POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Mieloma Multiplo: **Terapia alla diagnosi**

SISTEMA SANITARIO REGIONALE
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Disclosures of Maria Teresa Petrucci

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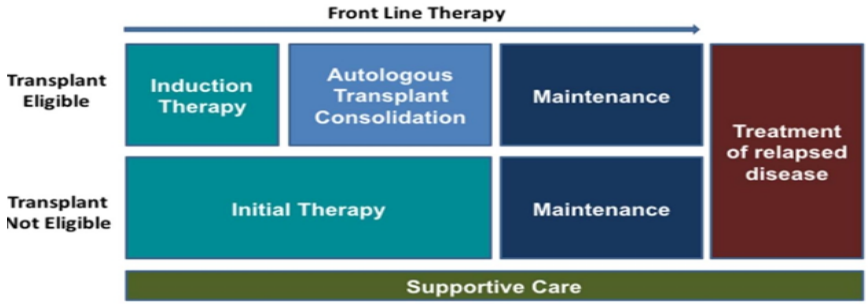
Janssen-Cilag	X	X	X
Takeda	X	X	X
AbbVie	X		
Amgen	X	X	X
GSK	X	X	
Menarini		X	
Sanofi	X	X	X
Oncopeptides		X	
Pfizer	X	X	

Punti chiave da discutere

- ✓ Il trapianto è ancora necessario?
  - ➢ Dobbiamo ancora distinguere i pazienti eleggibili dai non eleggibili?
- ✓ Quadrupletta per tutti?
  - ➢ Quale paziente, quale anti–CD38 e quale PI?
- ✓ Quale è la migliore terapia di mantenimento?
  - ➢ Chi beneficia dagli anti–CD38?
  - ➢ Per quanto tempo il mantenimento?
- ✓ Dove stiamo andando?
  - ➢ Quale è il ruolo della immunoterapia e dei nuovi agenti?

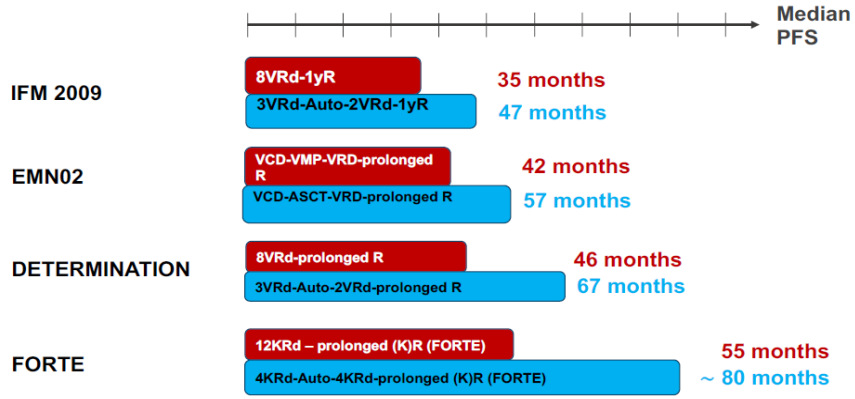
Conventional Treatment Paradigm for NDMM



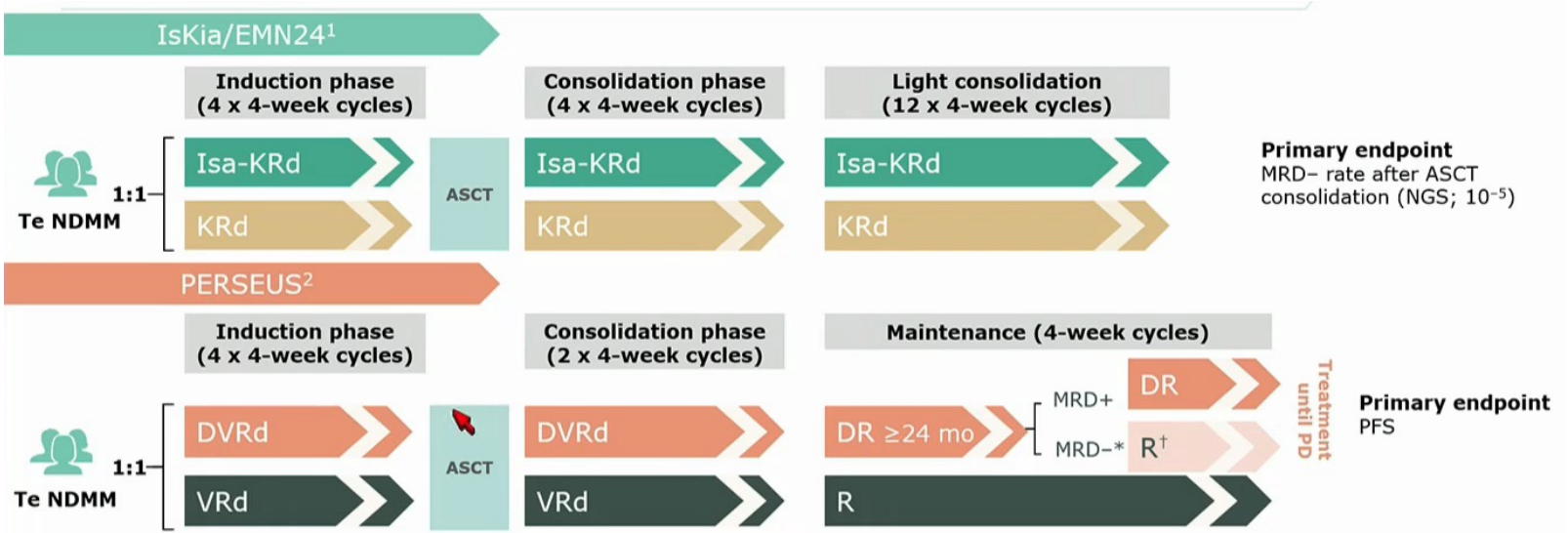
mOS in NDMM

Rischio Standard: ~ 13 anni
Alto Rischio : ~ 7 anni

Triplette senza/con ASCT



Phase III trials will provide further insights on the role of quadruplets with both V- and K- based bacbones inTE NDMM

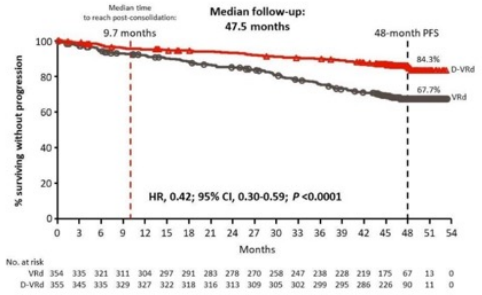


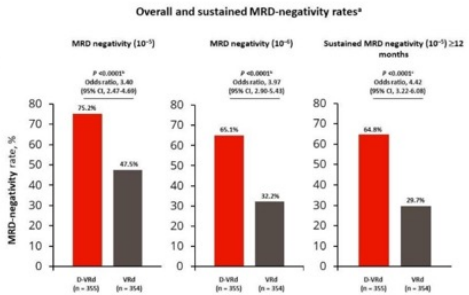
Evaluation of quadruplets with different PI backbones may offer physicians greater choice in tailoring treatment to patients

*≥12 month sustained; at 10^{-5} by NGS
†Opportunity to restart D upon loss of CR or MRD–
ASCT, autologous stem cell transplant; D, daratumumab, d, dexamethasone; K, carfilzomib; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; R, lenalidomide; Te, transplant eligible; V, bortezomib

1. Clinicaltrials.gov NCT04483739;
2. Clinicaltrials.gov NCT03710603

PERSEUS: PFS and MRD negativity



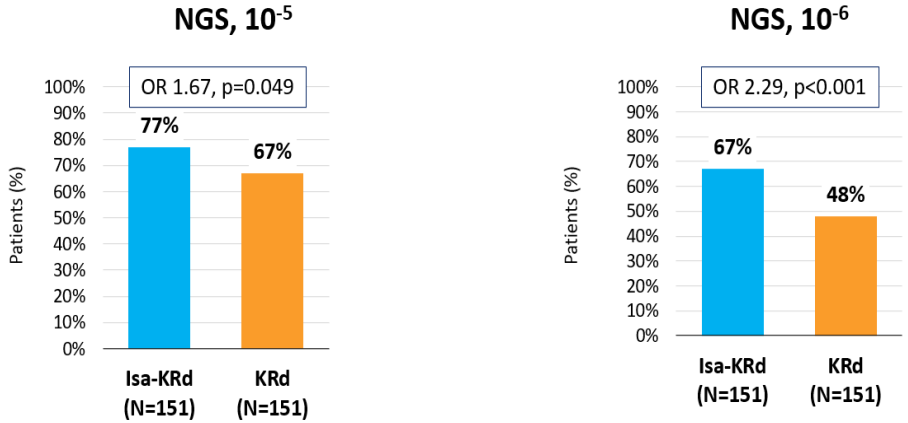


58% reduction in the risk of progression or death in patients receiving D-VRd

Deep and durable MRD negativity achieved with D-VRd

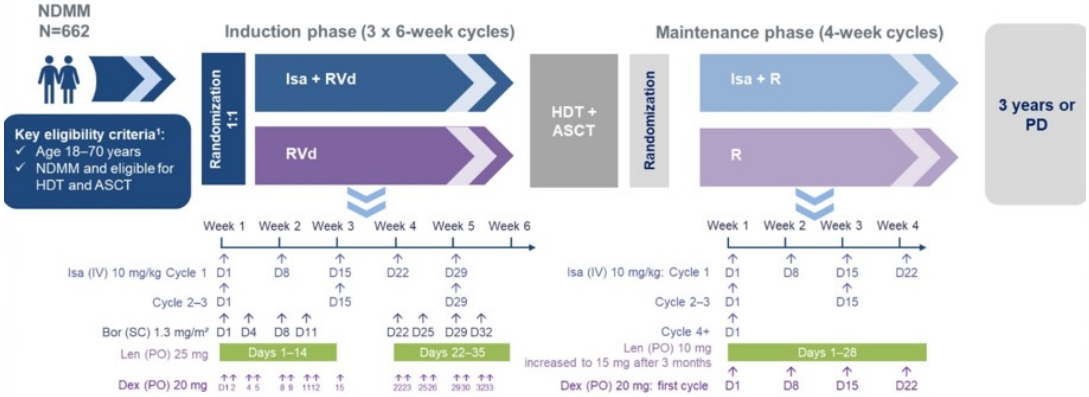
Sonneveld P et al. ASH 2023. Abstract LBA1.
Sonneveld P et al. *N Engl J Med*. 2024;390(4):301-313.

IsKIA/EMN24: Post consolidation MRD negativity



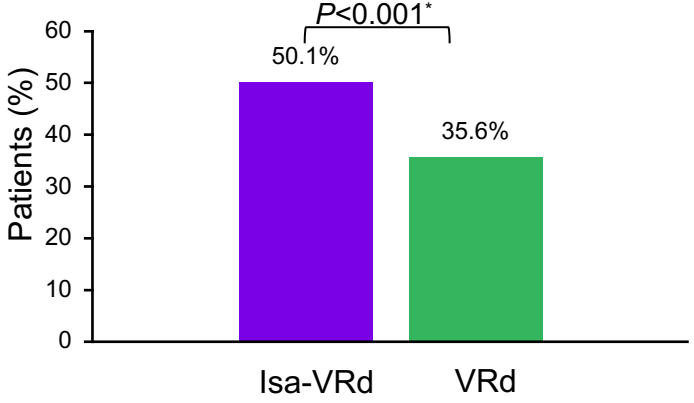
≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.
Consistent MRD results were detected by next-generation flow
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

GMMG-HD7: The First Phase 3 Study Evaluating Isa + RVd for Induction and Maintenance in TE NDMM Patients

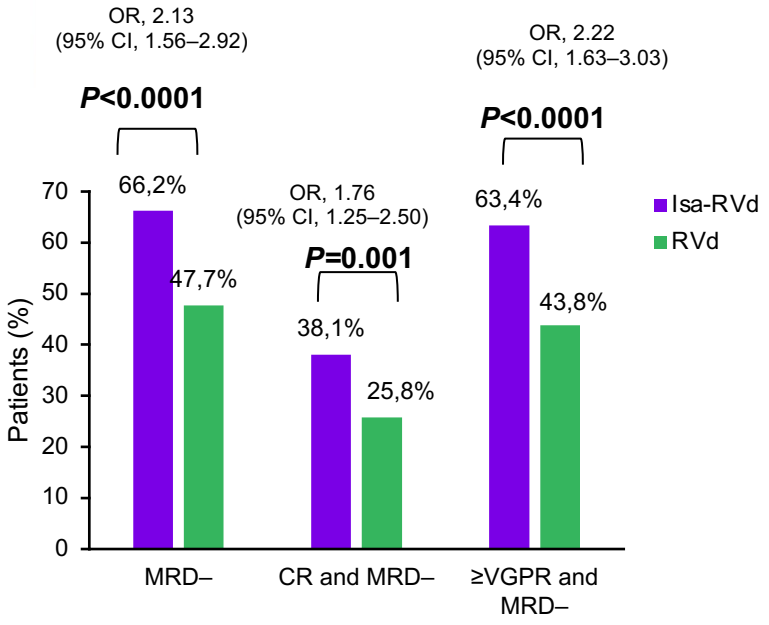


Patients with MRD– at the end of induction therapy

OR, 1.83 (95% CI, 1.34–2.51)

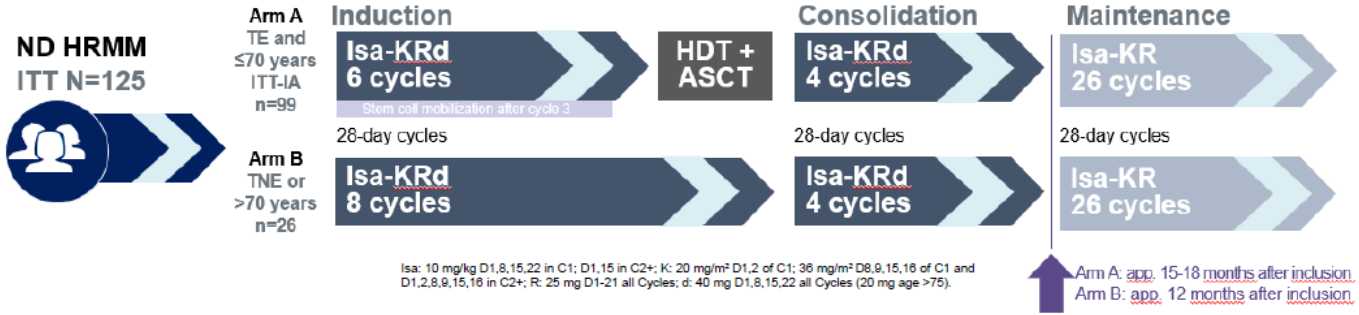


MRD– rates post transplant in the ITT population



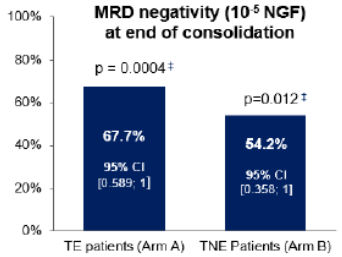
Goldschmidt H et al ASH 2024

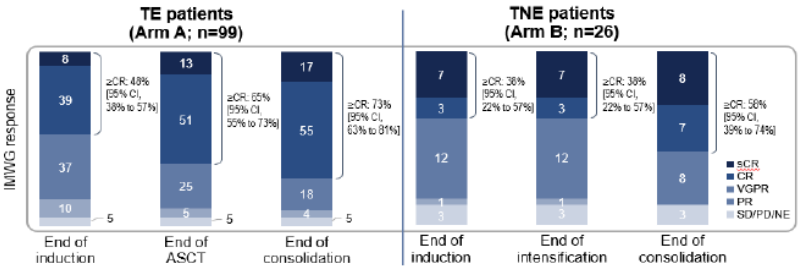
GMMG-CONCEPT: Isa-KRD in Two Cohorts of patients with High-Risk NDMM



- **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; Key tertiary objectives: ORR, OS, safety

MRD negativity and IMWG response



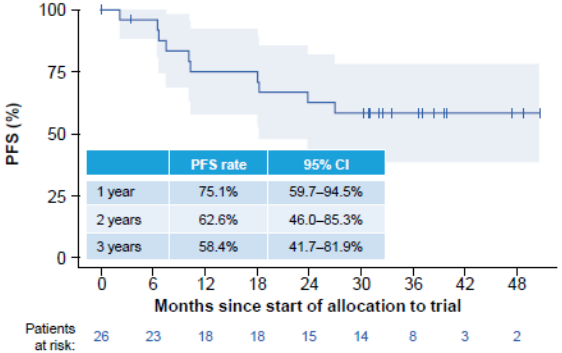


MRD status, n (%)	TE patients (Arm A) (n=93*)	TNE patients (Arm B) (n=24†)
Negative	63 (67.7)	13 (54.2)
Positive	3 (3.2)	0 (0)
Not done/missing	2 (2.2)	0 (0)
Time point not reached	25 (27.0)	11 (45.8)

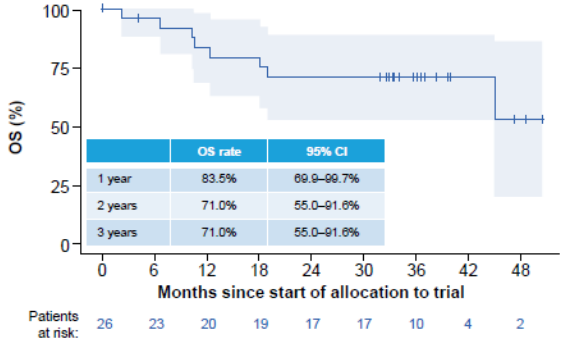
6 TE and 2 TNE patients were not assessable

- The trial met its primary endpoint with MRD negativity rates of 67.7% (TE) and 54.2% (TNE) at the end of consolidation
- Responses deepened over time with ≥CR-rates of 72.7% (TE) and 57.7% (TNE) as best response

GMMG-CONCEPT: PFS and OS



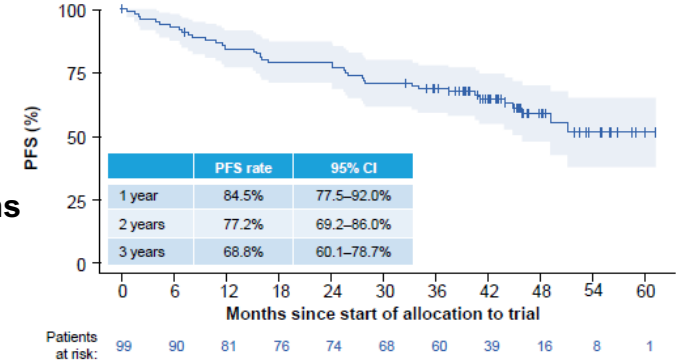
	PFS rate	95% CI
1 year	75.1%	59.7–94.5%
2 years	62.6%	46.0–85.3%
3 years	58.4%	41.7–81.9%



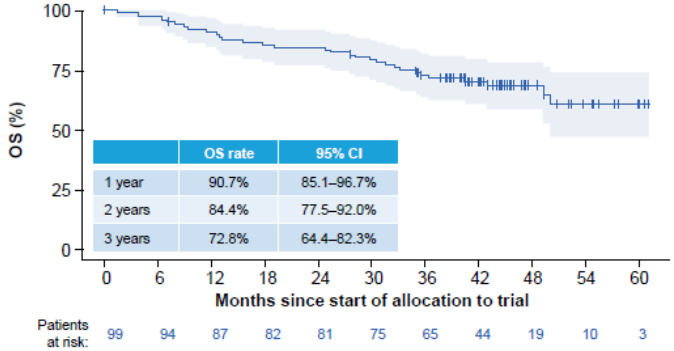
	OS rate	95% CI
1 year	83.5%	69.9–99.7%
2 years	71.0%	55.0–91.6%
3 years	71.0%	55.0–91.6%

TNE NR follow up 35 months

TE NR follow up 44 months



	PFS rate	95% CI
1 year	84.5%	77.5–92.0%
2 years	77.2%	69.2–86.0%
3 years	68.8%	60.1–78.7%



	OS rate	95% CI
1 year	90.7%	85.1–96.7%
2 years	84.4%	77.5–92.0%
3 years	72.8%	64.4–82.3%

Dara-KRd for High-Risk DMM: Phase 2 IMF 2018-04 Study

2018-04 study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p Del, t(14;16)
- ECOG 0-2

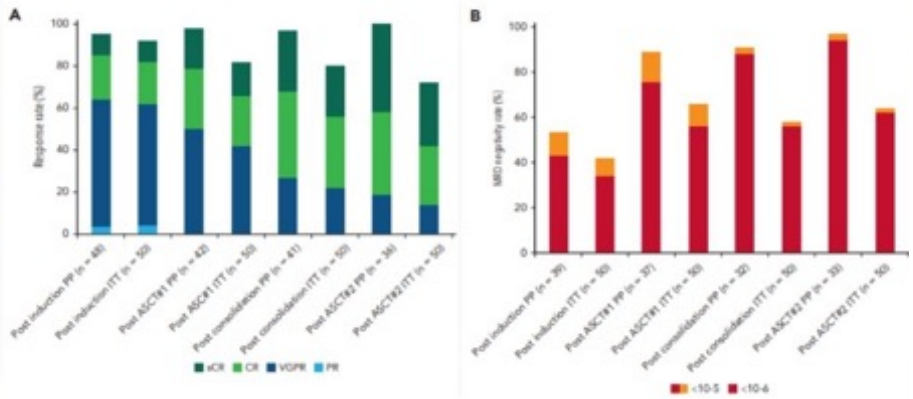
Objectives:

- **Primary Objective :** Feasability (primary endpoint : >70% patients completed 2nd transplant)
- **Secondary Objectives:** Safety, ORR, PFS, OS, stem-cell

Induction Dara-KRd x 6 → **Stem cell collection** → **ASCT#1** → **Consolidation** Dara KRd x 4 → **ASCT#2** → **Maintenance** Dara Len 2 years

Induction			Consolidation		Maintenance
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 and 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex : 20 mg** D1-2, 8-9, 15-16, 22-23 **28-day cycle**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara : 16 mg/kg IV** D1 D15 **K : 56 mg/m2 IV** D1, 8, 15 **Len : 15 mg** D1-21 **Dex : 40 mg** D1, 8, 15, 22 **28-day cycle**	**Mel 200**	**Dara : 16 mg/kg IV** every 8 weeks **Len : 10 mg** 21/28

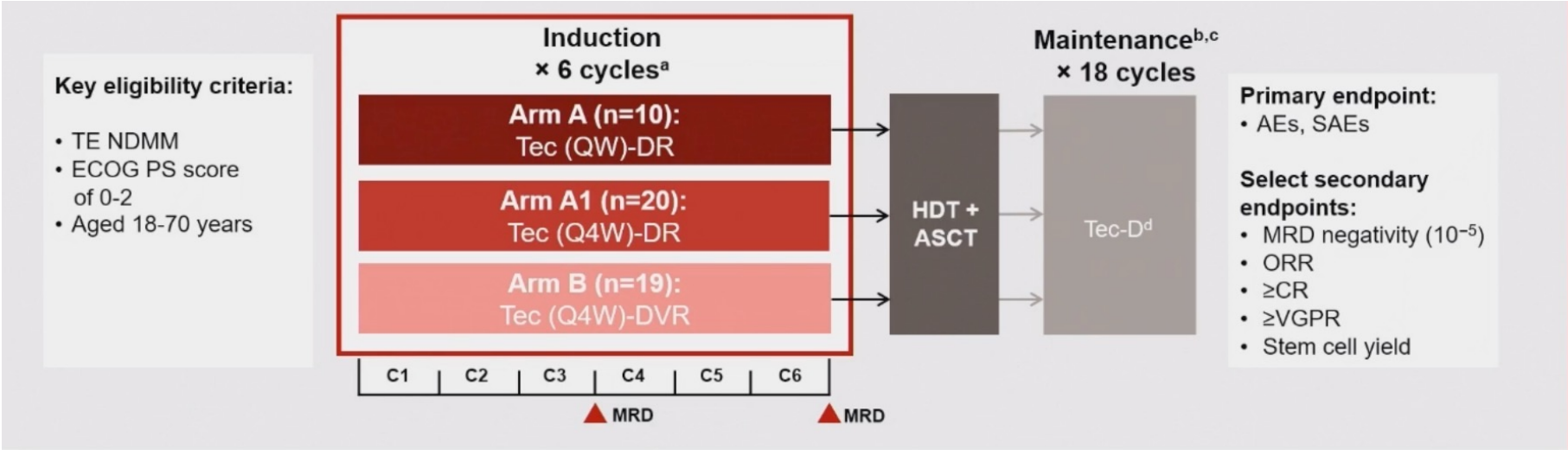
Dara-KRd induction : Response rates and MRD



- 36 of 50 patients (72%) of patients completed 2nd transplant
- ORR = 100% (81% CR) in patients who completed 2nd transplant
- Premaintenance MRD– rate (10^{-6}) = 94%
- 30-month PFS = 80%; OS = 91%

Touzeau C. et al Blood 2024

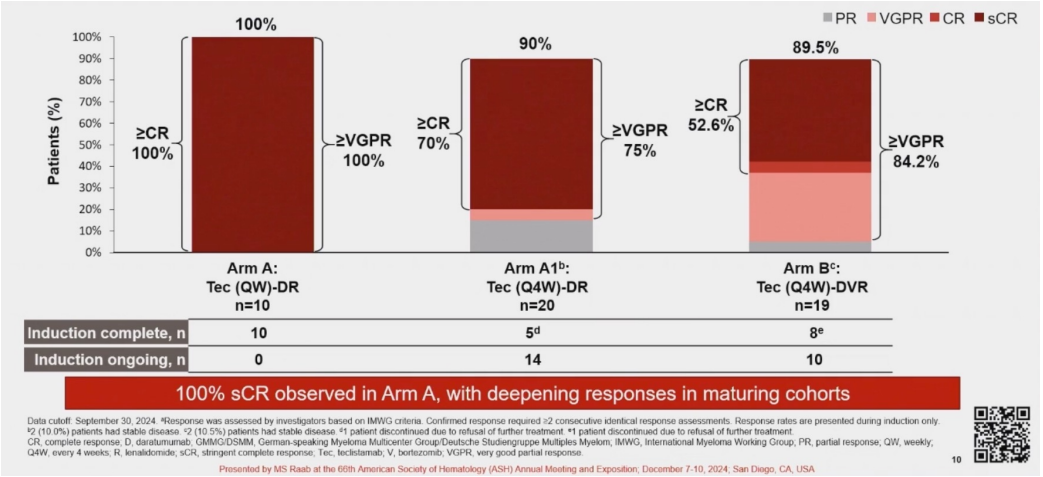
GMMG-HD 10/DSMM-XX/MajesTEC-5:Study Design



- Per protocol, MRD assessments by NGF were planned following completion of C3 and C6 in all patients
- Additional cohorts evaluating Tal and Tec/Tal combinations are also being investigated as part of this study

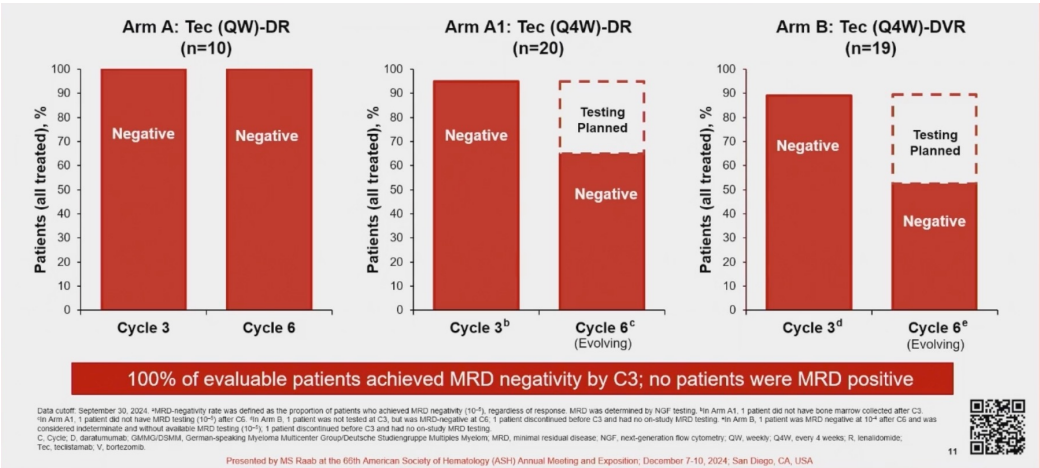
[a]Each cycle is 28 days. Dexamethasone was also administered in C1 and C2. Stem cell collection was planned after 3 cycles of induction. [b]Following maintenance therapy, patients could receive additional SoC maintenance treatment per institutional standard and local investigator decision. [c]Maintenance treatment can be discontinued when 12 months of sustained MRD negativity (10^{-5}) have been observed, beginning in induction. [d]Planned maintenance treatment in Arm A was Tec-DR. A protocol amendment permitted patients initially assigned to Tec-DR maintenance to receive Tec-D maintenance per investigator's choice (patients who started Tec-DR may have discontinued Len to receive Tec-D per investigator's choice).
AE, adverse event; ASCT, autologous stem cell transplant; C, Cycle; CR, complete response; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; HDT, high-dose therapy; Len, lenalidomide; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next-generation flow cytometry; ORR, overall response rate; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; SAE, serious adverse event; SoC, standard-of-care; Tal, talquetamab; TE, transplant-eligible; Tec, teclistamab; V, bortezomib; VGPR, very good partial response.

Presented by MS Raab at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA



Response Rate

MRD Negativity (10^{-5})



INFECTIONS

TEAE, n (%)[a]	Arm A: Tec (QW)-DR (n=10)		Arm A1: Tec (Q4W)-DR (n=20)		Arm B: Tec (Q4W)-DVR (n=19)		Total (N=49)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Any infection	10 (100)	4 (40)	18 (90)	9 (45)	11 (57.9)	4 (21.1)	39 (79.6)	17 (34.7)
Infections[b]								
URTI	6 (60)	0	8 (40)	1 (5)	6 (31.6)	0	20 (40.8)	1 (2)
COVID-19	2 (20)	0	4 (20)	1 (5)	3 (15.8)	3 (15.8)	9 (18.4)	4 (8.2)
Nasopharyngitis	3 (30)	0	2 (10)	0	2 (10.5)	0	7 (14.3)	0
Bronchitis	2 (20)	0	0	0	0	0	2 (4.1)	0
Infection (NOS)	0	0	1 (5)	1 (5)	2 (10.5)	1 (5.3)	3 (6.1)	2 (4.1)
Pneumonia	1 (10)	1 (10)	1 (5)	0	2 (10.5)	2 (10.5)	4 (8.2)	3 (6.1)

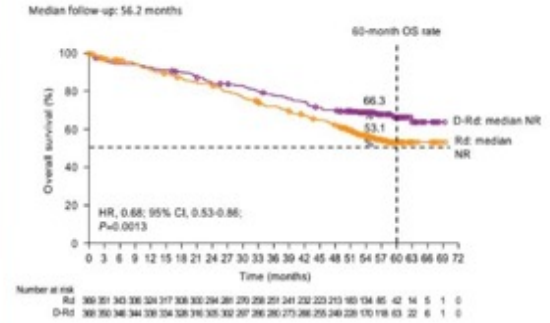
- 17 (34.7%) patients had grade 3/4 infections
  - URTI and COVID-19 were the most common all grade
  - No discontinuations due to infection
  - No grade 5 infections
- Hypogammaglobulinemia[c] was reported in 45 (91.8%) patients
  - 44 (89.8%) received ≥1 dose of IVIg[d]
- Infection prophylaxis, including Ig replacement, was strongly recommended[e]

Data cutoff: September 30, 2024. [a]AEs are graded according to the NCI-CTCAE Version 5.0. [b]Infections reported in >10% of patients in any arm. [c]Includes patients with ≥1 TEAE of hypogammaglobulinemia or post-baseline IgG value <400 mg/dL. [d]Includes patients who started IVIg prior to Tec. [e]Prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes zoster reactivation was also recommended, as well as routine antibiotic prophylaxis.
D, daratumumab; GMMG/DSMM, German-speaking Myeloma Multicenter Group/Deutsche Studiengruppe Multiples Myelom; Ig, immunoglobulin; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NOS, not otherwise specified; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; TEAE, treatment-emergent adverse event; Tec, teclistamab; URTI, upper respiratory tract infection; V, bortezomib.

Presented by MS Raab at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA, USA

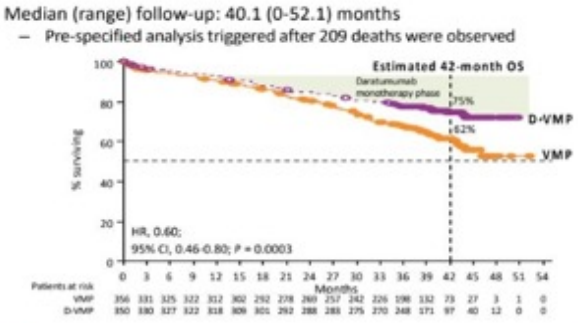
Treatment Landscape for Transplant-Ineligible NDMM

MAIA trial[1]



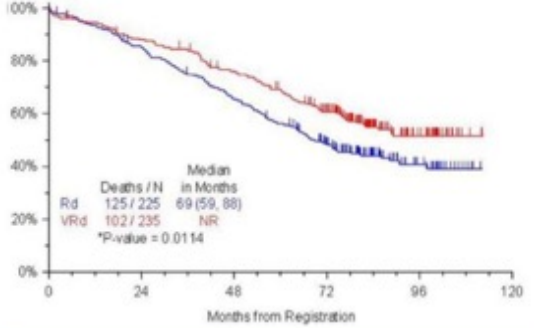
32% reduction in risk of death in patients receiving D-Rd vs Rd

ALCYONE trial[2]



40% reduction in risk of death in patients receiving D-VMP vs VMP

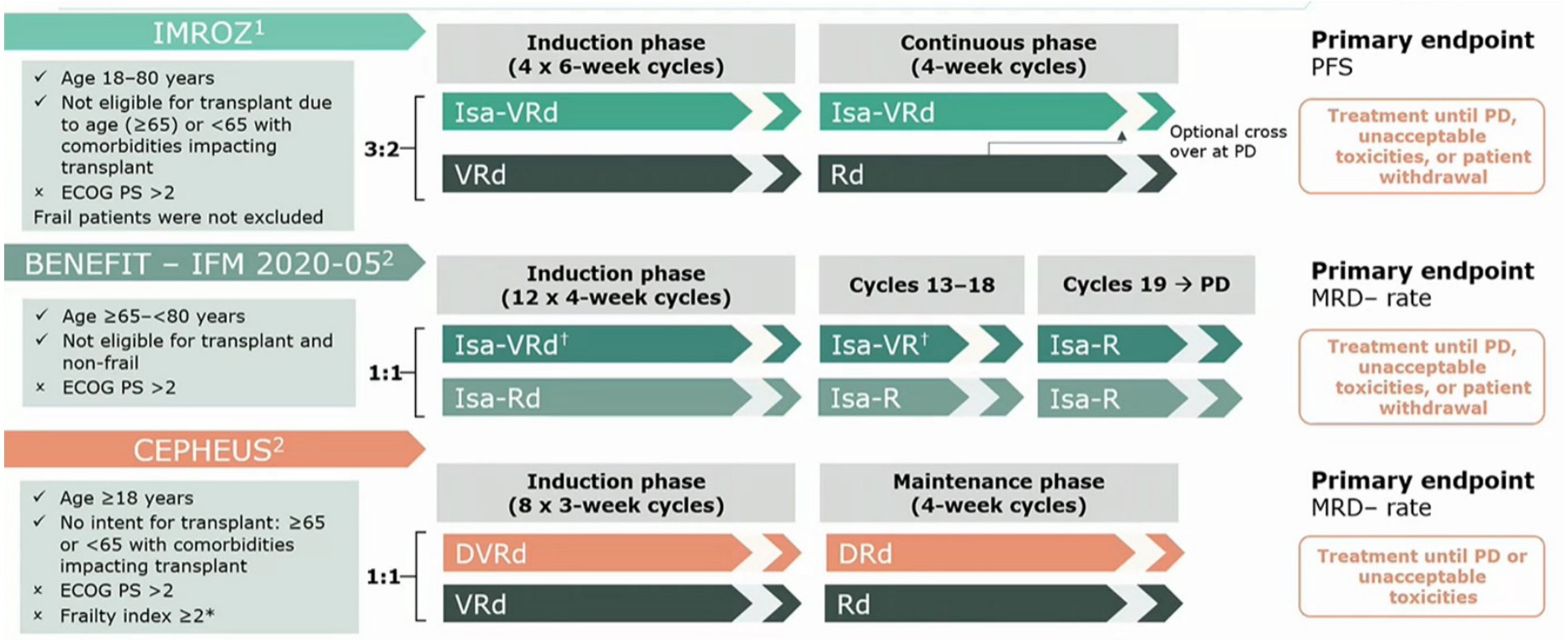
SWOG S0777 trial[3]



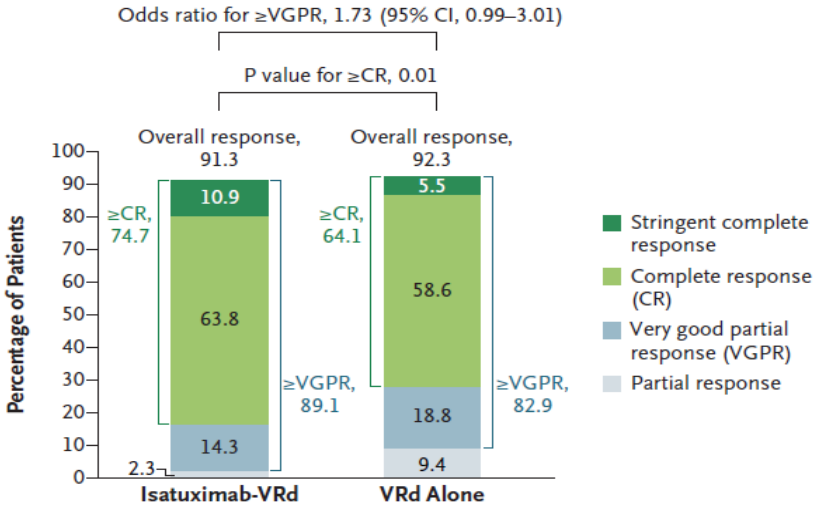
31% reduction in risk of death in patients receiving VRd vs Rd

1. Facon T et al. *Lancet Oncol.* 2021;22(11):1582-96; 2. Mateos MV et al. *Lancet.* 2020;395(10218):132-41; 3. Durie BGM et al. *Blood Cancer J.* 2020;10(5):53.

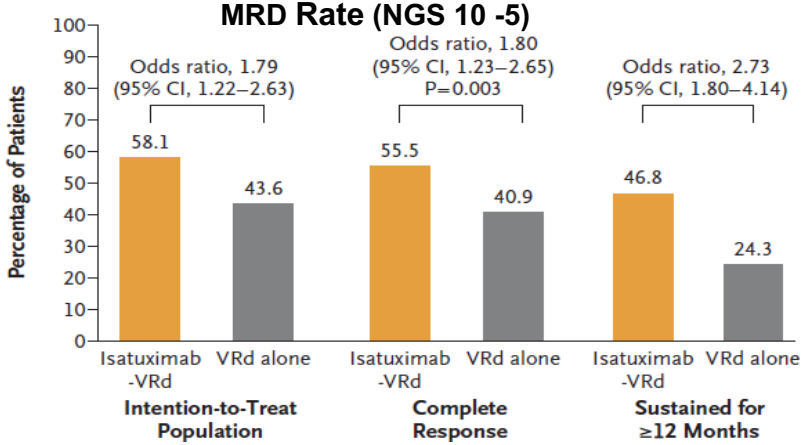
Studies in **TI NDMM** will help elucidate the patient populations that can benefit from quadruplets over triplets



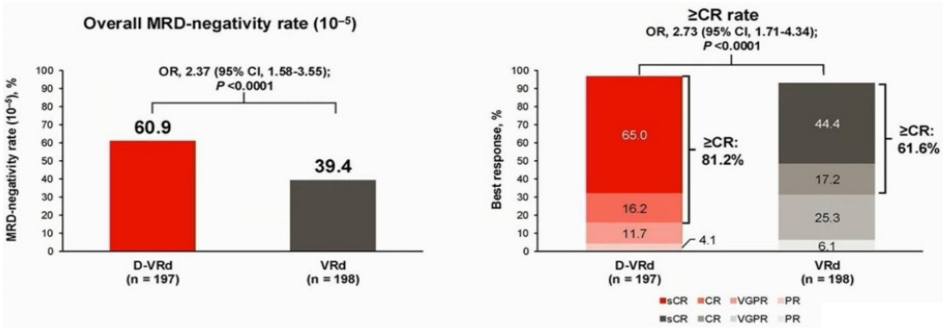
IMROZ-Treament Response



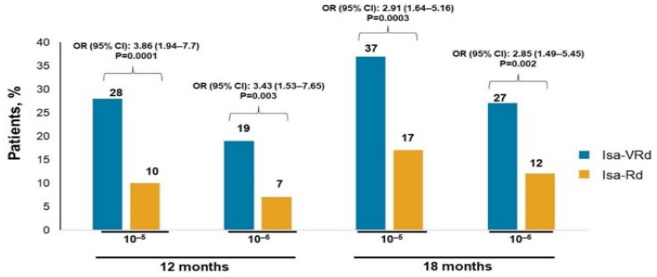
MRD Rate (NGS 10 -5)



CEPHEUS: Primary Endpoint – MRD - Negativity



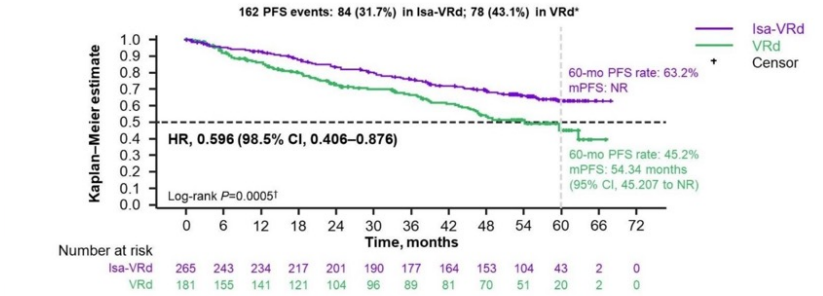
BENEFIT (IFM 2020-05) Study: MRD – CR Rate at 18 months



Isa-VRd resulted in a significant improvement in the MRD– CR rate at 12 and 18 months, and at 10^{-5} and 10^{-6} in the ITT population

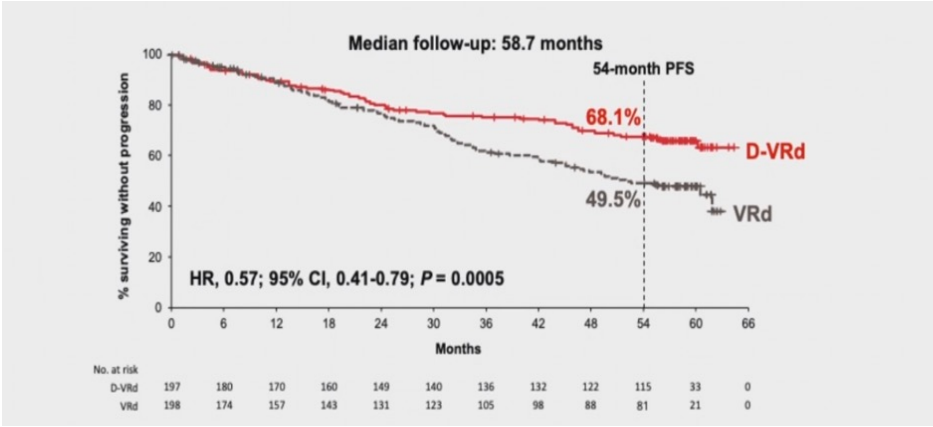
Facon Tet al. NEJM 2024; Usmani SZ et al IMS 2024; Leleu XP et al ASCO2024

IMROZ: Primery Endpoint - PFS

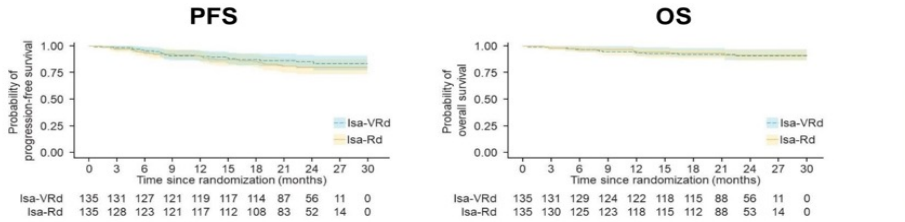


At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

CEPHEUS: PFS



BENEFIT (IFM 2020-05) Study: PFS and OS



Estimated 24 months PFS
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

Estimated 24 months OS
91.1% (95%CI 86.1–96.4) for Isa-VRd
91.5% (95%CI 86.5–96.8) for Isa-Rd

At a median follow-up of 23.5 months, survival is still immature

Facon Tet al. NEJM 2024; Usmani SZ et al ASH 2024; Leleu XP et al ASCO2024

Quadruplet vs Triplet Therapy for TIE NDMM: Safety Data

	CEPHEUS trial		IMROZ trial		BENEFIT trial	
Combination regimen	Dara-VRd	VRd	Isa-VRd	VRd	Isa-VRd	Isa-Rd
Maintenance	Dara-Rd	Rd	Isa-Rd	Rd	Isa-R	Isa-R
Any infection	92% any grade 40% grade ≥3	86% any grade 32% grade ≥3	91% any grade 45% grade ≥3	87% any grade 38% grade ≥3	93% any grade 71% grade ≥2	83% any grade 68% grade ≥2
Pneumonia	*Not reported*		30% any grade 20% grade ≥3	19% any grade 13% grade ≥3	48% any grade 35% grade ≥2	47% any grade 40% grade ≥2
URI	40% any grade 0.5% grade ≥3	33% any grade 0.5% grade ≥3	*Not reported*		*Not reported*	
Peripheral neuropathy	56% any grade 8% grade ≥3	61% any grade 8% grade ≥3	54% any grade 7% grade ≥3	61% any grade 6% grade ≥3	52% any grade 27% grade ≥2	28% any grade 10% grade ≥2
Eye disorders	*Not reported*		38% any grade 16% grade ≥3	25% any grade 11% grade ≥3	15% any grade 7% grade ≥2	14% any grade 8% grade ≥2
SPM	7.6% any grade	9.2% any grade	9.5% any grade 5.7% grade ≥3	5.5% any grade 4.4% grade ≥3	4% any grade 4% grade ≥2	4% any grade 4% grade ≥2

Facon Tet al. NEJM 2024; Usmani SZ et al ASH 2024; Leleu XP et al ASCO2024

IFM2017-03: Study Design

- Randomized, open-label, multicenter phase III trial[1]

Stratification by ISS (I vs II vs III) and age (<80 vs ≥80 yr)

Patients aged ≥65 yr with newly diagnosed MM; IFM frailty score ≥2* (N = 295)

Randomized 2:1

DR† (n = 200)
Daratumumab SC 1800 mg Q1W for 8 wk; then Q2W for 16 wk; then Q4W thereafter
Lenalidomide 25 mg Days 1-21 Q28D

Rd (n = 95)
Lenalidomide 25 mg Days 1-21 Q28D
Dexamethasone 20 mg Days 1, 8, 15, 22 Q28D

Treatment continued until PD or unacceptable AE

Interim analysis at 12 mo of therapy: ORR, ≥VGPR, MRD rate, grade ≥3 AEs

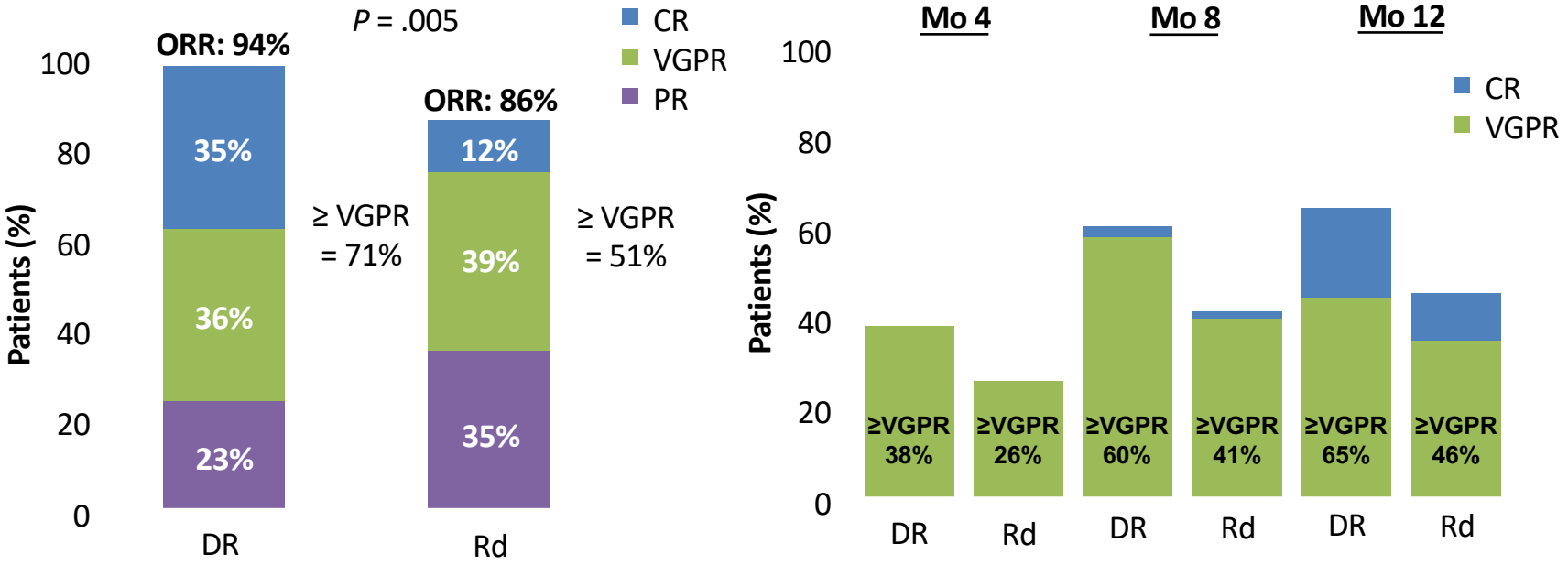
*IFM frailty score (age, ECOG PS, Charlson index)[2]: 0-1 = fit; ≥2 = frail.

†DR included low-dose dexamethasone 20 mg/wk during cycles 1,2, along with SC daratumumab dosing.

- **Primary endpoint:** PFS
- **Secondary endpoints:** ORR, rate of ≥VGPR, rate of MRD negativity, OS, safety

1. Manier. ASH 2024.2. Facon. Leukemia. 2020

IFM2017-03: Response Rates

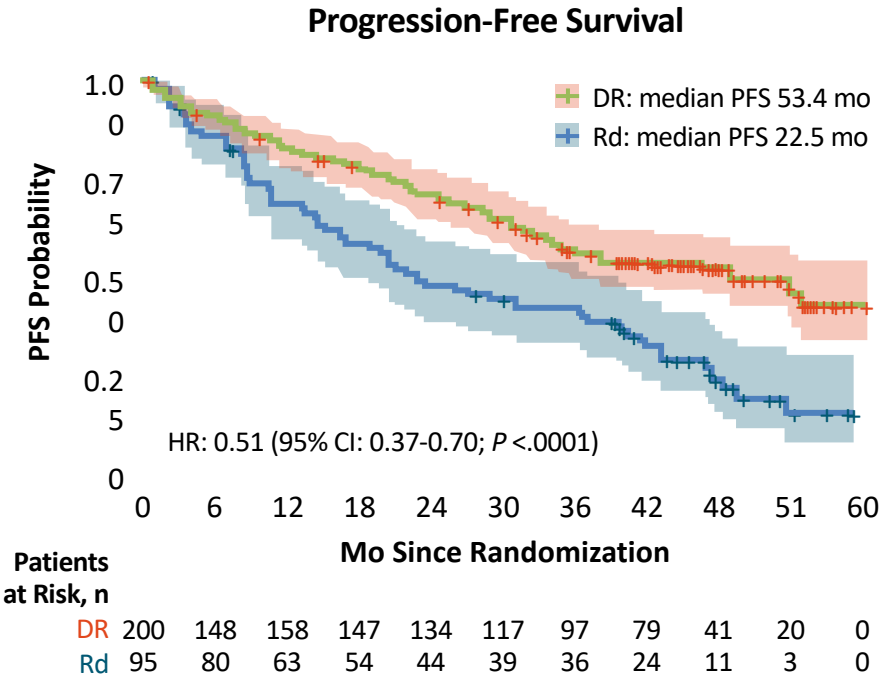


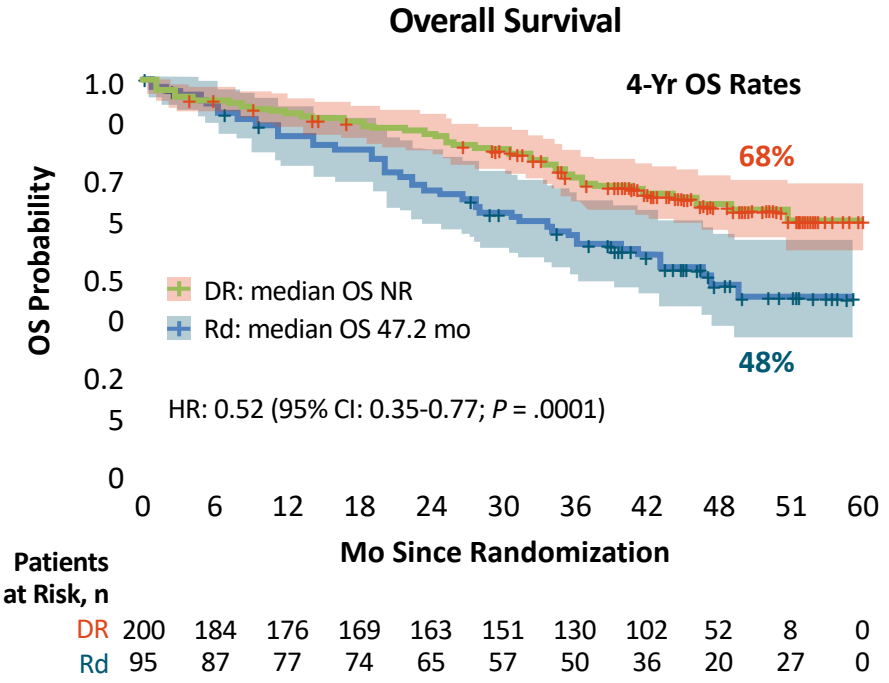
- VGPR or better rate was substantially greater in the DR group
- DR was associated with deeper responses at all time points, including early time points

Manier. ASH 2024

IFM2017-03: PFS (Primary Endpoint) and OS

Median follow-up: 46.3 mo





Manier. ASH 2024

IFM2017-03: Most Common Grade ≥3 AEs

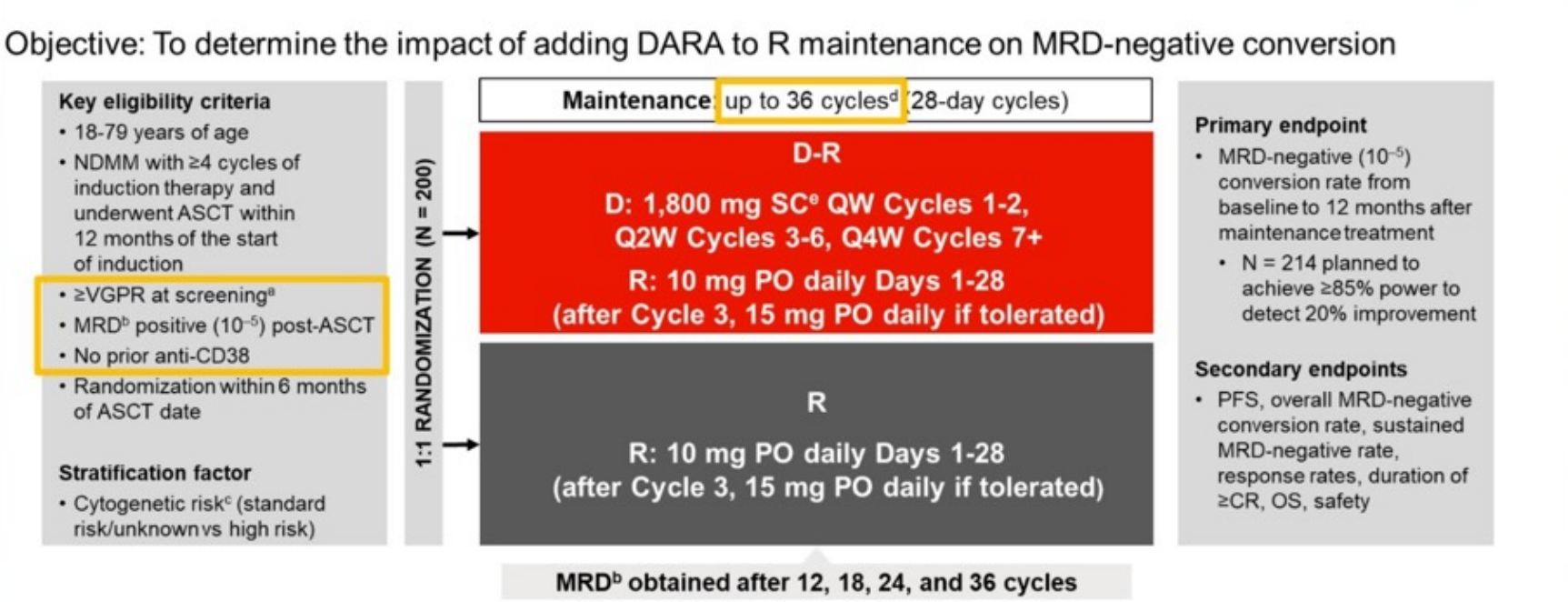
Outcome	Grade ≥3 AEs	
	DR (n = 200)	Rd (n = 95)
Median treatment duration, mo	31.6	14.3
All grade ≥3 AEs, n (%)	178 (89)	75 (79)
All grade 5 AEs, n (%)	23 (12)	12 (13)
Grade 3 hematologic AEs, n (%)	123 (62)	32 (34)
▪ Neutropenia	110 (55)	23 (24)
▪ Anemia	24 (12)	3 (3)
▪ Thrombocytopenia	19 (10)	5 (5)
Nonhematologic AEs, n (%)	132 (66)	68 (72)
Infection, n (%)	38 (19)	20 (21)
▪ Pneumonia	11 (6)	8 (8)
Infection rate per patient-yr	0.07	0.09
Treatment discontinuation due to AE, n (%)	60 (30)	32 (34)

- Patients receiving DR experienced no increased rates of infection or treatment discontinuation

Manier. ASH 2024

Quale è la migliore terapia di mantenimento?

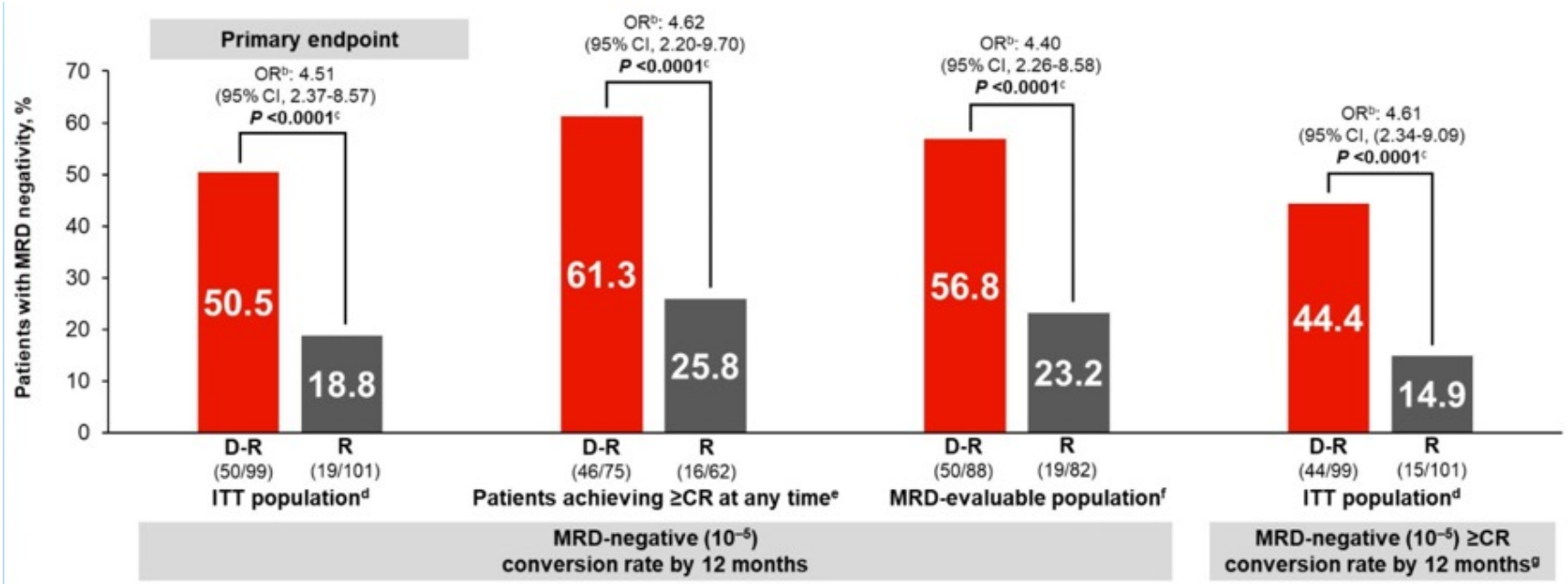
Phase 3 AURIGA Trial: Dara-R vs Maintenance After Triplet



[d]After 36 months, if no PD, treatment continuation at discretion of investi

Bardos A et al IMS 2024

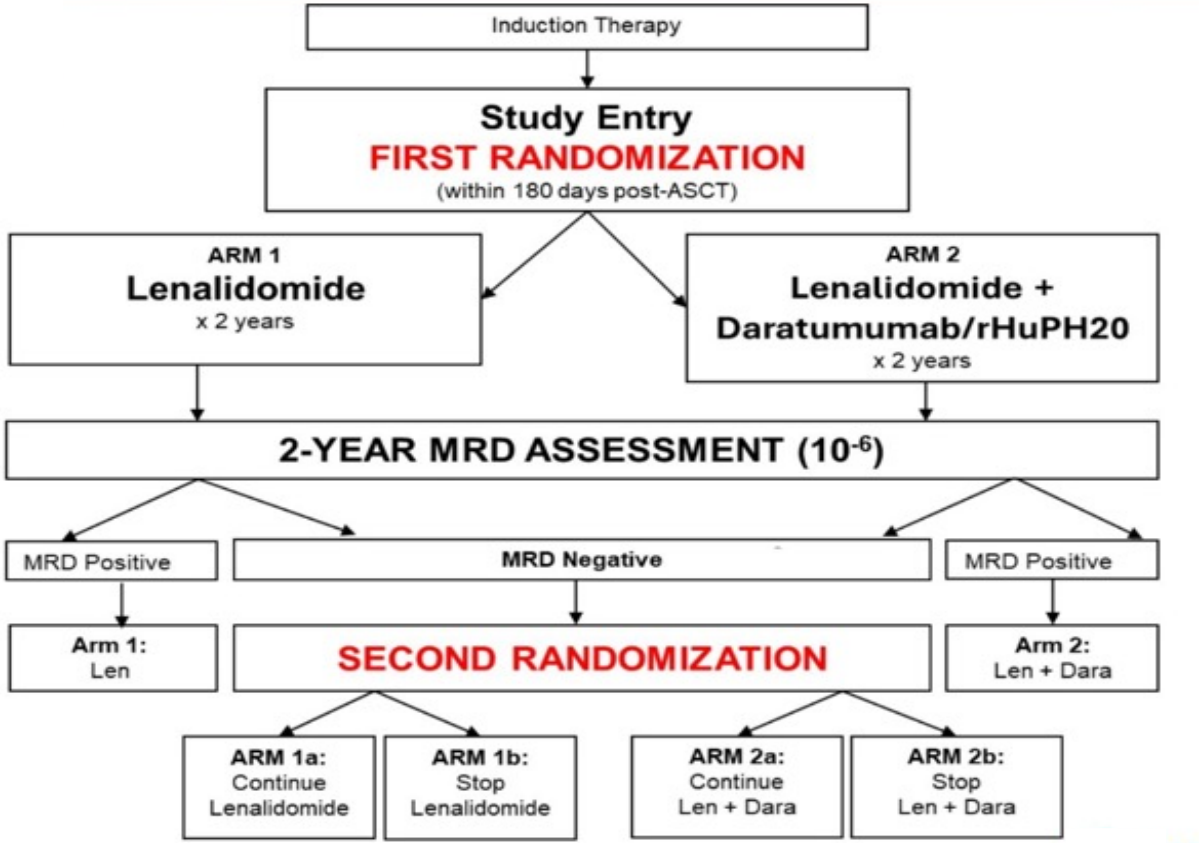
AURIGA Trial: MRD-Negative Conversion Rate at 12 Months



AURIGA data demonstrate the benefit of D-R maintenance therapy versus R alone in patients who were MRD positive after triplet induction and ASCT.

Bardos A et al IMS 2024

S1803 DRAMMATIC: DR vs R Maintenance with MRD-Guided Therapy Duration

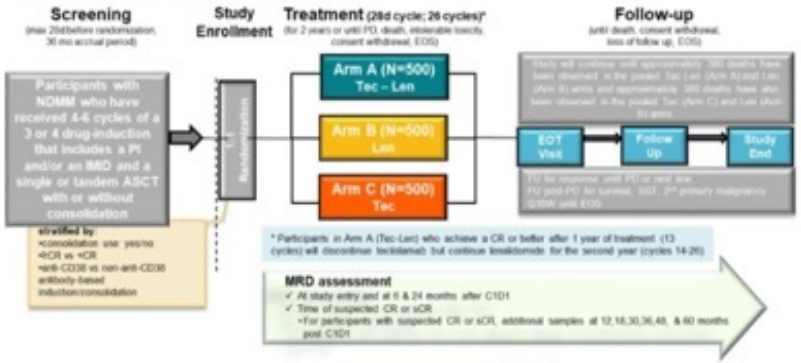


Krishnan A et al ASH 2024

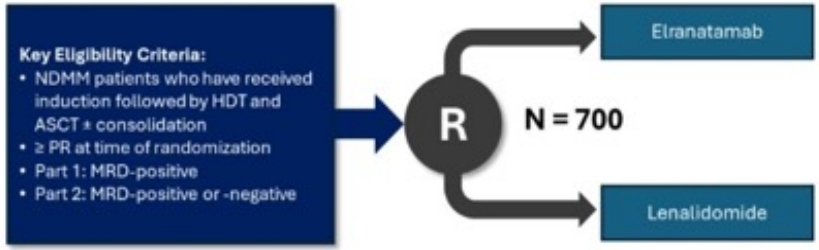

Future Directions

Frontline Immunotherapies for TE-NDMM Patients

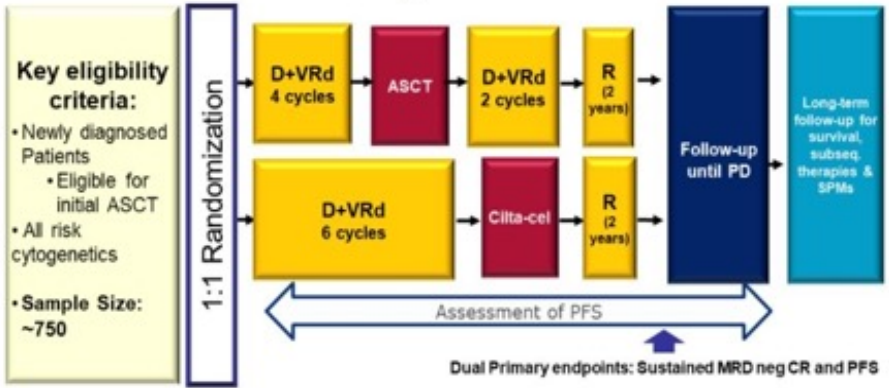
MajesTEC-4



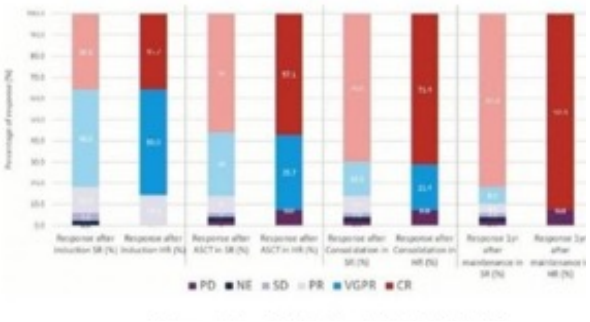
MagnetisMM-7



CARTITUDE-6



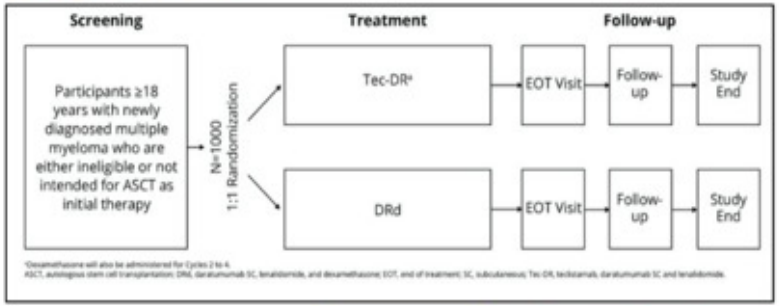
GEM-BELA-VRd



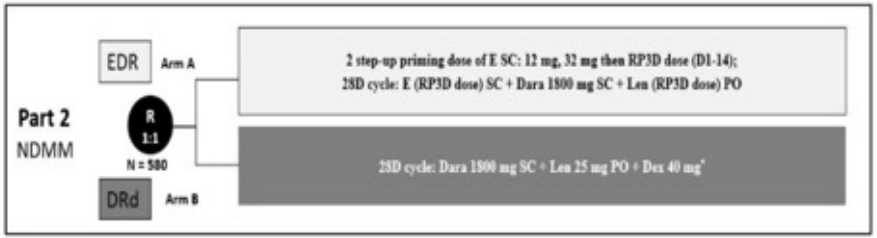
Gonzales-Calle V et al IMS 2024

Frontline Immunotherapies for TI-NDMM Patients

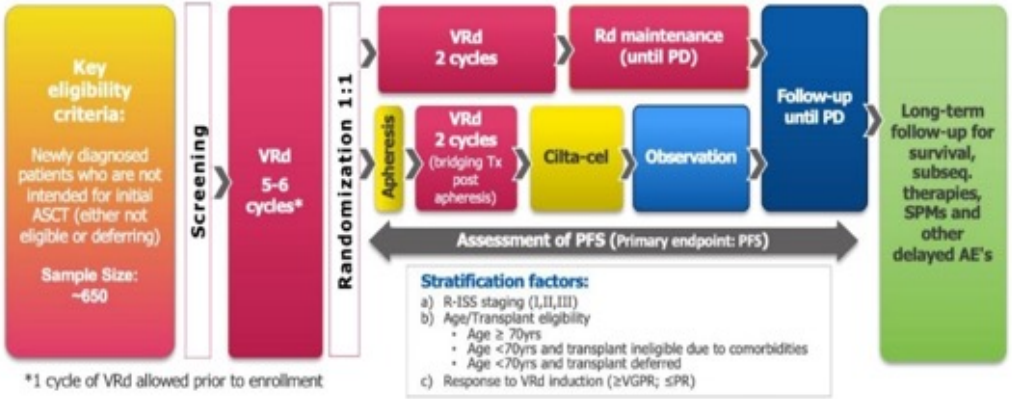
MajesTEC-7



MagnetisMM-6



CARTITUDE-5



Gonzales-Calle V et al IMS 2024

Punti chiave da discutere

- ✓ *Il trapianto è ancora necessario?*
  - ➢ *Dobbiamo ancora distinguere i pazienti eleggibili dai non eleggibili?*
    - ❖ **Si è ancora da considerare la terapia standard. Continuiamo a distinguere i pazienti tra eleggibili e non eleggibili, ma forse più corretto valutare anche «fit vs frail»**
- ✓ *Quadrupletta per tutti?*
  - ➢ *Quale paziente, quale anti – CD38 e quale PI?*
  - ❖ **Nuove terapie standard per i pazienti eleggibili e pazienti fit non eleggibili (terapie settimanali con dosaggi ridotti per tutti gli altri**
- ✓ *Quale e la migliore terapia di mantenimento?*
  - ➢ *Chi beneficia dagli anti – CD38?*
  - ➢ *Per quanto tempo il mantenimento?*
  - ❖ **Anti-CD38 hanno guadagnato il favore, ma la dose e la durata devono essere ancora valutati**
- ✓ *Dove stiamo andando?*
  - ➢ *Quale è il ruolo della immunoterapia e dei nuovi agenti?*
  - ❖ **CAR-T invece del trapianto, CELMoDs e/o anticorpi bispecifici come terapia di mantenimento, nuovi farmaci target**


Grazie!!