City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Frontline Treatment Updates: Multiple Myeloma

Sarah S. Lee, MD

Assistant Professor

Department of Hematology/Hematopoietic Cell Transplantation Division of Multiple Myeloma

City of Hope

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

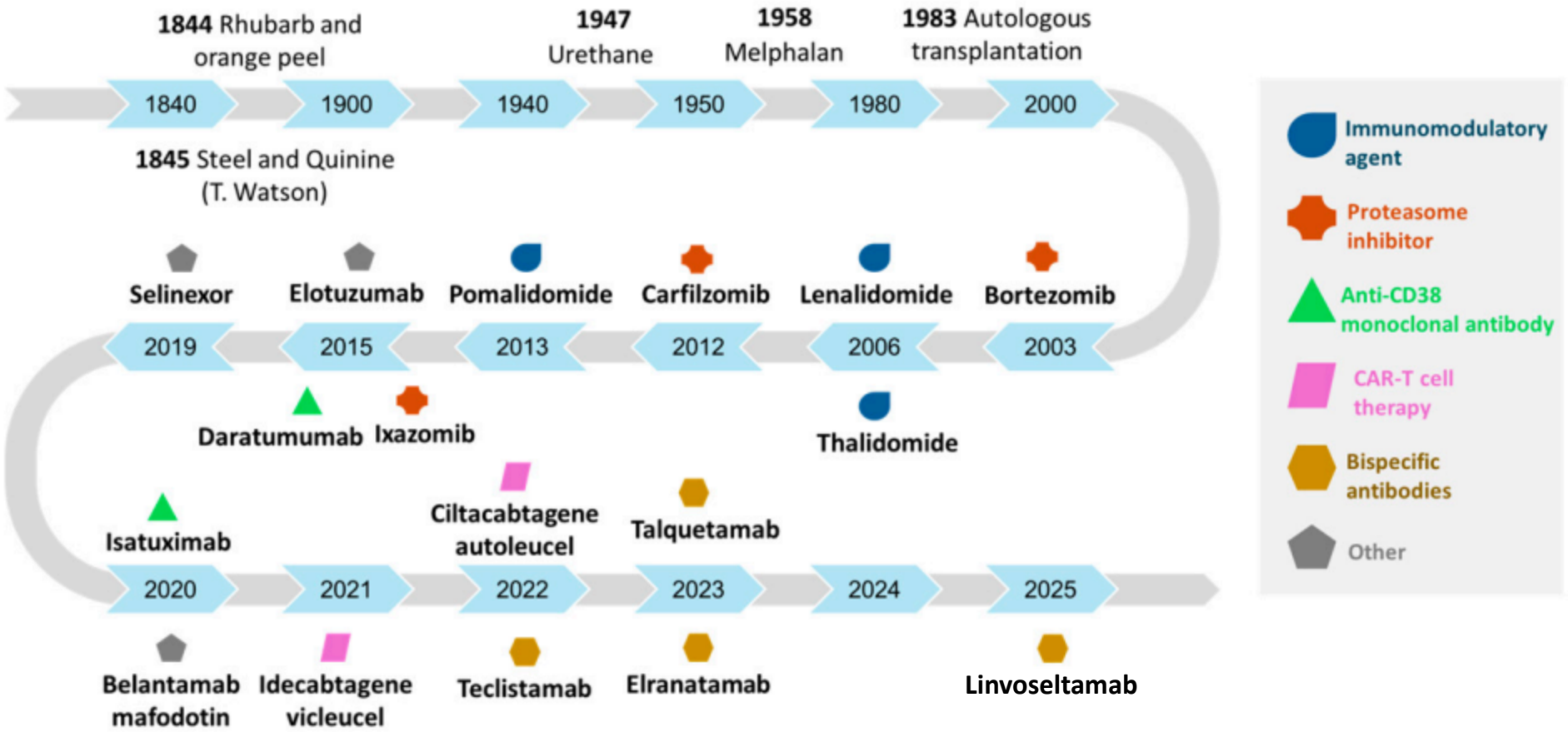
The following CLC & IB components will be addressed in this presentation:

- *Will discuss possible barriers to accessing treatment based on race, ethnicity, socioeconomic status.*
- *Will discuss disparities in care between patient populations*

Objectives

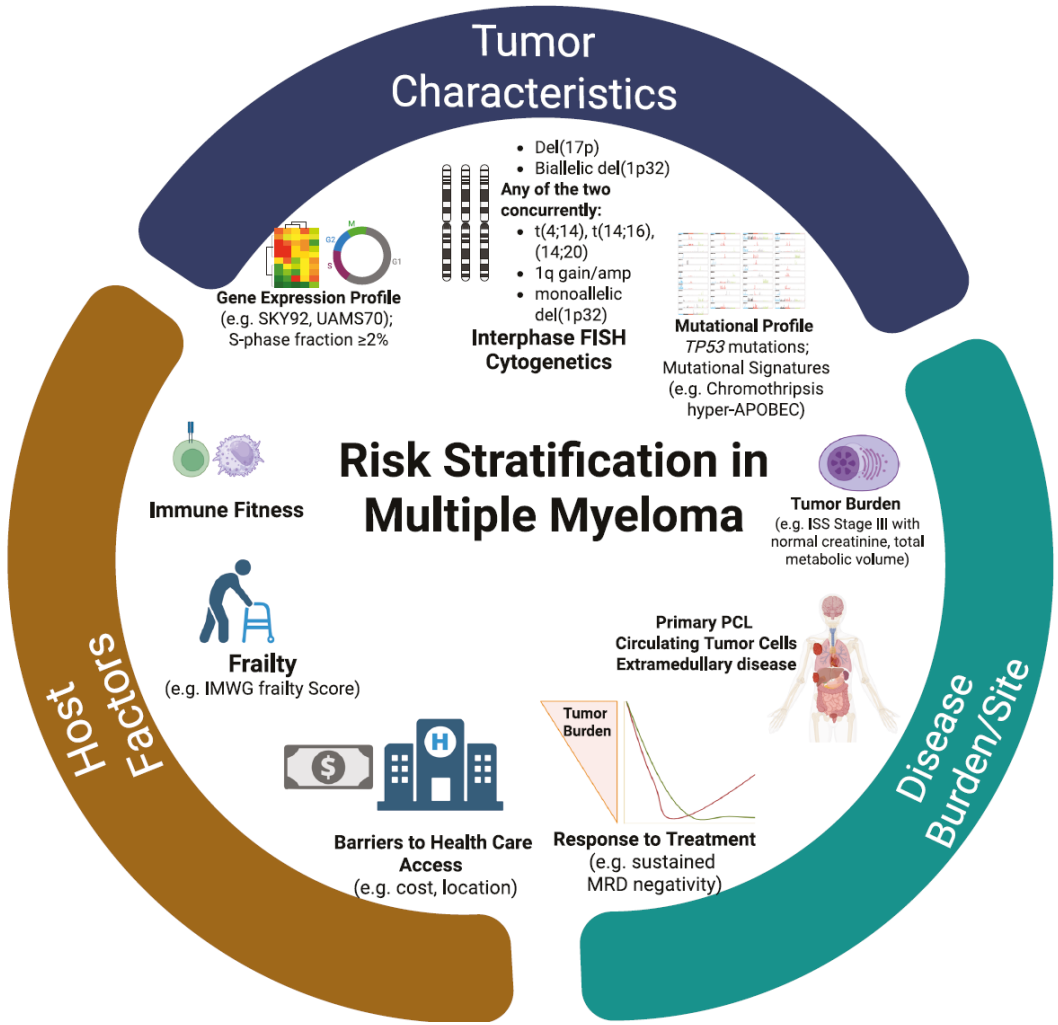
- Review current frontline standards for transplant eligible and ineligible patients
- Discuss tailoring therapy for sub-group populations
- Explore emerging immunotherapy approaches in frontline

Evolution of Frontline Therapy -MM Care Evolution and Drugs by Year of FDA Approval



Slide from Dr. Amrita Krishnan. Adapted from Besliu C, et al. *Cancers*. 2025 (17):535.

Evolution of Frontline Therapy



Zanwar, S., Rajkumar, S.V. *Leukemia* (2025).

IMS/IMWG Definition for High-risk MM

Presence of any one of the following:

- Del(17p)[a] and/or TP 53 mutation[b]
- Biallelic del (1p32)
- t(4;14), t(14;16), or t(14;20) co-occurring with 1q21+[c] or monoallelic del(1p32)
- Monoallelic del)1p32) co-occurring with 1q21+[c]
- Elevated beta-2 macroglobulin (>5.5 mg/dL) with normal renal function (creatinine <1.2 mg/dL)

Mayo Supplemental Criteria for High-risk multiple myeloma

- Primary plasma cell leukemia
- Newly diagnosed myeloma with extramedullary disease
- High plasma cell S-phase fraction (≥ 2%)

Mayo Supplemental Criteria for Double-hit multiple myeloma

- Two or more of the 4 IMS/IMWG high risk qualifying abnormalities listed above with the exception of elevated beta-2 microglobulin

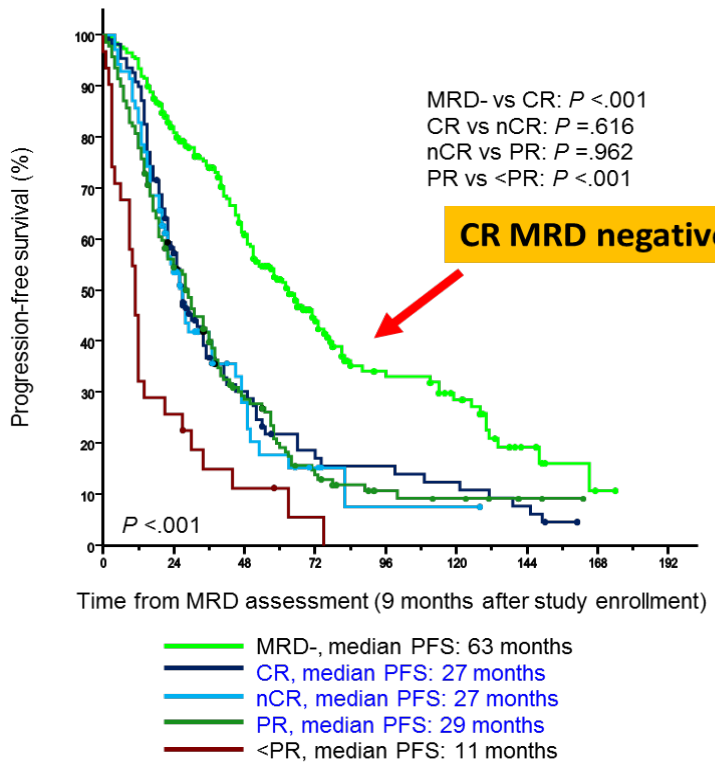
[a]At least a 20% cancer clonal fraction in CD138-sorted plasma cells.
[b]Assessed by a next generation sequencing-based method.
[c]Gain (3 copies) or amplication (4 or more copies) of chromosome 1q.

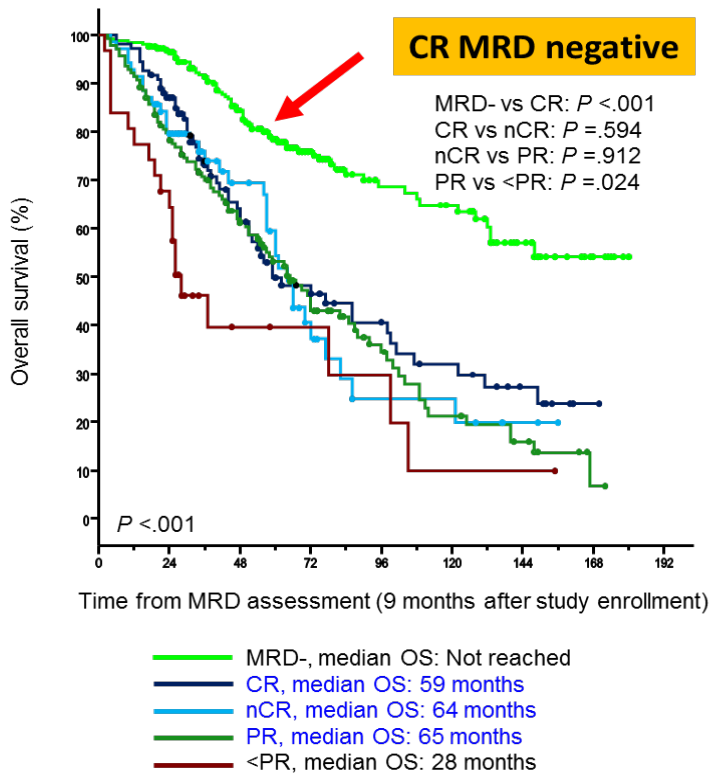
Zanwar, S., Rajkumar, S.V. *Leukemia* (2025).

General Principles for Frontline treatment

1. Combination therapy
   - Doublet → Triplets → QUADRUPLETS
2. Goal is for a deep and durable response
   - No saving the best for last
3. Decide early on whether someone is transplant eligible
   - Risk stratification
   - Age
   - Performance status
   - Comorbidities
   - Organ function

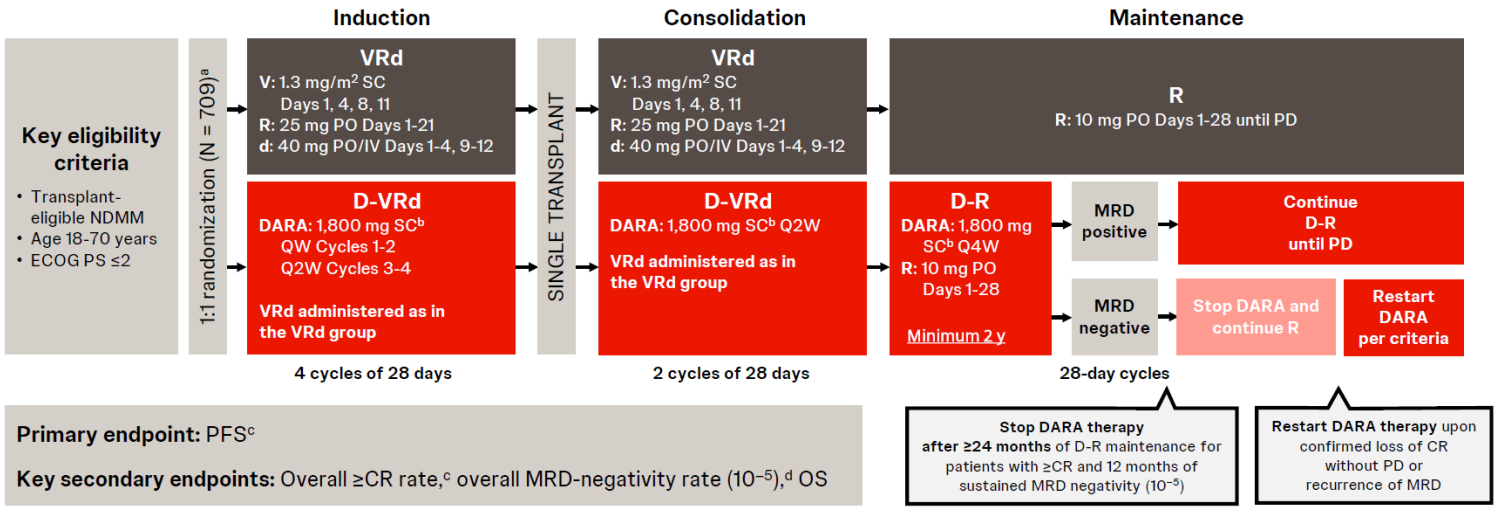
MRD is prognostic for both PFS and OS



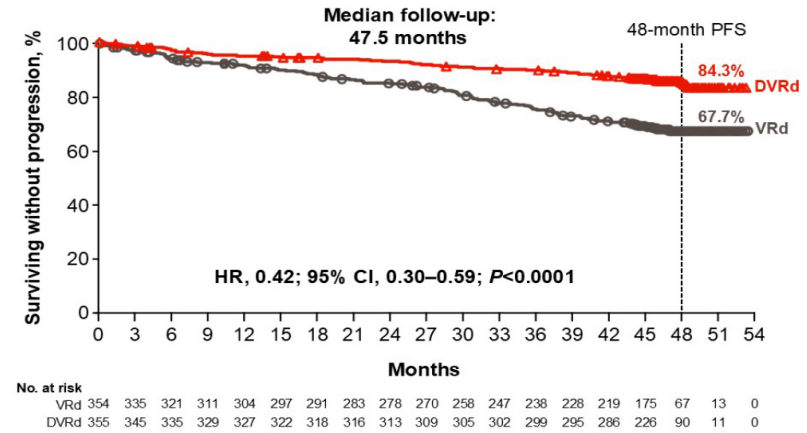


Lahuerta JJ, Paiva B, et al. J Clin Oncol. 2017; 35(25): 2900-2910.

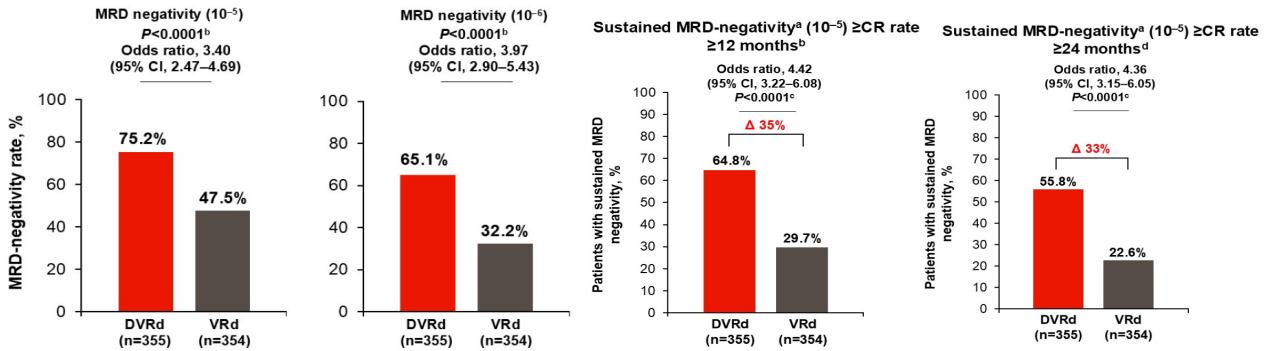
Transplant-Eligible: Quadruplets (PERSEUS)



PFS by Treatment Arm

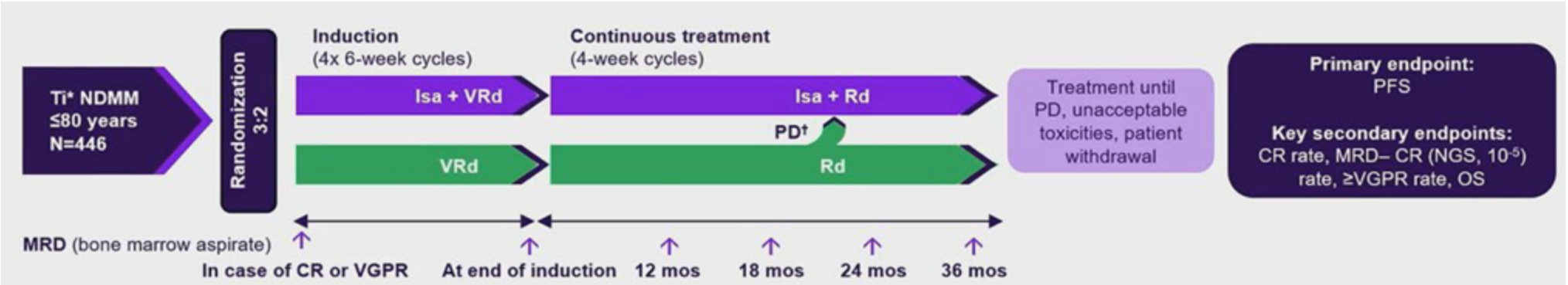


Overall and Sustained MRD Negativity

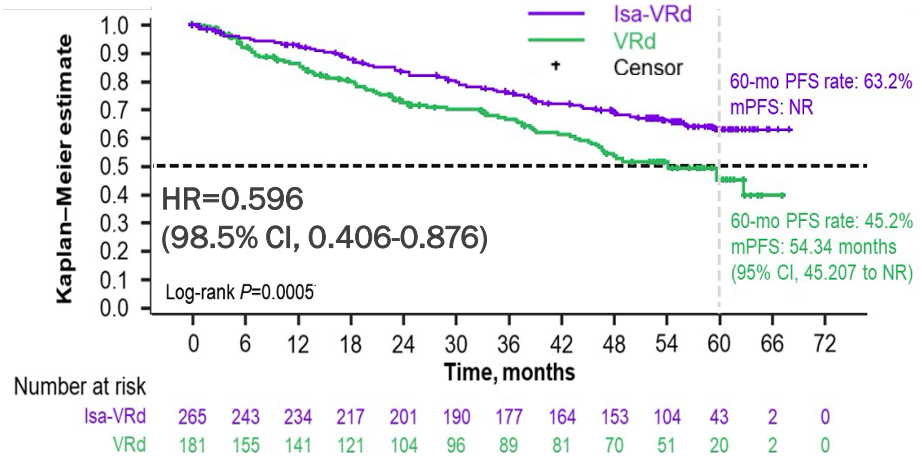


Sonneveld P, et al. EHA 2024. Abstract S201.

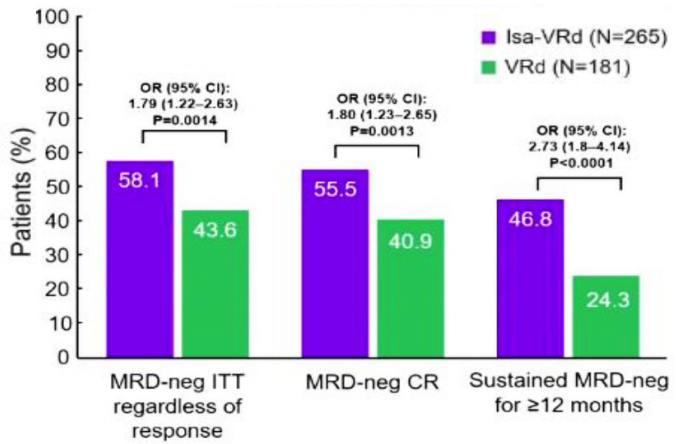
Transplant-Eligible: Quadruplets (IMROZ)



PFS



MRD Negativity (10^{-5})



Facon T, et al. ASCO 2024. Abstract 7500.

Transplant-Eligible: Quadruplets

	PERSEUS	IMROZ
Phase/design	Phase 3, randomized, open-label	
Population	NDMM, transplant-eligible	
Sample size	~700 patients	662 patients
Treatment	Dara-RVD vs RVD	Isa-RVD vs RVD
Primary endpoint	PFS	
Key secondary endpoints	MRD negativity, OS (immature), CR rate	
PFS hazard ratio	HR 0.42 (significant benefit)	HR 0.57 (significant benefit)
MRD negativity	65% vs 30%	56% vs 39%
Depth of response	≥CR rate higher with D-RVD	≥CR rate higher with Isa-RVD
Safety	No new safety signals; cytopenias, infusion reactions	

Matero MV el al. NEJM 2024; 391:1321-34. Moreau P et al. NEJM 2024

Transplant Eligible: Role of Autologous SCT

- Transplant is still a standard of care practice and relevant part of upfront treatment for NDMM
- Short and long-term toxicity should not be overlooked
- Is it mandatory?
  - Individualized, patient centered decision making
  - MIDAS
- Maintenance therapy post-transplant remains an important component in extending PFS benefit

**** Refer patients to a transplant center to determine transplant eligibility**

Summary of Data for Transplant Eligible NDMM

	GRIFFIN[1,2]	PERSEUS[3]	GMMG-HD7[4,5]	MASTER[6]	MIDAS[7,8]	GMMG-CONCEPT[9,10]	IsKia[11,12]
Induction maintenance	**Dara-RVd vs RVd Dara-R vs R**	**Dara-RVd vs RVd Dara-R vs R**	**Isa-RVd vs RVd Isa-R vs R**	**Dara-KRd R/MRD surveillance**	**Isa-KRd R or Isa-Iber**	**Isa-KRd Isa-KR**	**Isa-KRd vs KRd R**
Total N	104 vs 103	355 vs 354	331 vs 329	123	791	219 (TE, high-risk disease)	151 vs 151
Median follow-up	49.6 mo	47.5 mo	48 mo	42.2 mo	NA	43 mo	35 mo
≥VGPR[a] ≥CR[a]	90% vs 73% 52% vs 42%	NA 88% vs 70%	83% vs 69% 44% vs 34%	NA 86%	92% 64% to 66%[b]	91%[d] 73%[d]	94% vs 94%[e] 74% vs 72%[e]
MRD-neg 10^{-5} [a]	50% vs 20%	75% vs 48%	66% vs 48%	81%	63%[c]	73%	77% vs 67%
PFS[a]	4 year: 87% vs 70%	4 year: 84% vs 68%	4-year: 76% vs 69%	3-year: 72%	NA	mPFS: 72.8 mo	1-year: 95% vs 95%[e]
PFS HR (95% CI)	0.45 (0.21-0.95)	0.42 (0.30-0.59)	0.70 (0.52-0.95)	NA	Not reported	NA	Not reported
Grade 5 AEs	0% vs 1%	4% vs 5%	1% vs 2%	2%	<1%	Not reported	Not reported
Serious TEAEs	46% vs 52%	57% vs 49%	35% vs 36%	9%	Not reported	Not reported	Not reported
D/C due to TRAEs	25% vs 51%	9% vs 23%	Not reported	0%	Not reported	2%[d]	Not reported
Infections	93% vs 66%	87% vs 77%	Not reported	45%	46%	61%[d]	36% vs 32%[e]
Peripheral neuropathy	60% vs 73%	54% vs 52%	8% vs 7%	22%	13%	35%[d]	15% vs 17%[e]

No direct comparisons can be made without head-to-head studies. [a] After consolidation in transplant-eligible patients. [b] Near CR to CR. [c] After induction in transplant-eligible patients. [d] Earlier data cutoff with 99 patients. [e] Earlier data cutoff.

Slide courtesy of Dr. Amrita Krishnan

1. Voorhees PM, et al. *Lancet Haematol* 2023;10(10):e825-e837. 2. **Sborov DW, et al. IMS 2022. Abstract OAB-057. 3.** Sonneveld P, et al. ASH 2023. Abstract LBA-1. 4. Goldschmidt H, et al. ASH 2024. Abstract 769. 5. Raab MS, et al. EHA 2024. Abstract S202. 6. Costa LJ, et al. *Lancet Haematol* 2023;10(11):e890-e901. 7. Perrot A, et al. IMS 2024. Poster OA-54. 8. Perrot A, et al. *New Engl J Med*. 2025 Jun 3. Published online ahead of print. 9. Leypoldt LB, et al. ASCO 2025. Abstract 7509. 10. Leypoldt LB, et al. *J Clin Oncol*. 2024;42(1):26-37 11. Gay F, et al. ASCO 2025. Abstract 7502. 12. Gay F, et al. ASH 2023. Abstract 4.

Summary of Data for Transplant Eligible NDMM

	GRIFFIN[1,2]	PERSEUS[3]	GMMG-HD7[4,5]	MASTER[6]	MIDAS[7,8]	GMMG-CONCEPT[9,10]	IsKia[11,12]
Induction maintenance	**Dara-RVd vs RVd Dara-R vs R**	**Dara-RVd vs RVd Dara-R vs R**	**Isa-RVd vs RVd Isa-R vs R**	**Dara-KRd R/MRD surveillance**	**Isa-KRd R or Isa-Iber**	**Isa-KRd Isa-KR**	**Isa-KRd vs KRd R**
Total N	104 vs 103	355 vs 354	331 vs 329	123	791	219 (TE, high-risk disease)	151 vs 151
Median follow-up	49.6 mo	47.5 mo	48 mo	42.2 mo	NA	43 mo	35 mo
≥VGPR[a] ≥CR[a]	90% vs 73% 52% vs 42%	NA 88% vs 70%	83% vs 69% 44% vs 34%	NA 86%	92% 64% to 66%[b]	91%[d] 73%[d]	94% vs 94%[e] 74% vs 72%[e]
MRD-neg 10^{-5} [a]	50% vs 20%	75% vs 48%	66% vs 48%	81%	63%[c]	73%	77% vs 67%
PFS[a]	4 year: 87% vs 70%	4 year: 84% vs 68%	4-year: 76% vs 69%	3-year: 72%	NA	mPFS: 72.8 mo	1-year: 95% vs 95%[e]
PFS HR (95% CI)	0.45 (0.21-0.95)	0.42 (0.30-0.59)	0.70 (0.52-0.95)	NA	Not reported	NA	Not reported
Grade 5 AEs	0% vs 1%	4% vs 5%	1% vs 2%	2%	<1%	Not reported	Not reported
Serious TEAEs	46% vs 52%	57% vs 49%	35% vs 36%	9%	Not reported	Not reported	Not reported
D/C due to TRAEs	25% vs 51%	9% vs 23%	Not reported	0%	Not reported	2%[d]	Not reported
Infections	93% vs 66%	87% vs 77%	Not reported	45%	46%	61%[d]	36% vs 32%[e]
Peripheral neuropathy	60% vs 73%	54% vs 52%	8% vs 7%	22%	13%	35%[d]	15% vs 17%[e]

No direct comparisons can be made without head-to-head studies. [a] After consolidation in transplant-eligible patients. [b] Near CR to CR. [c] After induction in transplant-eligible patients. [d] Earlier data cutoff with 99 patients. [e] Earlier data cutoff.

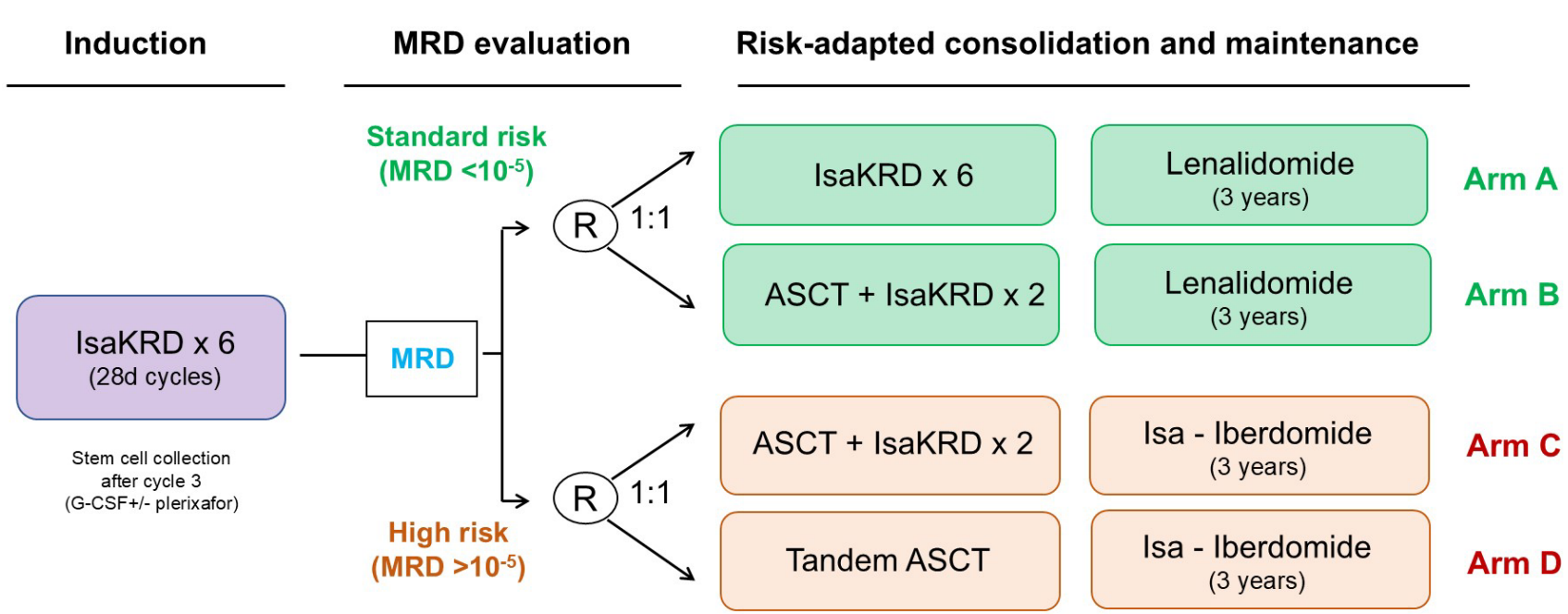
Slide courtesy of Dr. Amrita Krishnan

1. Voorhees PM, et al. *Lancet Haematol* 2023;10(10):e825-e837. 2. **Sborov DW, et al. IMS 2022. Abstract OAB-057. 3.** Sonneveld P, et al. ASH 2023. Abstract LBA-1. 4. Goldschmidt H, et al. ASH 2024. Abstract 769. 5. Raab MS, et al. EHA 2024. Abstract S202. 6. Costa LJ, et al. *Lancet Haematol* 2023;10(11):e890-e901. 7. Perrot A, et al. IMS 2024. Poster OA-54. 8. Perrot A, et al. *New Engl J Med*. 2025 Jun 3. Published online ahead of print. 9. Leypoldt LB, et al. ASCO 2025. Abstract 7509. 10. Leypoldt LB, et al. *J Clin Oncol*. 2024;42(1):26-37 11. Gay F, et al. ASCO 2025. Abstract 7502. 12. Gay F, et al. ASH 2023. Abstract 4.

MIDAS = MInimal residual disease adapted strategy

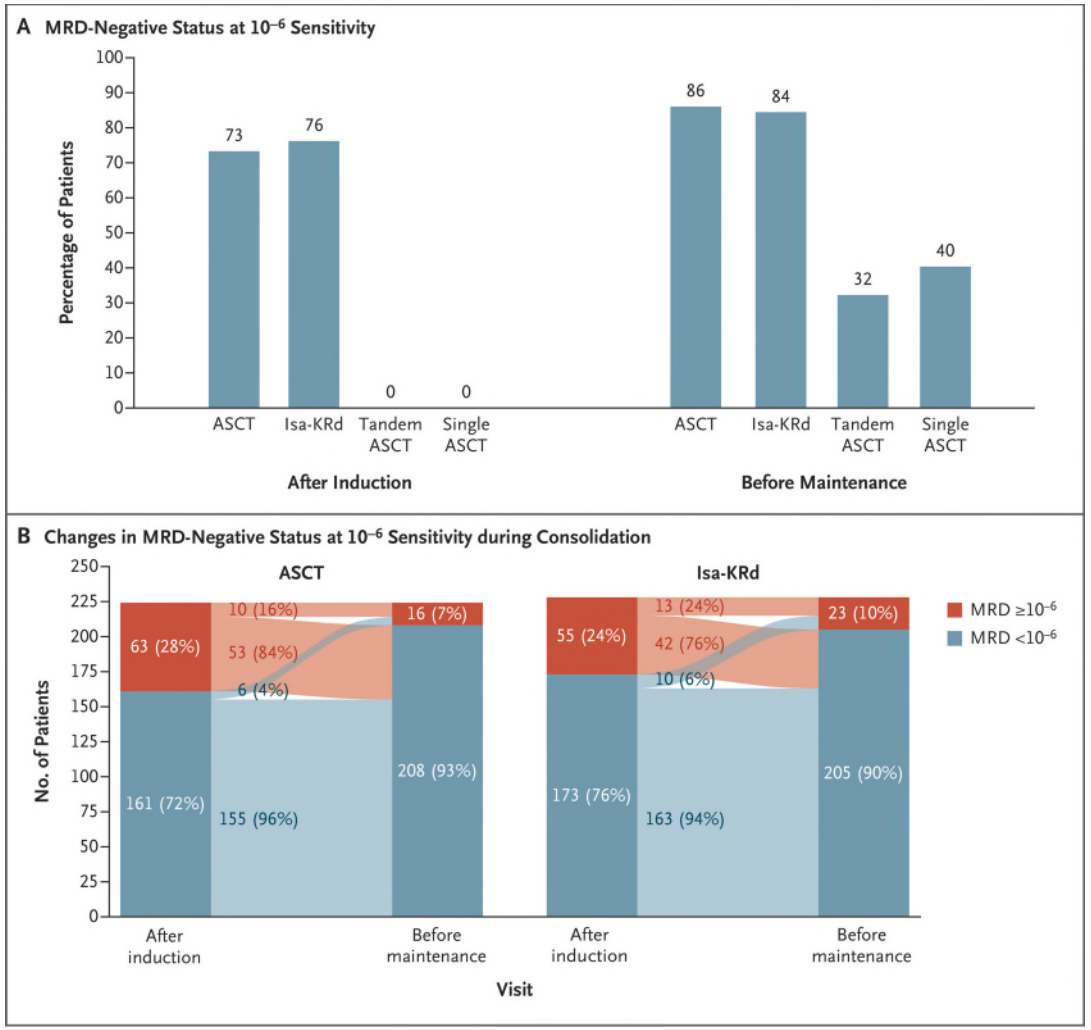
Study design

MIDAS = MInimal residual Disease Adapted Strategy



Perrot A, et al. ASCO 2025. Abstract 7500.

MIDAS = MInimal residual disease adapted strategy



RESULTS

Among MRD-negative patients, the percentage with an MRD-negative status before maintenance therapy was not significantly higher with ASCT plus Isa-KRd than with Isa-KRd alone. Among MRD-positive patients, the percentage with a premaintenance MRD-negative status was not significantly higher with tandem ASCT than with single ASCT plus Isa-KRd. No new safety concerns emerged.

CONCLUSIONS

After induction therapy for newly diagnosed myeloma, ASCT plus Isa-KRd did not significantly outperform Isa-KRd alone as consolidation among those who were MRD-negative, and tandem ASCT was not superior to single ASCT plus Isa-KRd as consolidation among those who were MRD-positive. Further follow-up is needed.

Perrot A, et al. NEJM 2025; 393:425-437

Maintenance in Transplant-Eligible Patients

- Lenalidomide remains standard for maintenance (meta-analyses, OS benefit)
- Is there a role for doublet or triplet maintenance?
  - Risk-adapted/MRD adapted maintenance trials ongoing

McCarthy PL et al. JCO 2017;35:3279–89; Holstein SA et al. JCO 2020;38:3086–94

Maintenance in Transplant-Eligible Patients (AURIGA)

Key eligibility criteria
- 18-79 years of age
- NDMM with ≥4 cycles of induction therapy and underwent ASCT within 12 months of the start of induction
- ≥VGPR at screening[a]
- MRD[b] positive (10^{-5}) post-ASCT
- No prior anti-CD38
- Randomization within 6 months of ASCT date

Stratification factor
- Cytogenetic risk[c] (standard risk/unknown vs high risk)

1:1 RANDOMIZATION (N = 200)

Maintenance: up to 36 cycles[d] (28-day cycles)

D-R

D: 1,800 mg SC[e] QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+
R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

R

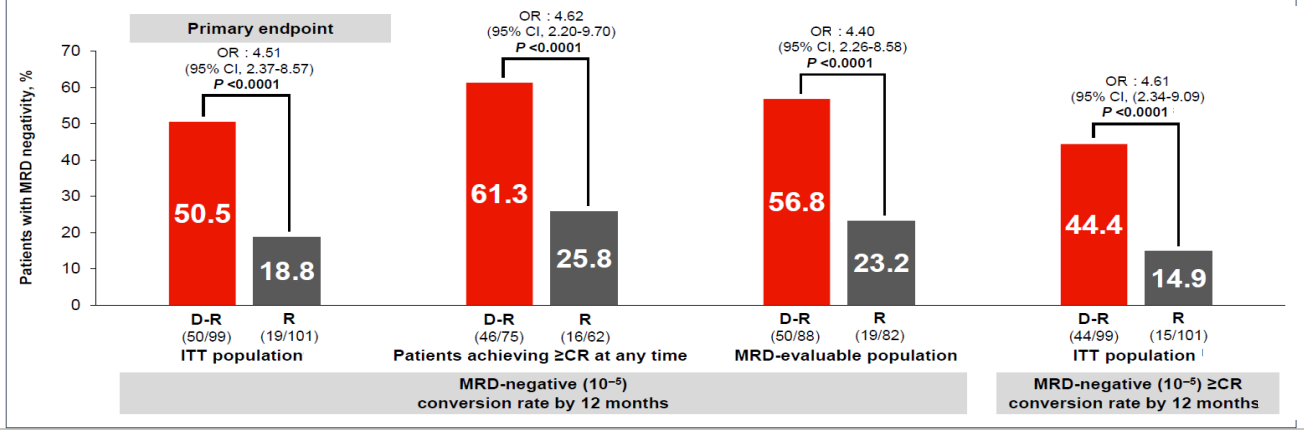
R: 10 mg PO daily Days 1-28 (after Cycle 3, 15 mg PO daily if tolerated)

MRD[b] obtained after 12, 18, 24, and 36 cycles

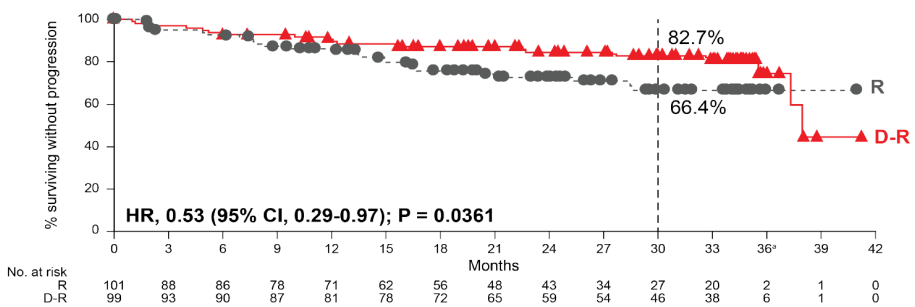
Primary endpoint
- MRD-negative (10^{-5}) conversion rate from baseline to 12 months after maintenance treatment
  - N = 214 planned to achieve ≥85% power to detect 20% improvement

Secondary endpoints
- PFS, overall MRD-negative conversion rate, sustained MRD-negative rate, response rates, duration of ≥CR, OS, safety

MRD Negative (10^{-5}) Conversion From Baseline to 12 Months



PFS



Badros A, et al. IMS 2024. Abstract OA-45.

Transplant-Ineligible

- Not all transplant ineligible patients are created equal
  - Due to age? Frailty score predicts tolerance more than age alone
  - Fit, intermediate-fit, frail?
  - Is performance status compromised by disease characteristics?
- Doublets, triplets, quadruplets, T-cell directed therapies are coming
  - MAIA – D-Rd vs Rd: landmark OS (HR 0.68) and PFS (doubling) benefit. Updated 5 year follow up with median OS ~90 months
  - SWOG S2209 currently enrolling

    Phase III randomized trial for NDMM patients considered frail or in a subset of intermediate fit comparing upfront three-drug induction regimens followed by double or single agent maintenance.

Facon T et al. NEJM 2019;380:2104–15; Mateos MV et al. Lancet Haematol 2024;11:e75–e87 (MAIA update). ***Mateos MV et al. ASH 2024, Abstract 752 (BENEFIT); Usmani SZ et al. ASH 2023, Abstract 751 (CEPHEUS)***

Summary of Data for Transplant Ineligible NDMM

		SWOG S0777[1]		MAIA[2-4]		BENEFIT[5-7]		IMROZ[8,9]		CEPHEUS[10,11]	
		VRd (n=235)	Rd (n=225)	Dara-Rd (n=368)	Rd (n=369)	Isa-VRd (n=135)	Isa-Rd (n=135)	Isa-VRd (n=285)	VRd (n=190)	D-VRd (n=144)	VRd (n=145)
	Population	Patients aged ≥18 y (includes transplant-deferred[a])		Inclusive of frail and older (aged >80 y) patients		Nonfrail patients 65-79 y (excludes frail and aged ≥80 y)		Patients 18-80 y (excludes patients aged >80 y)		Patients ≥18 y (excludes patients aged >80 y)	
	Bortezomib dose	IV biw q21d *6 mos		-		qw *12 mos; q2w *6 mos		biw *6 mos		biw *6 mos	
	Median follow-up	84 mo		89.3 mo		23.5 mo		59.7 mo		58.7 mo	
EFFICACY	**≥CR rate**	24.2%	12.1%	51.1%[b]	30.1%[b]	58%	31%	74.7%	64.1%	81.2%[d]	61.6%[d]
EFFICACY	**≥CR MRD-neg (10^{-5}) rate**	N/A	N/A	32.1%[b]	11.1%[b]	53%	26%	58.1%	43.6%	60.4%	39.3%
EFFICACY	**PFS**	41 mo	29 mo	60-mo: 52.1% Median: 61.9 mo[b]	60-mo: 29.6% Median: 34.4 mo[b]	24-mo: 85.2% Median: NR	24-mo: 80% Median: NR	60-mo: 63.2% Median: NR	60-mo: 45.2% Median: 54.3 mo	54-mo: 69.0%	54-mo: 48.0%
EFFICACY	**HR (95% CI)**	0.74 (0.59-0.93)		0.55 (0.45-0.67)		Not reported		0.60 (0.41-0.88)		0.57 (0.41-0.79)	
EFFICACY	**OS**	NR	69 mo	7-year: ~53.1% Median: 90.3 mo	7-year: ~39.3% Median: 64.1 mo	24-mo: 91.1%	24-mo: 91.5%	60-mo: 72.3%	60-mo: 66.3%	NR	NR
EFFICACY	**HR (95% CI)**	0.71 (0.54-0.93)		0.66 (0.53-0.83)		Not reported		0.78 (0.41-1.48)		0.66 (0.42-1.03)	
SAFETY	**Grade 5 AEs**	<3%	<2%	9.9%	9.3%	Not reported	Not reported	11.0%	5.5%	19 (13.2)[e]	13 (9.2)[e]
SAFETY	**Serious TEAEs**	N/A	N/A	78.8%	71.0%	34%	35%	70.7%	67.4%	72.2%	69.7%
SAFETY	**D/C due to TRAEs**	N/A	N/A	14.6%	23.8%	Not reported	Not reported	22.8%	26.0%	7.6%	19.0%
SAFETY	**Infections**	19% gr 3/4	14% gr 3/4	42.6% gr 3/4	29.6% gr 3/4	35% grade ≥2[c]	40% grade ≥2[c]	44.9% gr ≥3	38.1% gr ≥3	40.1% gr 3/4[e]	31.8% gr 3/4[e]
SAFETY	**Peripheral neuropathy**	Gr ≥3 neurologic AEs: 34.6%	Gr ≥3 neurologic AEs: 11.3%	2.5% gr 3/4	0.5% gr 3/4	27% grade ≥2	10% grade ≥2	7.2% gr ≥3	6.1% gr ≥3	9.7% gr 3/4	8.5% gr 3/4

No direct comparisons can be made without head-to-head studies. [a] Aged ≥65 years served as a proxy for transplant-ineligible status, as SWOG S0777 enrolled a mixed population of patients without intent for immediate transplant. [b] Median follow-up of 64.5 months. [c] Infections of the respiratory system. [d] Includes transplant-ineligible and transplant-deferred patients. [e] Non–COVID-19 grade 5 events.

Slide courtesy of Dr. Amrita Krishnan

1. Durie BGM, et al. *Blood Cancer J.* 2020;10(5):53. 2. Facon T, et al. EHA 2024. Abstract P968. 3. Kumar S, et al. ASH 2022. Poster 4559. 4. Facon T, et al. *Leukemia.* 2025. 5. Leleu X, et al. *Nature Med.* 2024. 6. Leleu XP, et al. ASCO 2024. Abstract 7501. 7. Leleu XP, et al. EHA 2024. Abstract S203. 8. Facon T, et al. ASCO 2024. Abstract 7500. 9. Facon T, et al. EHA 2024. Abstract S100. 10. Facon T, et al. ASCO 2025. Abstract 7516. 11. Facon T, et al. EHA 2025. Abstract PS1730.

Approach to Transplant-Ineligible

1. Determine fitness and risk assessment

    Truly frail – consider doublet or triplet (ex: D-Rd)

    Fit/intermediate fit – consider triplet or quadruplet

* Reassess fitness and frailty every 1-2 cycles and adjust treatment as tolerated

2. Dose modifications

    Dex 20 mg once a week max

    Start lenalidomide 10-15 mg

    Weekly bortezomib

3. Supportive care

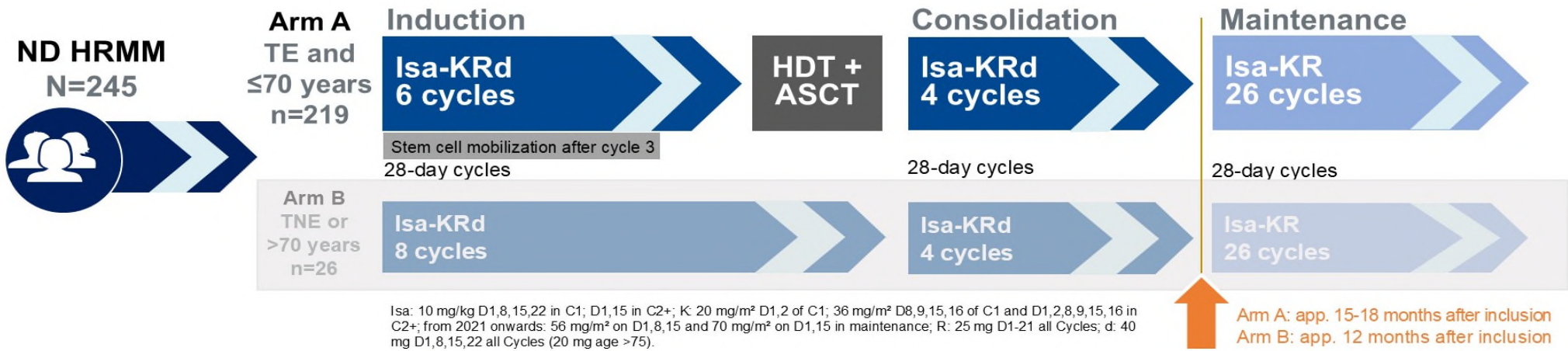
Bisphosphonate	Consider IVIG
VTE ppx	Early supportive care/palliative care
ID ppx	PT/OT

Facon T et al. NEJM 2019;380:2104–15; Mateos MV et al. Lancet Haematol 2024;11:e75–e87 (MAIA update). ***Mateos MV et al. ASH 2024, Abstract 752 (BENEFIT); Usmani SZ et al. ASH 2023, Abstract 751 (CEPHEUS)***

Special Populations

- High-risk cytogenetics (new criteria): Dara-VRd/Isa-VRd improve depth, but unmet need remains

GMMG-Concept: Phase 2 Study of Isa-KRd in High-Risk NDMM

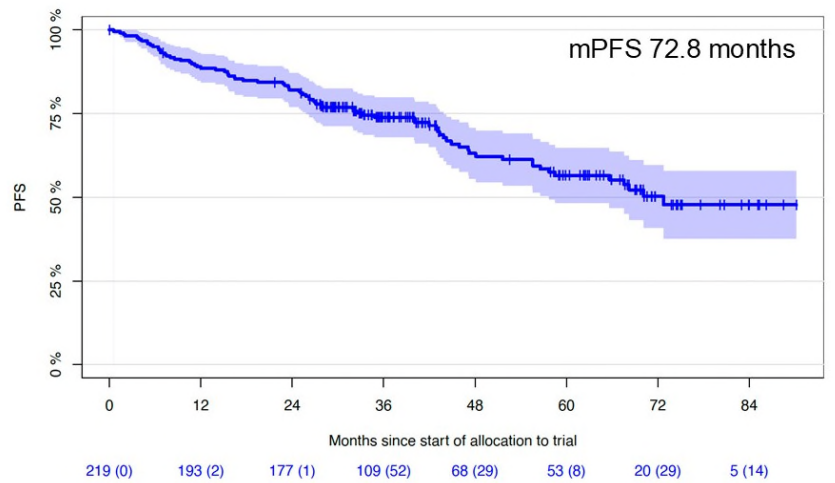


HRMM criteria: ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or ≥3 copies 1q21 (amp1q21)
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Selected tertiary objectives: ORR, OS

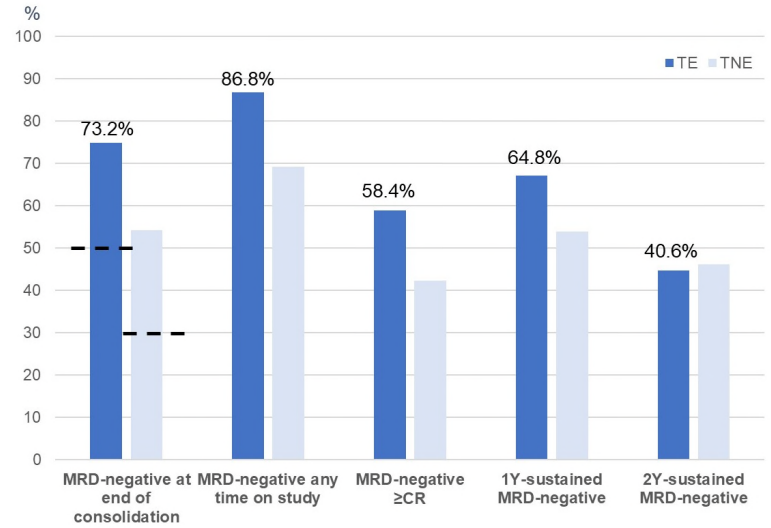
Leypoldt L, et al. ASCO 2025. Abstract 7509.

Special Populations – GMMG Concept

PFS: TE NDMM



MRD Negativity (10^{-5})



- Median follow-up: 43 months
- Safety:
  - Grade ≥3 infection: 28%
  - Grade ≥3 cardiac AEs: 2% (TE arm); 20% (TI arm)
- Carfilzomib dosing: once weekly (56 mg/m^2) vs twice weekly (36 mg/m^2) had more dose reductions but less carfilzomib discontinuations

Leypoldt L, et al. ASCO 2025. Abstract 7509.

Investigational & Future Approaches

MOA	Study	Phase	Setting	Arms
BsAb	MajesTEC-5	2	Induction in TE NDMM	Tec + Dara-VRd, Tec + Dara-Rd
	MajesTEC-7	3	Therapy of TI NDMM	Tec + Dara-R vs Dara-Rd
	MonumenTAL-2	1b	Therapy of TI NDMM	Tal + Dara-R
	MagnetisMM-6	3	Therapy of TI NDMM	Elra + Dara-R vs Dara-Rd
	MajesTEC-4	3	Maintenance post-ASCT	Tec + Len vs Len
	MagnetisMM-7	2	Maintenance post-ASCT	Elra vs Len
CAR T	CARTITUDE-6	3	Consolidation in TE NDMM	Dara-VRd then Cilta-cel vs Dara-VRd then ASCT
	CARTITUDE-5	3	Consolidation in TI NDMM	RVd followed by Cilta-cel vs RVd then Rd
	KarMMa-4	1	High-risk TE NDMM	Ide-cel
	KarMMa-2	2	Consolidation in TE NDMM	Ide-cel
ADC	DREAMM-9	3	Therapy of TI NDMM	Belamaf + VRd vs VRd
	DREAMM-10	3	Therapy of TI NDMM	Belamaf + Rd vs Dara-Rd

Slide courtesy of Dr. Amrita Krishnan

Key Takeaways

- Quadruplets = new standard for transplant eligible patients
    - Deep remissions and survival benefit
- Dara-Rd remains backbone for transplant ineligible patients, but quads may become new standard, in certain populations
- Personalization is essential: frailty, risk, MRD status
- High-risk disease may need more intense and continuous therapy
- Future directions:
    - Immunotherapies (CART and bispecifics) moving to upfront setting
    - Adaptive (MRD guided) strategies moving frontline – guide transplant and maintenance

Thank you