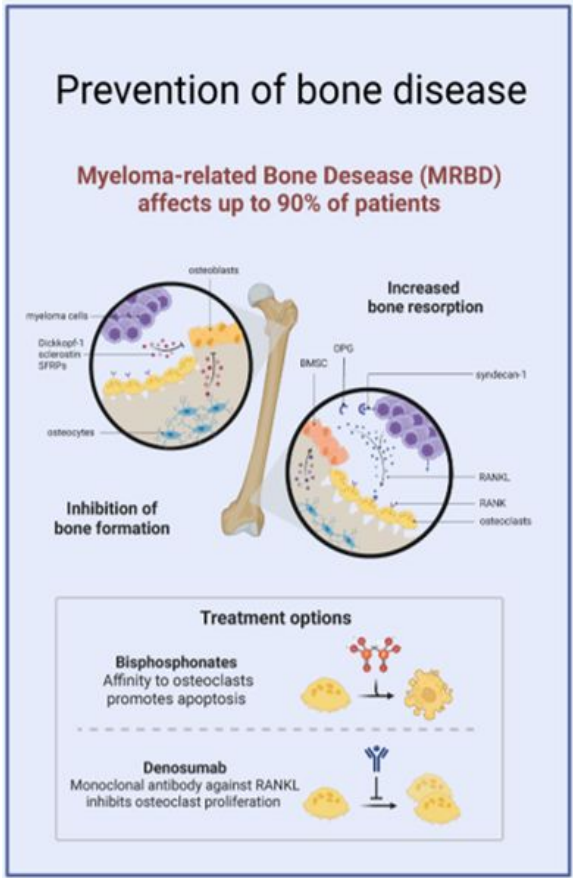
Event	D-VRd (N=351)		VRd (N=347)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	349 (99.4)	321 (91.5)	344 (99.1)	297 (85.6)
Hematologic adverse event				
Neutropenia	243 (69.2)	218 (62.1)	204 (58.8)	177 (51.0)
Thrombocytopenia	170 (48.4)	102 (29.1)	119 (34.3)	60 (17.3)
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
Nonhematologic adverse event				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	188 (53.6)	15 (4.3)	179 (51.6)	14 (4.0)
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infection	305 (86.9)	124 (35.3)	266 (76.7)	95 (27.4)
Coronavirus disease 2019	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)
Second primary cancer	37 (10.5)	NA	25 (7.2)	NA
Any infusion-related reaction	21 (6.0)	3 (0.9)	NA	NA

¹Sonneveld P, et al. N Engl J Med. 2024 Jan 25;390(4):301-31

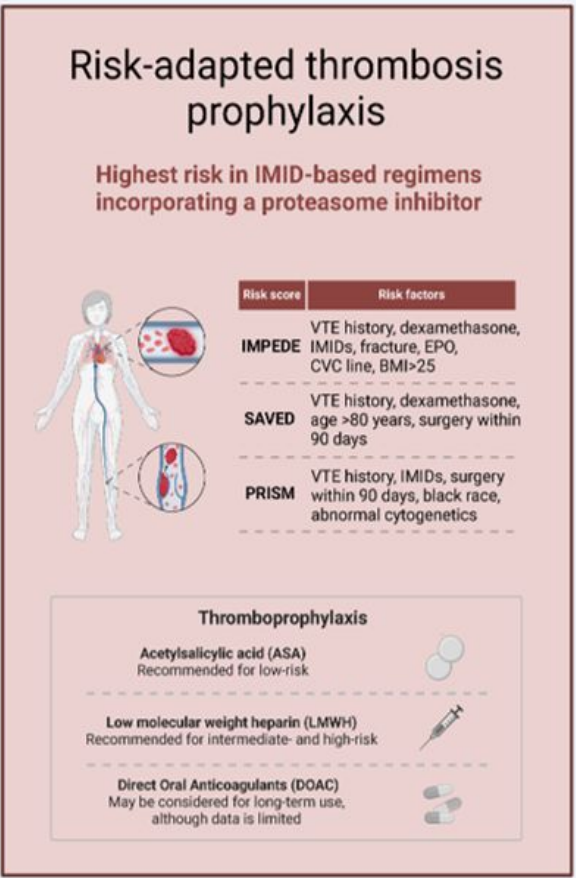
^{*} The safety population included patients who had received at least one dose of the assigned treatment. Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group are listed. NA denotes not applicable.

SUPPORTIVE CARE

Prevention of Skeletal Related Events¹



Prevention of Thrombosis¹



Infection Prophylaxis²

	Bacterial prophylaxis	Fungal prophylaxis	Viral prophylaxis
Low risk	None	None	None, unless a previous episode of herpes simplex virus; in which case, use acyclovir
Intermediate risk	Consider levofloxacin* 500 mg once daily	Consider fluconazole† or micafungin in the setting of severe mucositis and prolonged neutropenia (absolute neutrophil count ≤100 cells per µL for ≥7 days)	For patients who are seropositive for herpes simplex virus or herpes zoster virus, provide acyclovir (400 mg or 800 mg orally twice daily for herpes simplex virus and 800 mg orally twice daily for herpes zoster virus) or valacyclovir (500 mg orally twice daily).
High risk	Consider levofloxacin* 500 mg once daily	Consider fluconazole† or micafungin in the setting of prolonged neutropenia (absolute neutrophil count ≤100 cells per µL for ≥7 days) and severe mucositis; consider prophylaxis with voriconazole‡ or posaconazole‡ for patients with an absolute neutrophil count ≤100 cells per µL for >7 days; consider prophylaxis against <i>Pneumocystis jirovecii</i> pneumonia with trimethoprim-sulfamethoxazole or alternative agents, as clinically indicated‡	For patients who are seropositive for herpes simplex virus or herpes zoster virus, provide acyclovir (400 mg or 800 mg orally twice daily for herpes simplex virus and 800 mg orally twice daily for herpes zoster virus) or valacyclovir (500 mg orally twice daily); for patients who are seropositive for HBV, the risk for reactivation depends on HBV serostatus, and type and duration of immunosuppressive therapies. For patients at intermediate to high risk of HBV reactivation, consider prophylaxis; for patients at low risk, consider early pre-emptive treatment.§ Use tenofovir or entecavir, rather than lamivudine, for treatment and pre-emptive purposes and select tenofovir in patients with previous exposure to lamivudine; maintain antiviral therapy for several months and monitor HBV viral load. Consider stopping antiviral agents when HBV viral load normalises and stopping immunosuppressive agents.

HBV=hepatitis B virus. *Levofloxacin is preferred because the trial³ showing effective infection prevention in this setting used this agent. Additionally, drug-drug interactions exist between ciprofloxacin and pomalidomide, causing a significantly increased drug exposure of pomalidomide and potential toxicity. For patients who are intolerant to levofloxacin and other fluoroquinolones, consider trimethoprim-sulfamethoxazole. †Monitor for drug-drug interactions between antifungal triazoles and agents against multiple myeloma: fluconazole, itraconazole, voriconazole, and posaconazole with bortezomib and itraconazole, voriconazole, and posaconazole with panobinostat. The dose of levofloxacin (and other fluoroquinolones), trimethoprim-sulfamethoxazole, acyclovir, and valacyclovir might require a reduction in the presence of renal dysfunction. ‡Trimethoprim-sulfamethoxazole (160 mg or 800 mg twice a day, 2–3 days per week) is the agent of choice for prophylaxis against *P jirovecii* pneumonia. Alternative agents include aerosolised pentamidine (300 mg once monthly), dapsone (50 mg twice a day), or atovaquone (1500 mg daily). Consider alternative options for patients receiving immunomodulators (eg, thalidomide) because of potentially increased risk of severe skin toxicity with trimethoprim-sulfamethoxazole. §Intermediate to high risk of HBV reactivation (>1% risk): HBsAg-positive or negative but anti-HBc-positive. Low risk of HBV reactivation (<1%): HBsAg-negative and anti-HBc-negative. Patients with evidence of a low circulating viral load of HBV DNA can be given antiviral therapy or closely monitored and treated if there is evidence of increasing viraemia, regardless of serum concentrations of alanine aminotransferase.

Table 3: Recommendations for risk-adapted antimicrobial prophylaxis in patients with multiple myeloma

TEAMM TRIAL³: Addition of prophylactic levofloxacin (500mg PO qd) to active myeloma treatment during the first 12 weeks of therapy significantly reduced febrile episodes and deaths compared with placebo without increasing health care-associated infections.

Drug	Dose	Scheme of administration	Duration
Zoledronate IV ^a	4 mg	Monthly for 12 mo; if ≥VGPR after 12 mo consider a 3-mo dose interval.	At least 12 mo. If discontinued, reinitiate at biochemical relapse.
Pamidronate IV ^a	30 mg	See at zoledronate	See at zoledronate
Denosumab SC ^a	120 mg	Monthly	Continuously. If discontinued, administer 1 dose of zoledronate 6 mo after the last dose to prevent rebound effects

^aAll patients who are treated with bisphosphonates or denosumab should receive calcium and vitamin D supplementation.

¹Zweegman S, et al. Hematology Am Soc Hematol Educ Program (2024) 2024 (1): 569–581.

²Raje NS, et al. Lancet Haematol. 2022 Feb;9(2):e143-e161.

³Drayson M, et al. The Lancet Oncology, 2019; 20, 1760-1772

DOSE MODIFICATIONS

- **Daratumumab or Isatuximab:** dose usually remains the same
- **Lenalidomide:** renally adjust dose based on CrCl, can adjust from 25mg PO qd to 15mg or 10mg PO qd if adverse events unresponsive to supportive care (cytopenias, rash, GI symptoms, etc)
- **Bortezomib:** can adjust from 1.3mg/m² weekly to 1.0mg/m² weekly to 0.7mg/m² weekly depending on side effects (neuropathy, ocular side effects, etc)
- **Dexamethasone:** 20mg for age ≥75 and can adjust from 40mg weekly if intolerant as dose does not appear to impact outcomes¹

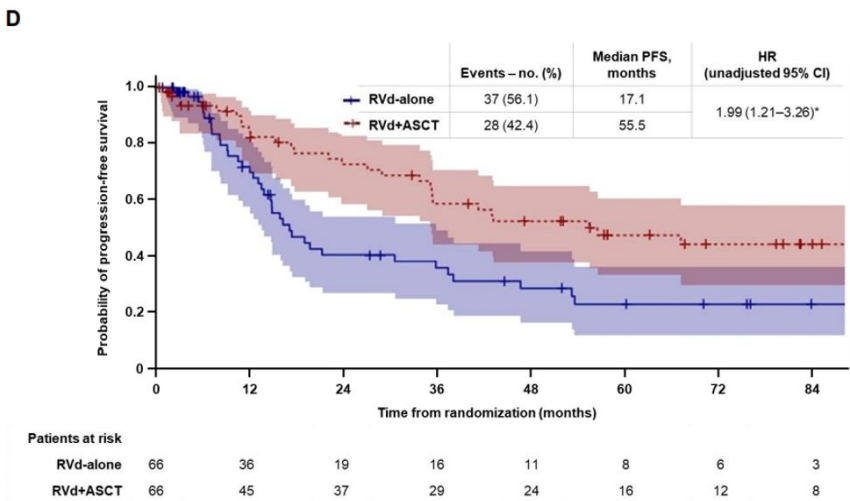
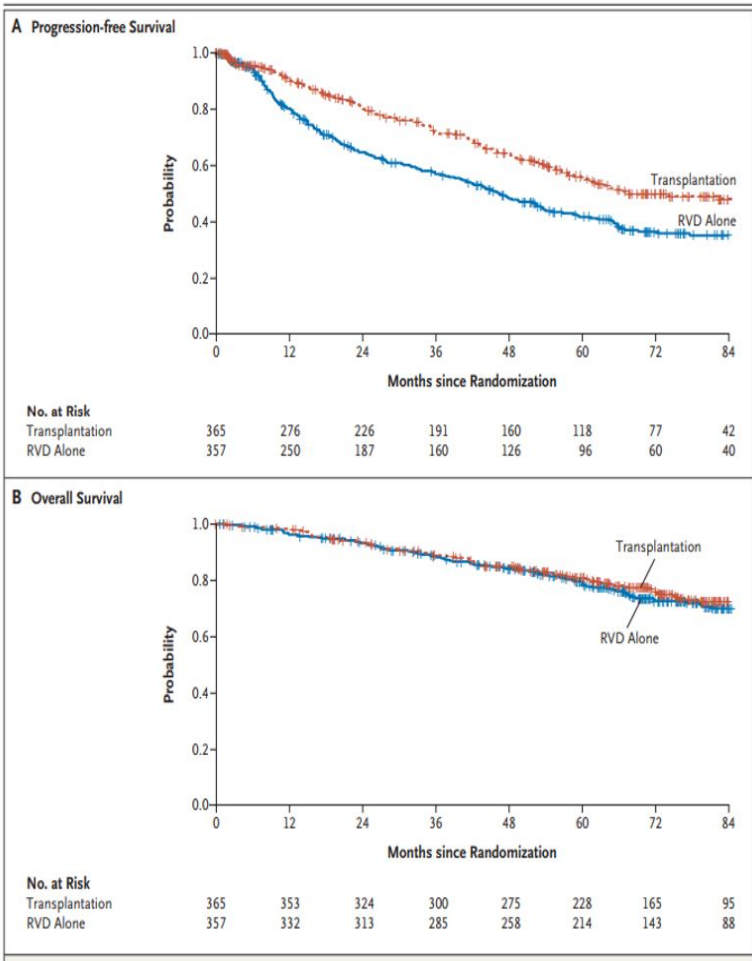
¹Banerjee R, et al. Blood. 2025 Jan 2;145(1):75-84.

AUTOLOGOUS TRANSPLANT TIMING

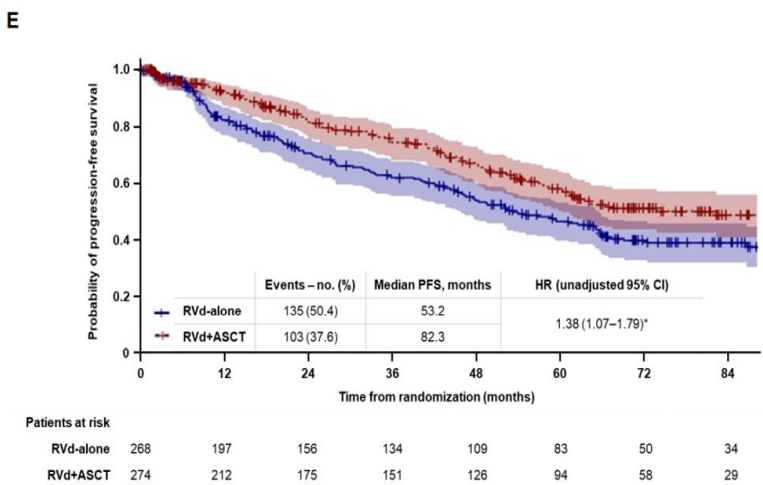
- 1st line consolidation vs. at 1st relapse?
- High Risk vs. Standard Risk?

DETERMINATION TRIAL

PFS for Patients with High Risk Cytogenetics (del17p, t(4;14), t (14;16))



PFS for Patients with Standard Risk Cytogenetics



- In the era of triplets, there was no OS difference with upfront vs. delayed transplant
- However, high risk patients had a higher magnitude of PFS benefit compared to standard risk
- There is limited data on omitting up front transplant in era of quadruplets but transplant recommended esp. for high-risk patients given that high risk patients:
 - relapse earlier
 - have shorter duration of MRD negativity
 - greater clonal heterogeneity and a higher likelihood of resistant subclones

CEPHEUS AND MIDAS TRIALS

CEPHEUS Trial¹

- In the phase III CEPHEUS trial of DVRd vs. VRd in transplant ineligible or deferred patients, there were no differences in PFS, MRD- or sustained MRD- between DVRd and VRd in high risk (although n=52 [13%] only)
- This suggests that high-risk patients may benefit from transplant

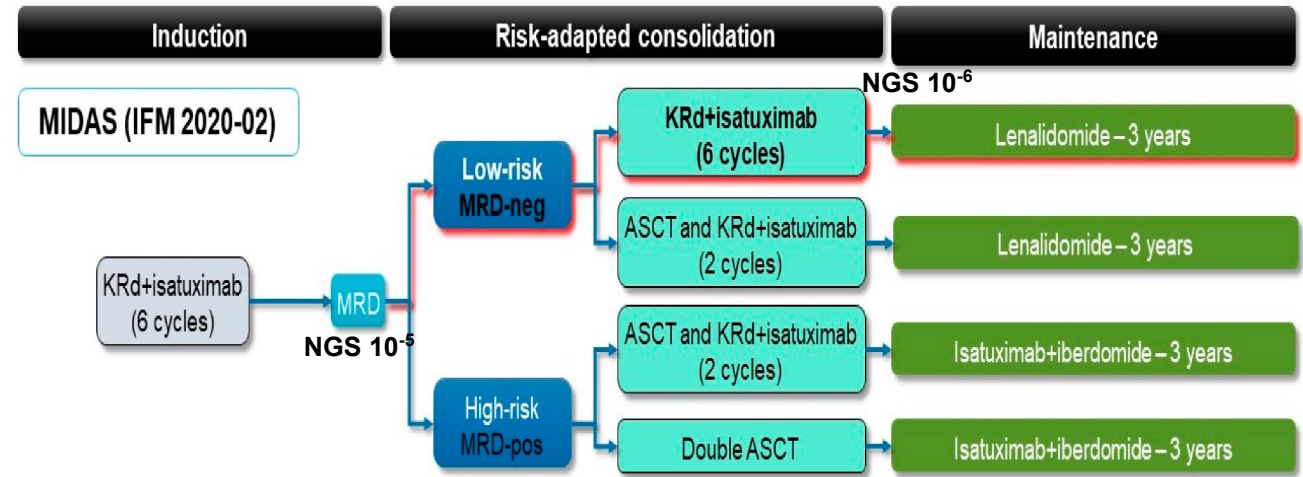
	DVRd		VRd		HR (95% CI); P-value
	n	mPFS, mo	n	mPFS, mo	
HiR ^a	25	39.8	27	31.7	0.88 (0.42–1.84); 0.7387
R-HiR	83	NE	84	45.6	0.73 (0.46–1.15); 0.1739
SR ^a	149	NE	149	60.6	0.61 (0.41–0.91); 0.0136
R-SR	94	NE	90	60.6	0.54 (0.32–0.91); 0.0189
Gain(1q) + other HRCAs	43	60.3	48	42.2	0.80 (0.45–1.43); 0.4496
Amp(1q) + other HRCAs	31	NE	20	NE	0.97 (0.38–2.47); 0.9525
1 revised HRCA	66	NE	72	47.2	0.63 (0.37–1.09); 0.0938
≥2 revised HRCA	17	22.7	12	29.7	1.01 (0.42–2.44); 0.9868

^aUnknown cytogenetic risk: DVRd, n=23; VRd, n=22.
mPFS, median PFS; NE, not estimable.

¹Bahlis NJ, et al. J Clin Oncol **43**, 7529-7529(2025)

²Perrot A, et al. N Engl J Med. 2025 Jul 31;393(5):425-437

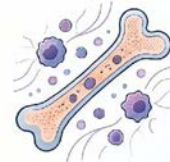
MIDAS Trial²



MIDAS Trial: Evaluating ASCT Omission in MRD-Negative Multiple Myeloma

Phase 3 MIDAS trial evaluates consolidation strategies in transplant-eligible, newly diagnosed multiple myeloma patients, stratified by MRD status after Isa-KRd induction to determine the most effective path.

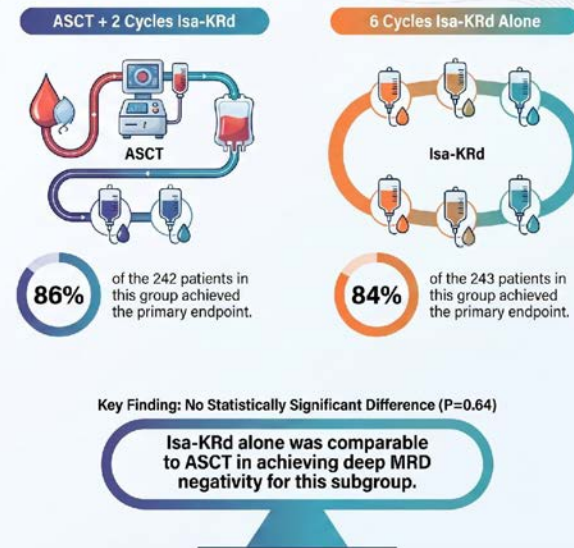
Trial Foundation & Primary Endpoint



Primary Endpoint:
MRD Negativity at 10⁻⁶
Achieving <1 cancer cell per million normal cells prior to maintenance therapy.



Focus Subgroup:
Post-Induction MRD-Negative
Analysis focuses on patients already MRD-negative (at 10⁻⁵ sensitivity) after 6 cycles of Isa-KRd induction.



- Follow-up is short, only 17 mo
- Only 17% high risk
- Longer follow-up is needed to see PFS and sMRD-

SUMMARY: TRANSPLANT ELIGIBLE PATIENTS SHOULD UNDERGO TRANSPLANT

- Based on the available data, transplant eligible patients should undergo upfront transplant
- There is no available data at this time on transplant deferred strategies for patients treated with quadruplets (several ongoing trials evaluating MRD-guided transplant omission: MIDAS, MILESTONE, ASCENT)
- Perhaps patients with standard risk disease who achieve MRD- after quadruplet induction therapy can undergo deferred transplant after careful consideration and acknowledgement of limited data? (CEPHEUS included transplant deferred patients)
- High Risk patient should undergo transplant in the front line after quadruplet induction

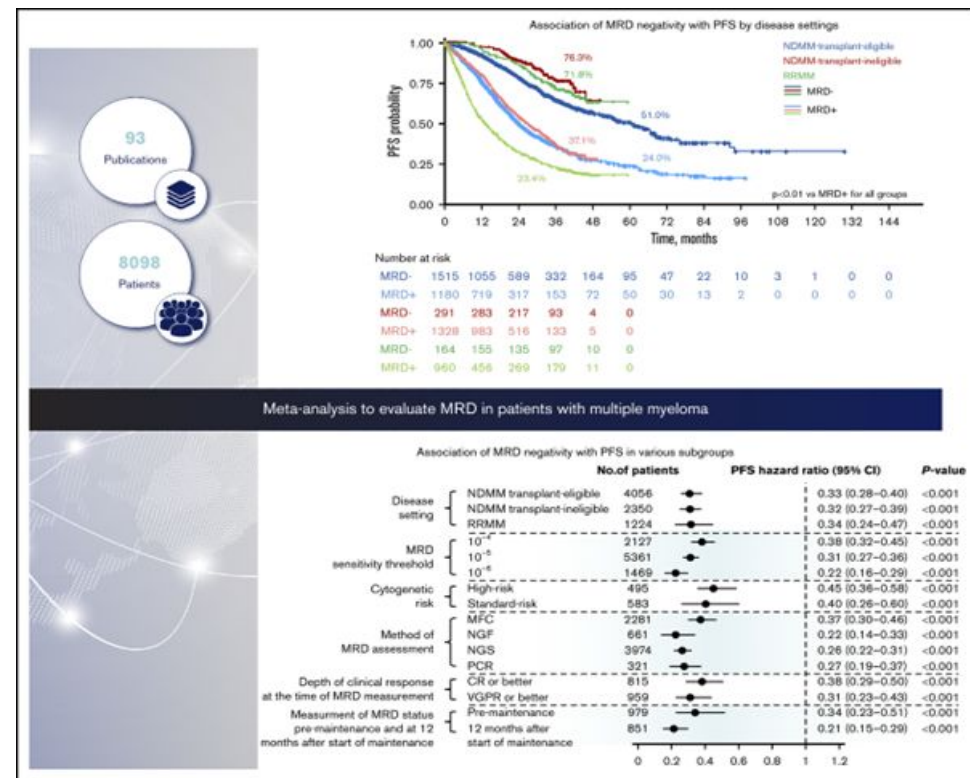
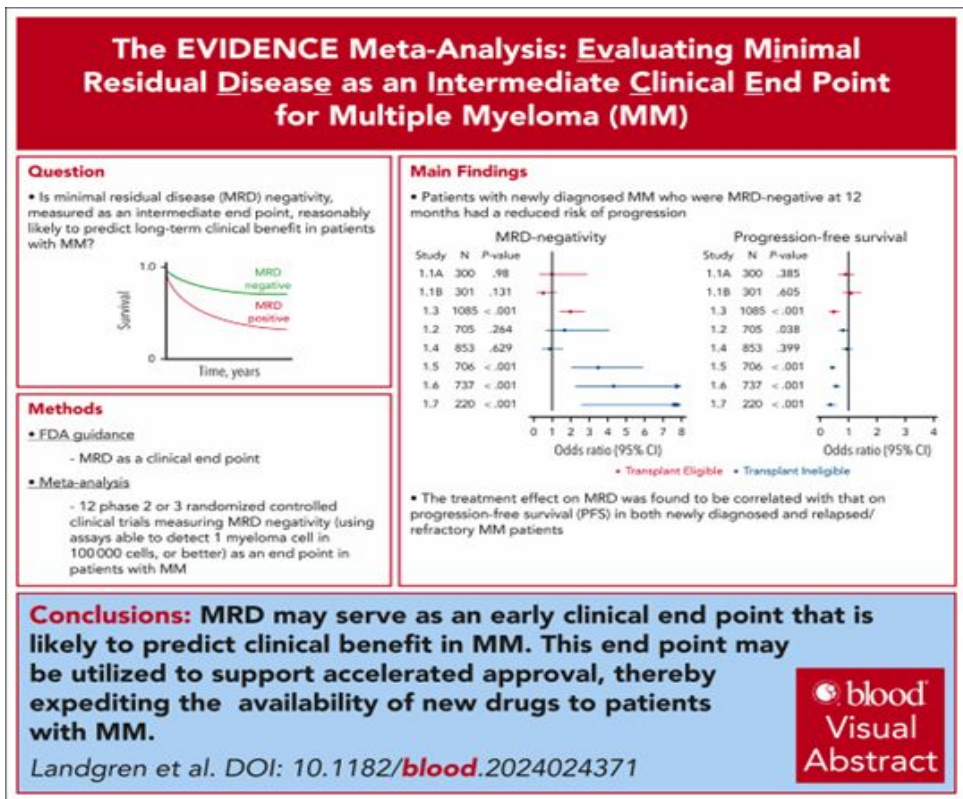


MRD GUIDED STRATEGIES: WHAT IS THE EVIDENCE

- Forego autologous transplant?
- Discontinue maintenance?

MRD NEGATIVITY: SURROGATE ENDPOINT

- Several Meta-Analysis have shown that achieving MRD negativity is a predictor of long-term prognosis (i.e. PFS) thus validating MRD negativity as a surrogate endpoint
- Because therapies are so effective with high overall response rates, complete response rates, and progression free and overall survival measured in years, novel endpoints are needed to accelerate drug approval
- FDA approved MRD (at least 10^{-5}) as a surrogate endpoint to support accelerated approval of new therapies for multiple myeloma on 4/29/2024



Landgren O, et al. EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical end point for multiple myeloma. *Blood* 2024; 144 (4): 359–367.

Munshi NC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv* 2020; 4 (23): 5988–5999.

MRD-GUIDED TREATMENT DE-ESCALATION

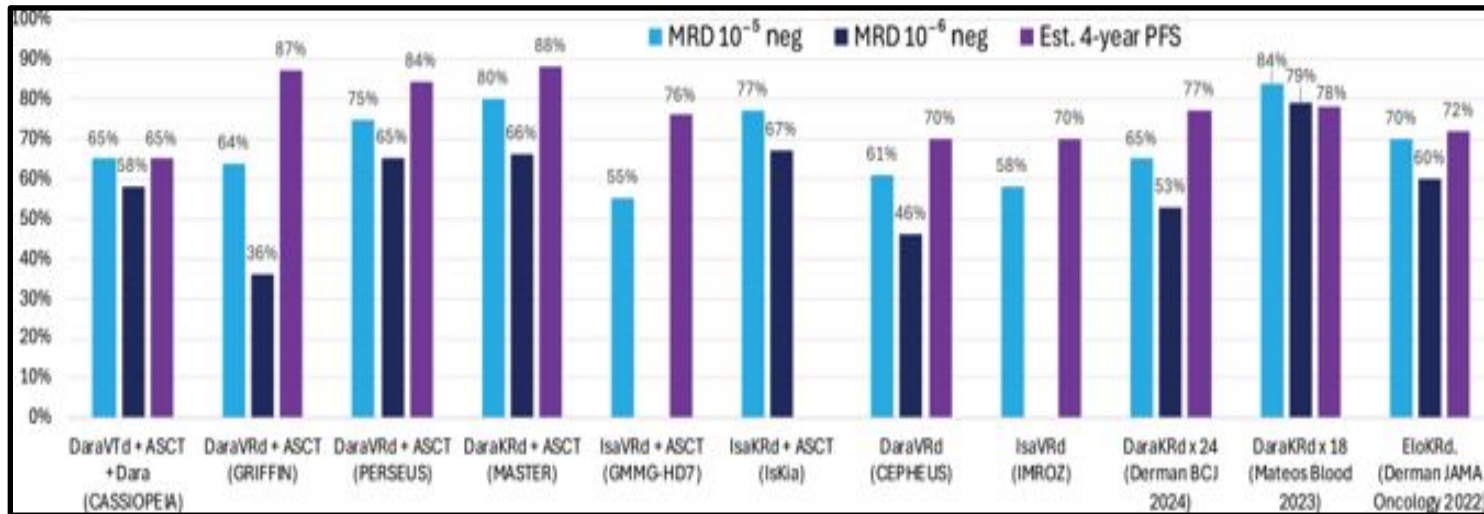


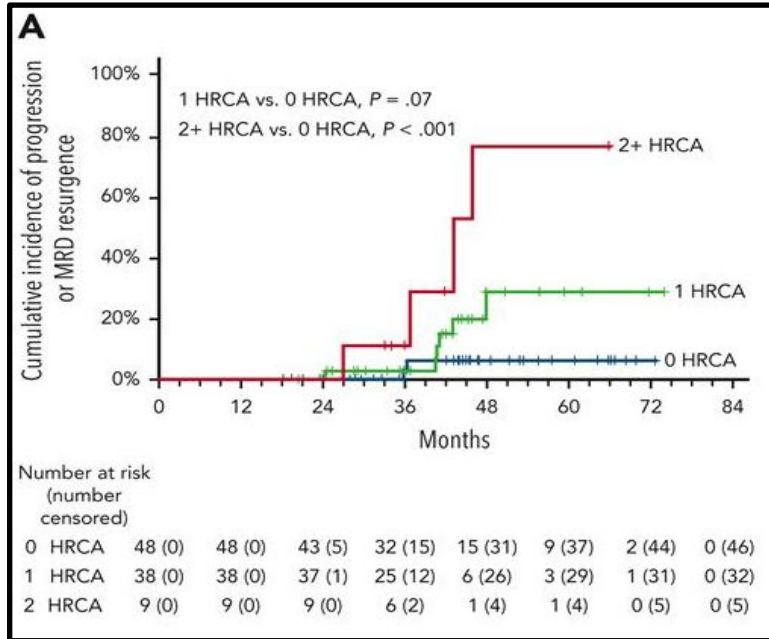
Table 1. Select trials of maintenance cessation in myeloma

Study	No. of patients in study	Trial design/treatment cessation plan	Outcomes	Notes
PUBLISHED				
MASTER	123	Dara-KRd × 4 cycles → ASCT and up to 8 cycles Dara-KRd +/- R maintenance. Patients with two consecutive MRD $<10^{-5}$ stopped treatment.	71% discontinued treatment. 36-month PFS: 73% (50% for 2+ HRCA)	Did not use sustained MRD negativity definition.
GEM2014MAIN (Phase 3)	332	Randomized to maintenance IRd vs Rd × 2 years. Maintenance cessation for MRD $<10^{-6}$ after 2 years.	4-year PFS from cessation: 82.8%	No randomization among MRD negative patients
MRD2STOP	47	Maintenance cessation for patients receiving ≥1 year of maintenance, PET-neg and MRD $<10^{-6}$.	3-year PFS from cessation: 85% 3-year MRD resurgence: 20% (11% with progression)	43% received quad induction; 77% received consolidation; 64% received ASCT.
Terpos et al.	52	Maintenance cessation after 36 months of maintenance AND 3 consecutive MRD $<10^{-6}$ and PET negative results. Restart treatment for MRD resurgence.	MRD 10^{-6} resurgence: 23% 3-year treatment-free survival: 75.8%	All received triplet induction and ASCT; consolidation strategies varied.

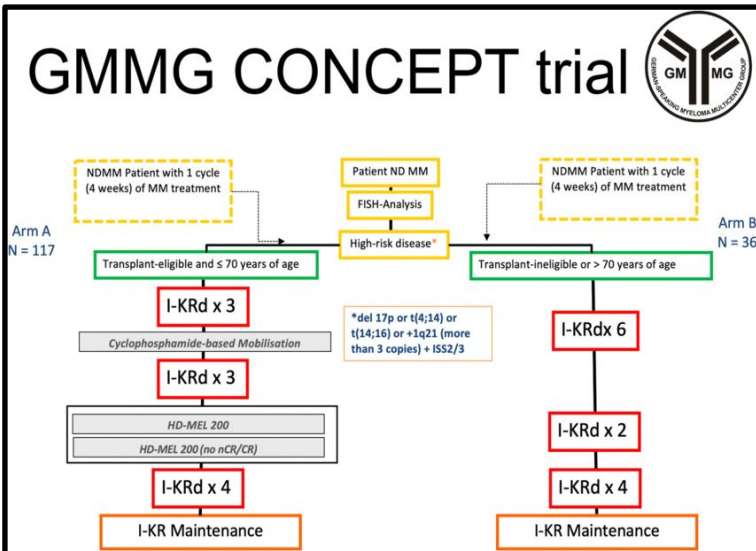
- With triplet and quadruplet induction therapies achieving unprecedented MRD negativity levels, can transplant or continuous therapy be discontinued?
- Data is emerging regarding the cessation of maintenance therapy based on MRD negativity
- MIDAS trial suggests patients who achieve MRD- after 6 cycles of Isa-KRd may not benefit from ASCT but longer follow-up is needed

MRD-GUIDED DE-ESCALATION IN HIGH-RISK?

Pooled data from MASTER study and institutional data

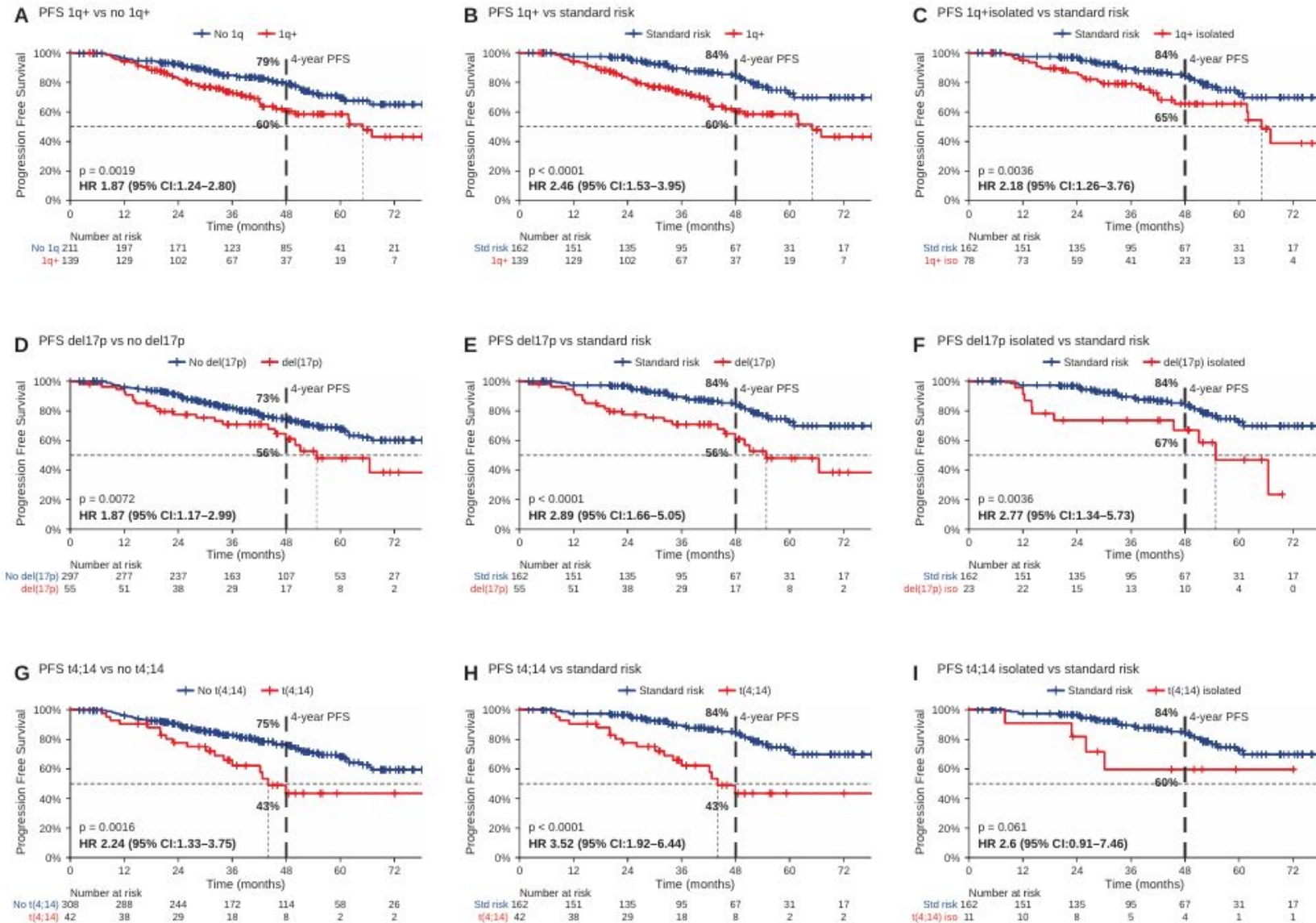


- Sustained MRD- at 10^{-5} for ≥ 12 months in patients with standard risk disease treated with quadruplets and ASCT and post-ASCT quadruplet consolidation results in low risk of progression or MRD resurgence after therapy discontinuation
- Patients with high-risk disease do better with continuous therapy and don't benefit from MRD-guided therapy cessation in the post transplant setting due to high risk of progression and MRD resurgence
- More data is needing from prospective trials looking at maintenance therapy discontinuation, especially in high-risk patients (i.e. SWOG S1803, FREEDMM, RADAR)



219 patients (35.6% had ≥ 2 HRCA), 58.4% reached MRD-neg (10^{-5}) $\geq$ CR, 86.8% reached MRD-neg at any time. mPFS for transplant eligible patients was 69.7 months

MRD-GUIDED DE-ESCALATION IN HIGH-RISK?



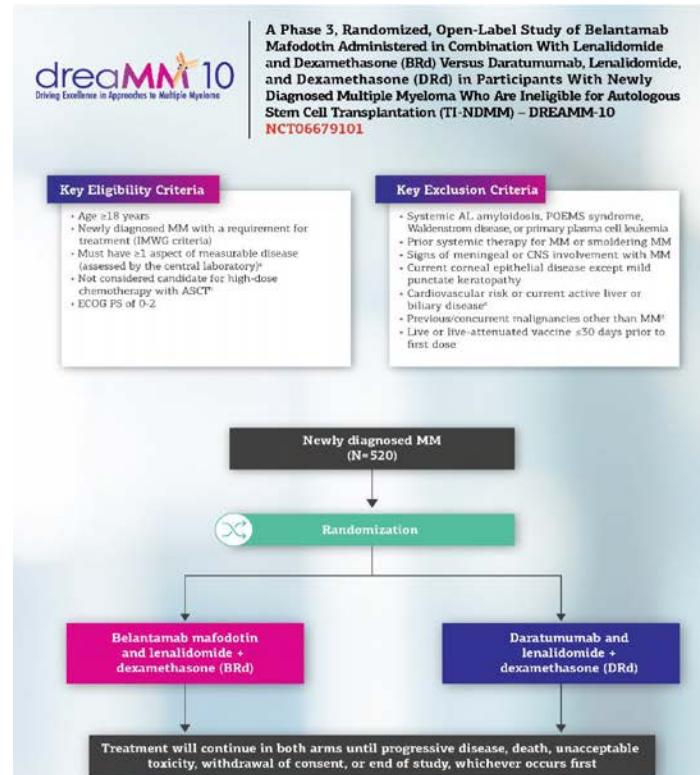
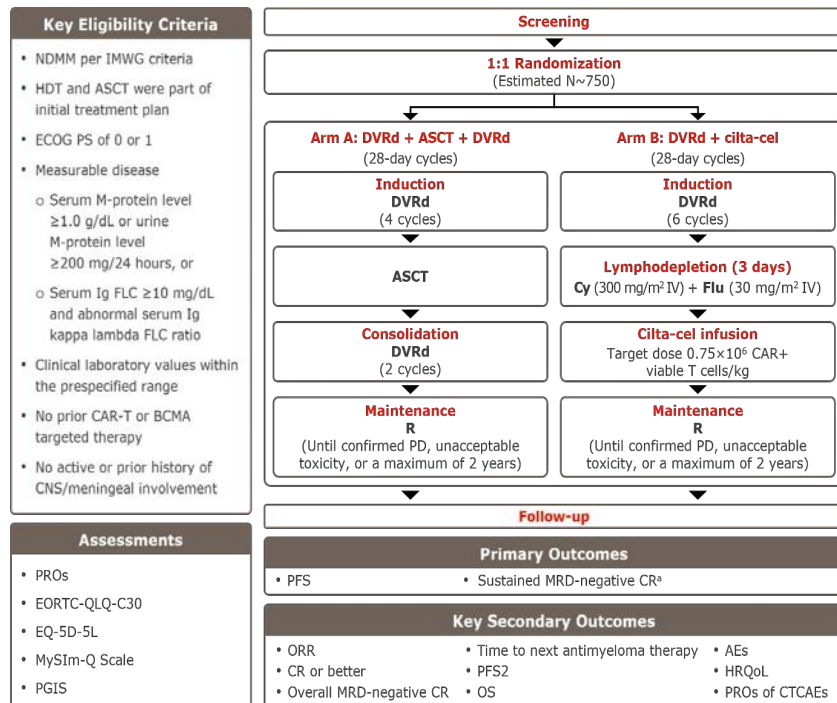
- Despite achieving MRD- (10^{-5}) post ASCT, patients with high-risk cytogenetics still have inferior PFS and OS compared to standard risk patients

FUTURE OUTLOOK: WHERE THE FIELD IS GOING

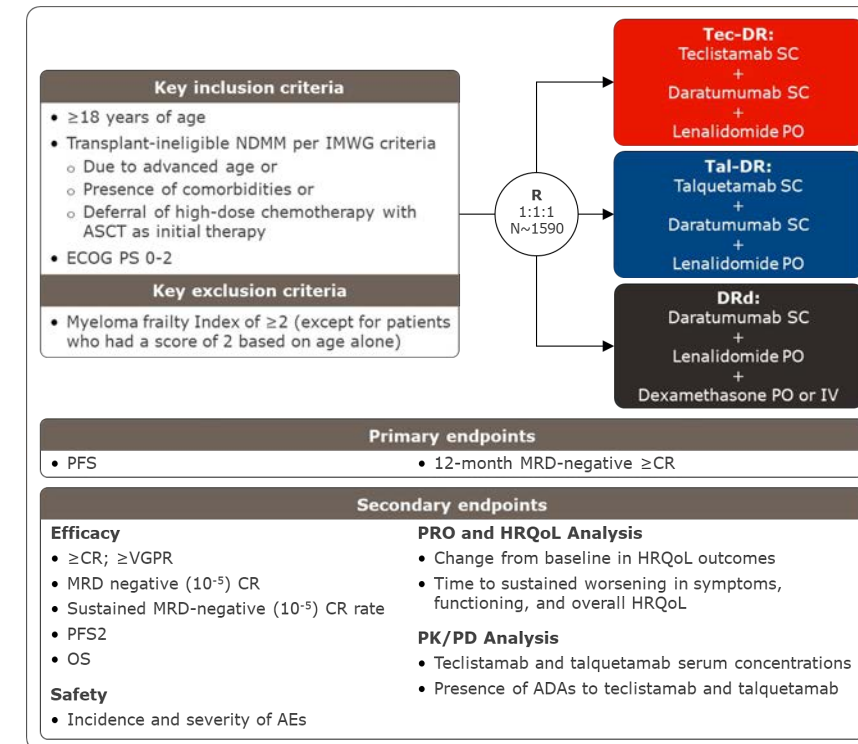
- BCMA immunotherapies will likely be the front-line therapy over the next 3-5 years
- BCMA immunotherapies have already proven their superiority to Anti-CD38/PI/IMiDs in the relapsed setting

DREAMM-10

CARTITUDE-6



MAJESTEC-7



CONCLUSIONS

- NDMM patients should be treated with a quadruplet
- NDMM patients that are frail and/or ≥ 80 years of age should be treated with a DRd triplet
- Supportive care is important – bone health, infection, thrombosis
- Transplant eligible patients should be offered transplant up front, especially if high risk
- MRD-guided therapy cessation/transplant omission strategies are emerging



THANK YOU

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