La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Royal Hotel Continental • 14–15 Maggio 2026

Tempo di strategia MRD guided: la rivoluzione clinica della malattia minima residua nel mieloma multiplo e focus sulla prima linea

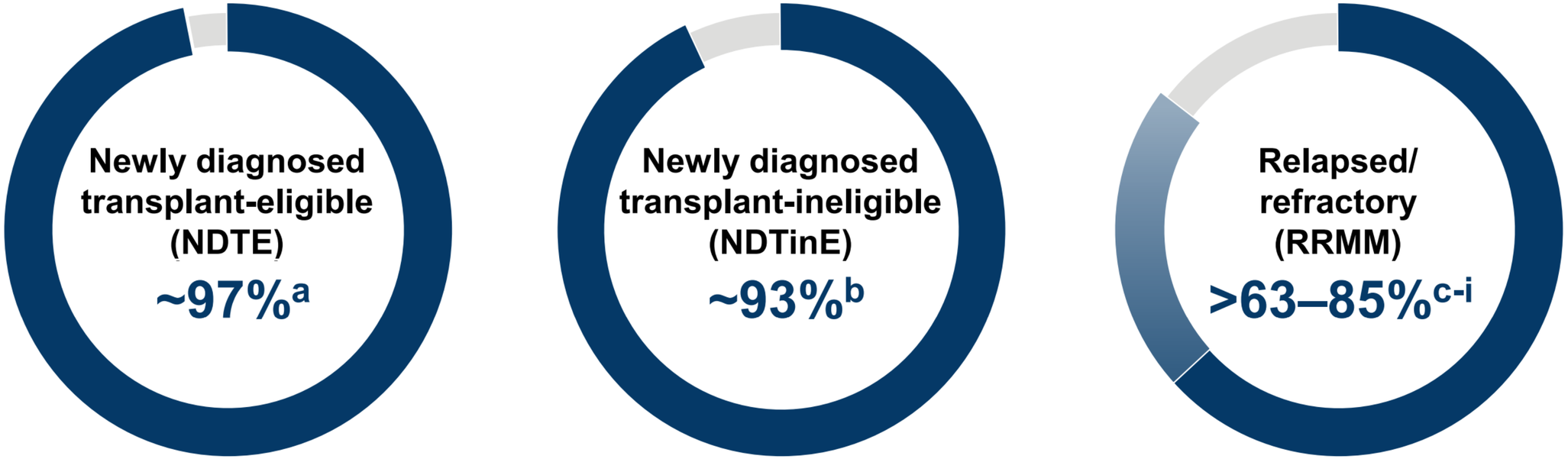
Cirino Botta

Disclosures of Cirino Botta

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
J&J			x		x	X	
Pfizer	x		x		x	X	
AMGEN					x	X	
SANOFI					x	X	
Oncopeptides	x					X	
GSK					x	X	

Perchè ci serve valutare la Malattia Minima Residua

Overall Response Rates (ORR) Are Nearing 100% with Standards of Care



a: PERSEUS (Sonneveld, *N Engl J Med* 2023); b: MAIA (Facon, *Lancet Oncol* 2021); c: ICARIA (Moreau, *Lancet Oncol* 2021); d: CANDOR (Usmani, *Lancet Oncol* 2022); e: APOLLO (Dimopoulos, *Lancet Oncol* 2021); F: Talquetamab (Chari *N Engl J Med* 2022); g: Teclistamab (Moreau *N Engl J Med* 2022); h: KarMMa-3 (Rodriguez-Otero, *N Enal J Med* 2023); I: CARTITUDE-4 (San-Miguel, *N Enal J Med* 2023)

B. Paiva ODAC/FDA presentation April 2024

Minimal Residual Disease (MRD) nel mieloma multiplo: perché è importante?

IMWG MRD criteria (requires a	
Sustained MRD-negative	MI fu
Flow MRD-negative	Ab mu
Sequencing MRD-negative	Ab DN ce
Imaging plus MRD-negative	MI m

- **MRD negative CR** - Absence of aberrant clonal plasma cells by NGF or NGS on bone marrow aspirates with a minimum sensitivity of at least 1 in 10^5 nucleated cells
  - MRD rate at 10^{-6} rates should be reported when feasible designated as **MRD negative CR 10^{-6}**
  - If MRD negative as defined above but no negative immunofixation, should be defined as NGF/NGS negative (without CR) at either threshold
- **Imaging negative MRD neg** – MRD as defined above at either threshold with a functional imaging (PET-CT or WB-DWI MRI) negative
- **Sustained MRD negative CR**– MRD negative CR as defined above at either threshold with two negative MRD tests at least 24 months apart, and without any positive test in between

t evaluations can be used to

dure for MRD detection in

ncing reads obtained after
tivity of 1 in 10^5 nucleated

T/CT or decrease to less

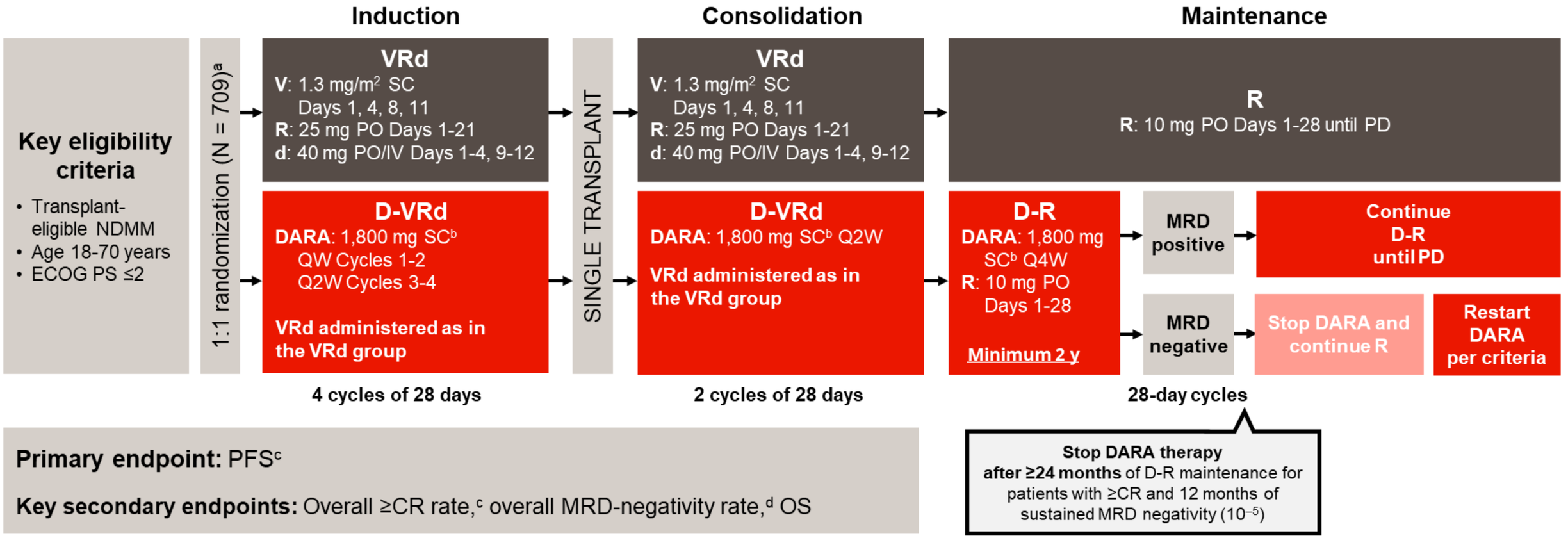
Kumar S, Lancet Oncology 2016

Shaji Kumar, IMS 2025

Ma perché abbiamo deciso di applicarla solo ora?

First MRD-driven risk-adapted therapy in MM

PERSEUS: D-VRD + ASCT



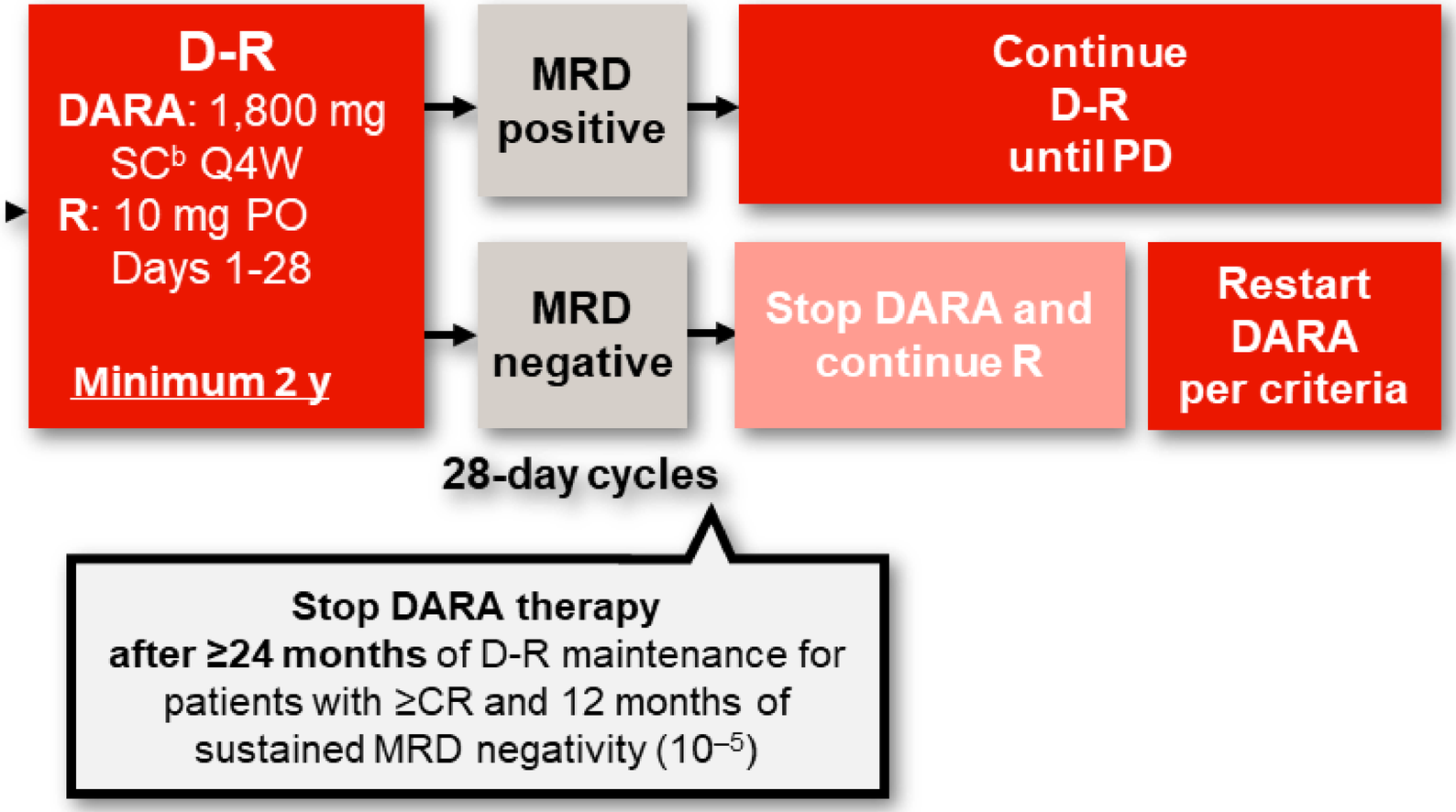
Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

mFU: 47.5 months Rodriguez-Otero P et al. ASCO 2024

First MRD-driven risk-adapted therapy in MM

PERSEUS: D-VRD + ASCT



mFU: 47.5 months Rodriguez-Otero P et al. ASCO 2024

Avevamo già evidenze cliniche?

MRD nel mieloma multiplo: quanto è frequente?

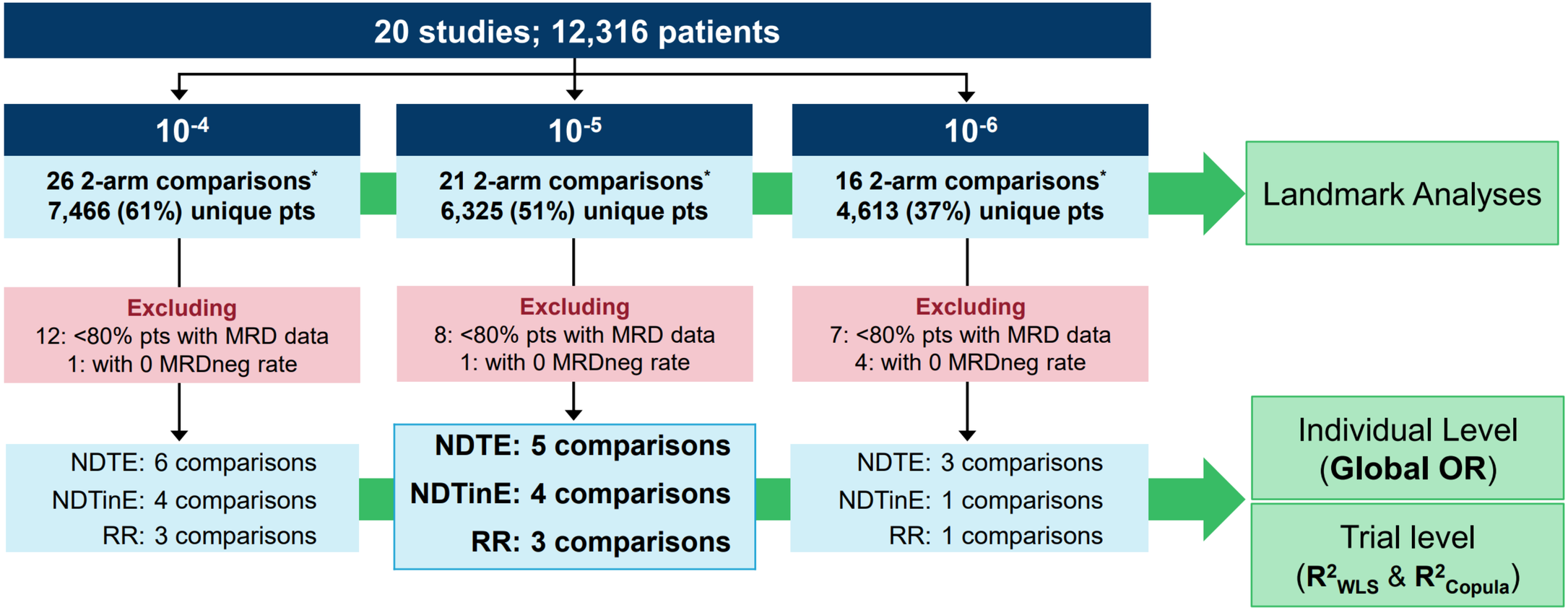
Clinical trial (phase)	NCT	Disease setting	Randomization	MRD method	MRD^{-ve} rates (%)	Median PFS (mo)
ATLAS (3)	NCT02659293	NDTE	KRD vs R alone	NGS	53% vs 31%	59.1 vs 41.4
CASSIOPEIA (3)	NCT02541383	NDTE	DaraVTD vs VTD	NGF	64% vs 43.5%	NR vs 51.5
DETERMINATION (3)	NCT01208662	NDTE	VRD-ASCT vs VRD alone	NGS	13% vs 12%	67.5 vs 46.2
GEM2012MENOS65 (3)	NCT01916252	NDTE	VRD-BuMel vs VRD-Mel	NGF	58% vs 55.5%	NR vs 75.3
GRIFFIN (2)	NCT02874742	NDTE	DaraVRD vs VRD	NGS	64% vs 30%	NR vs NR
IFM 2009 (3)	NCT01191060	NDTE	VRD-ASCT vs VRD alone	NGS	21% vs 15%	50.0 vs 36.0
ALCYONE (3)	NCT02195479	NDTI	DaraVMP vs VMP	NGS	28% vs 7%	36.4 vs 19.3
CLARION (3)	NCT01818752	NDTI	KMP vs VMP	NGF	5% vs 5%	22.3 vs 22.1
MAIA (3)	NCT02252172	NDTI	DaraRD vs RD	NGS	31% vs 10%	62.0 vs 34.3
APOLLO (3)	NCT03180736	RRMM	DaraPD vs PD	NGS	9% vs 2%	12.4 vs 6.9
BOSTON (3)	NCT03110562	RRMM	SelVD vs VD	NGF	5% vs 4%	13.9 vs 9.5
CANDOR (3)	NCT03158688	RRMM	DaraKD vs KD	NGS	18% vs 4%	28.6 vs 15.2
CASTOR(3)	NCT02136134	RRMM	DaraVD vs VD	NGS	15% vs 2%	16.7 vs 7.1
IKEMA (3)	NCT03275285	RRMM	IsaKD vs KD	NGS	30% vs 13%	NR vs 19.2
POLLUX (3)	NCT02076009	RRMM	DaraRD vs RD	NGS	33% vs 17%	45.0 vs 17.5

Paiva B, Blood Advances, 2023

MRD nel mieloma multiplo: quanto è frequente? - update

Trial	MRD
Isa-KRD in ND HR MM (GMMG-CONCEPT)	**67.7% in TE patients, 54.2% in NTE patients**
Dara-VRD vs VRD in NDMM (PERSEUS)	**75.2% (D-VRD) vs 47.5% (VRD)**
Isa-VRD vs VRD in TIMM (IMROZ)	**58.1% (I-VRD) vs 43.6% (VRD)**
Dara-VRD vs VRD in TIMM (CEPHEUS)	**60.9% (D-VRD) vs 39.4% (VRD)**
Isa-KRD vs KRD in NDMM (ISKIA)	**77% (I-KRD) vs 67% (KRD)**
KRD-ASCT vs KRD12 vs KCD-ASCT (FORTE)	**80% (KRD-ASCT) vs 69% (KRD12) vs 43%**

MRD: chi raggiunge lo stato di undetectable ha il miglior outcome



*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory

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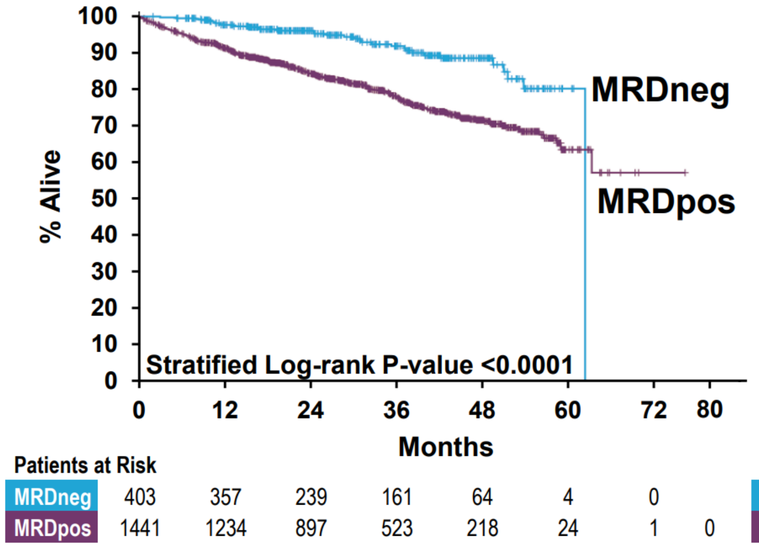
O. Landgren ODAC/FDA presentation April 2024

MRD: chi raggiunge lo stato di undetectable ha il miglior outcome

Clinical Endpoint: Overall Survival

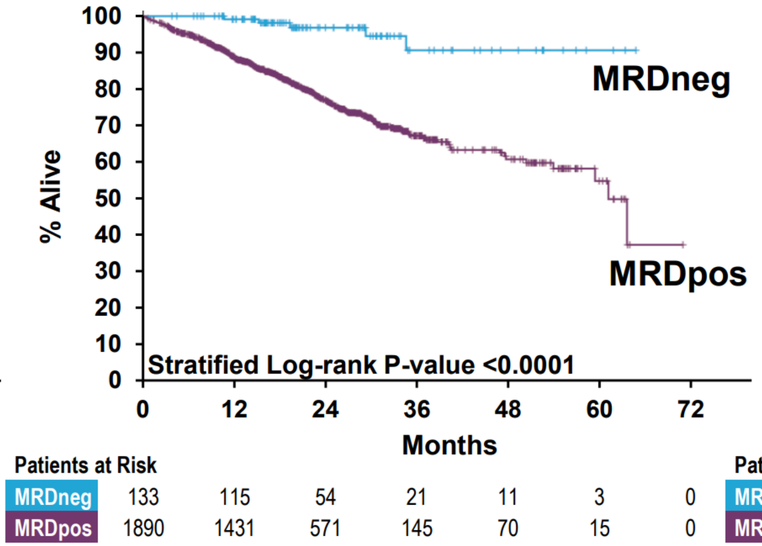
NDTE MM



Patients at Risk								
MRDneg	403	357	239	161	64	4	0	
MRDpos	1441	1234	897	523	218	24	1	0

HR=0.38 (0.27-0.56)

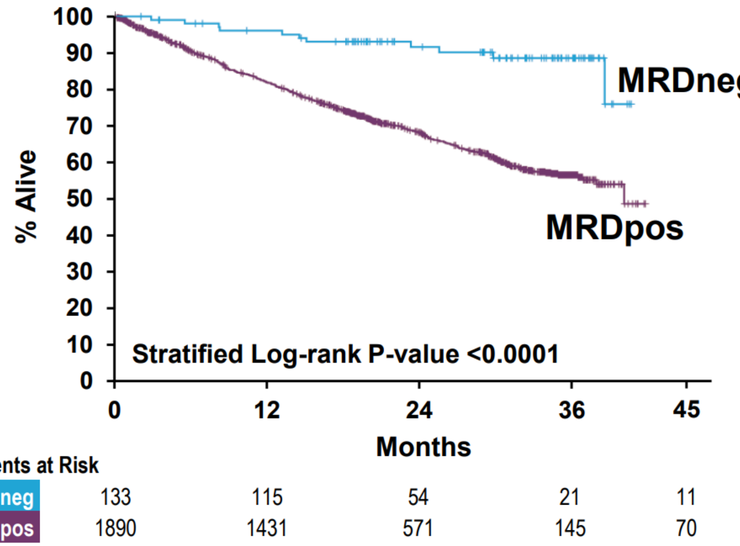
NDTinE MM



Patients at Risk							
MRDneg	133	115	54	21	11	3	0
MRDpos	1890	1431	571	145	70	15	0

HR=0.16 (0.07-0.38)

RR MM



Patients at Risk					
MRDneg	133	115	54	21	11
MRDpos	1890	1431	571	145	70

HR=0.25 (0.14-0.46)

CC-38

Stratified by studies

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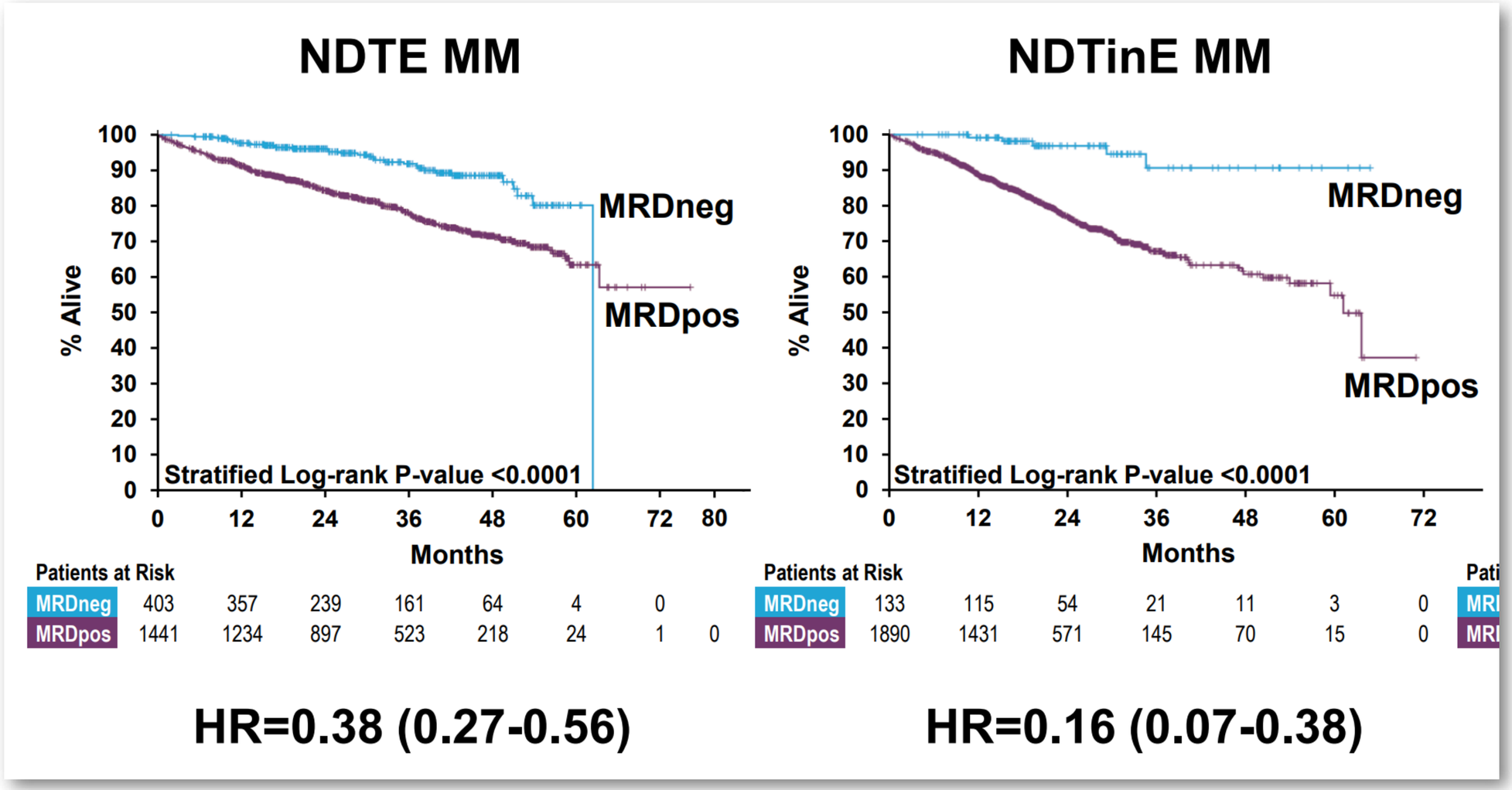
MRD: chi raggiunge lo stato di undetectable ha il miglior outcome



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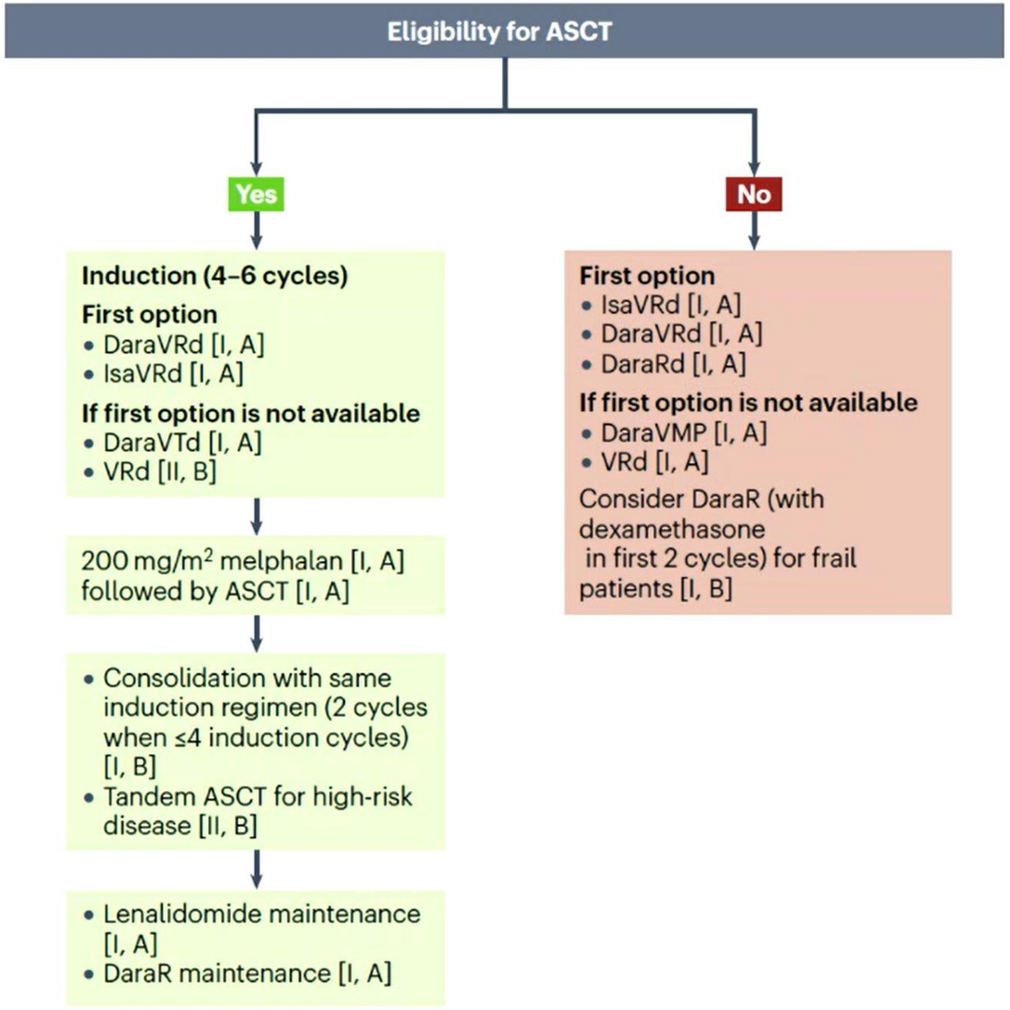
Ma torniamo alla prima linea…

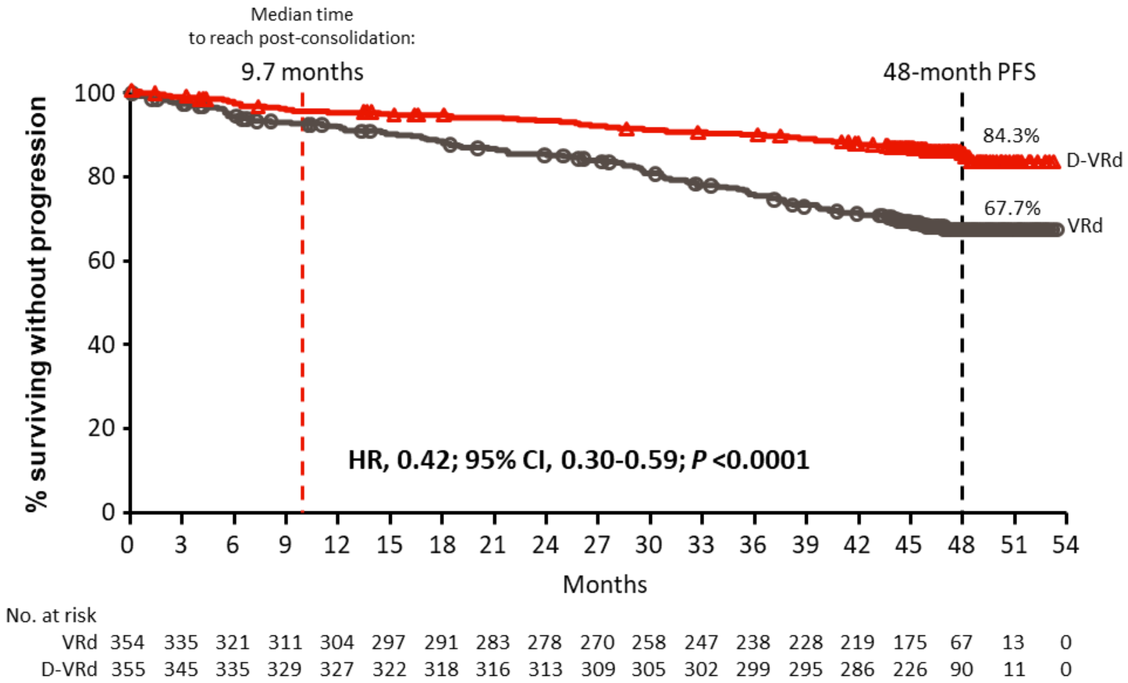
First Line Therapy for Myeloma



Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol 2025; in press

First MRD-driven risk-adapted therapy in MM

PERSEUS: D-VRD + ASCT



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

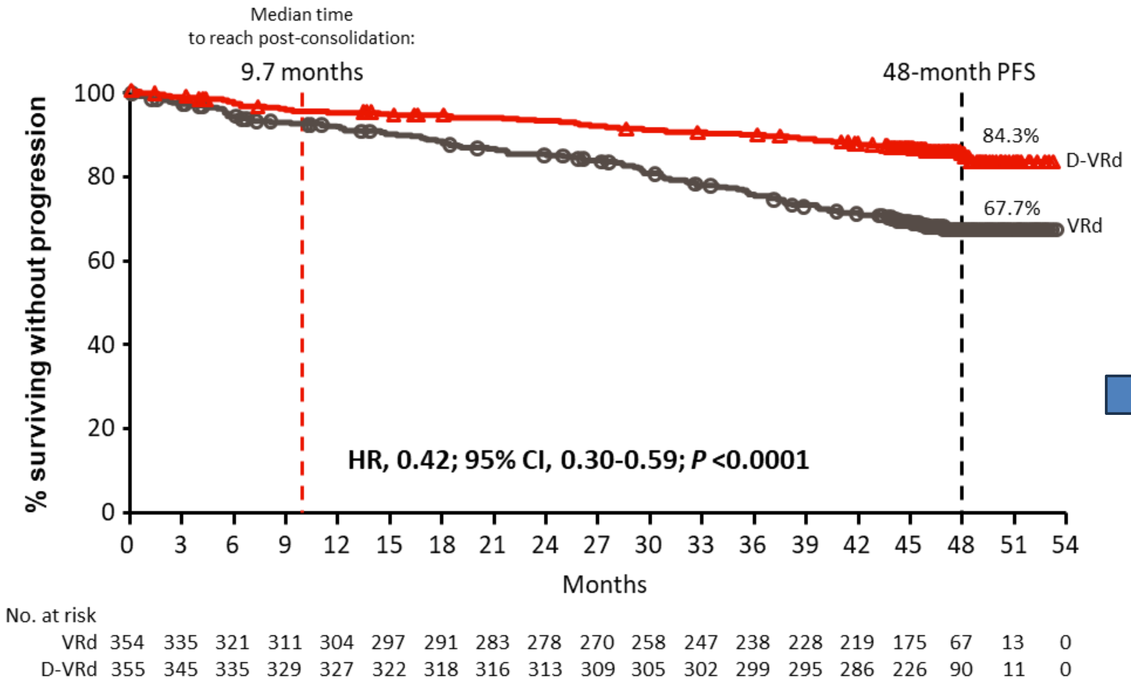
HR, hazard ratio; CI, confidence interval. [a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test. [c]*P* value was calculated with the use of Fisher's exact test.

1. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301-313.

mFU: 47.5 months Rodriguez-Otero P et al. ASCO 2024

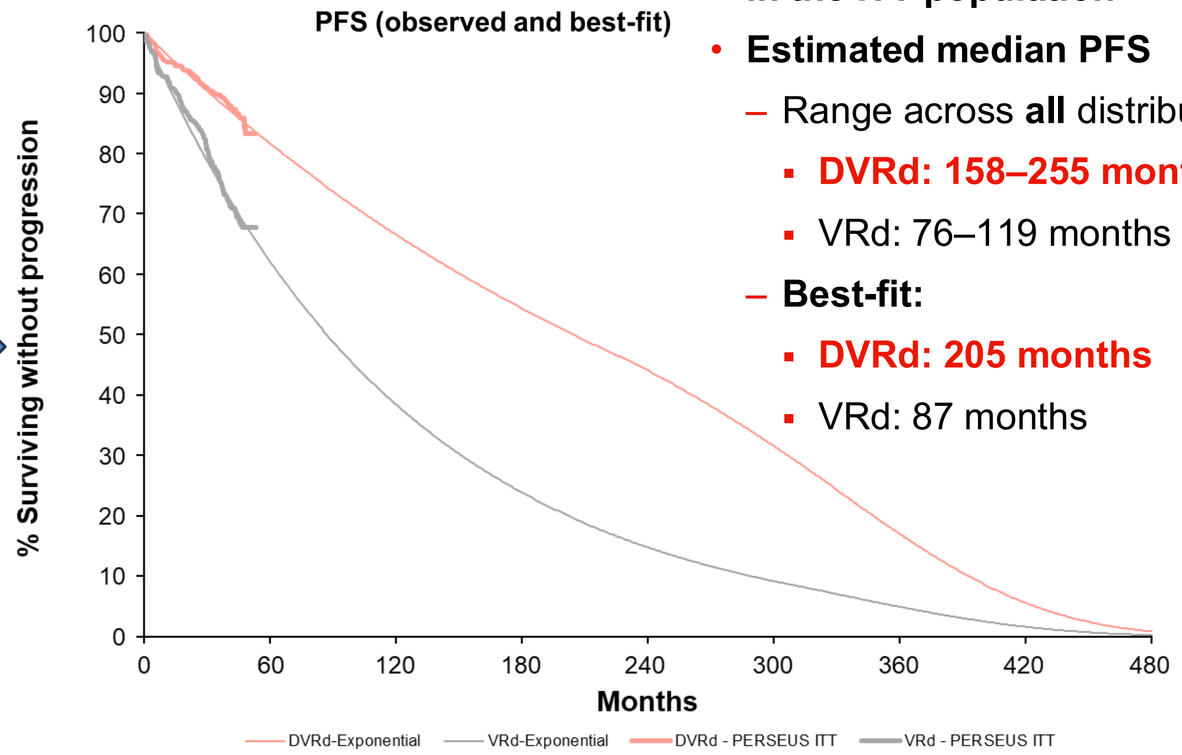
First MRD-driven risk-adapted therapy in MM

PERSEUS: D-VRD + ASCT



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

Rodriguez-Otero P et al. ASCO 2024

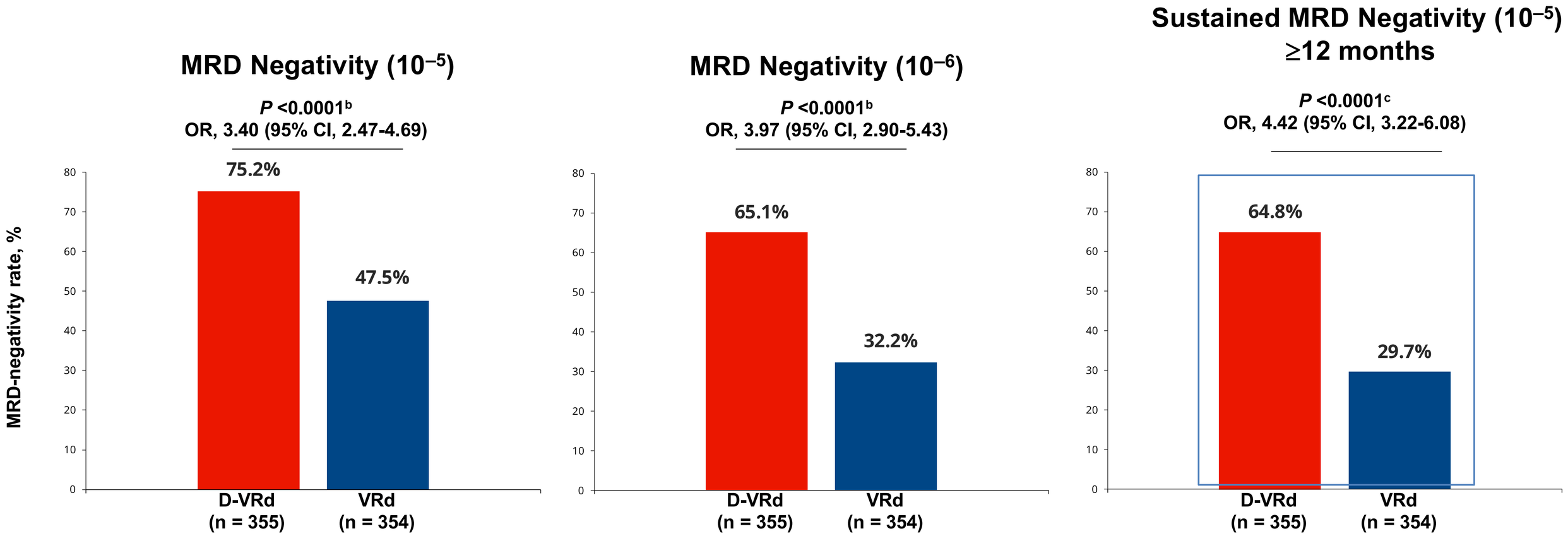


- **Median PFS not reached in the ITT population**
- **Estimated median PFS**
  - Range across **all** distributions:
    - **DVRd: 158–255 months**
    - VRd: 76–119 months
  - **Best-fit:**
    - **DVRd: 205 months**
    - VRd: 87 months

Presented by S Zweegman at the 6th European Myeloma Network (EMN) Meeting; April 10–12, 2025; Athens, Greece

mFU: 47.5 months

Overall and Sustained Minimal Residual Disease–negativity Rates

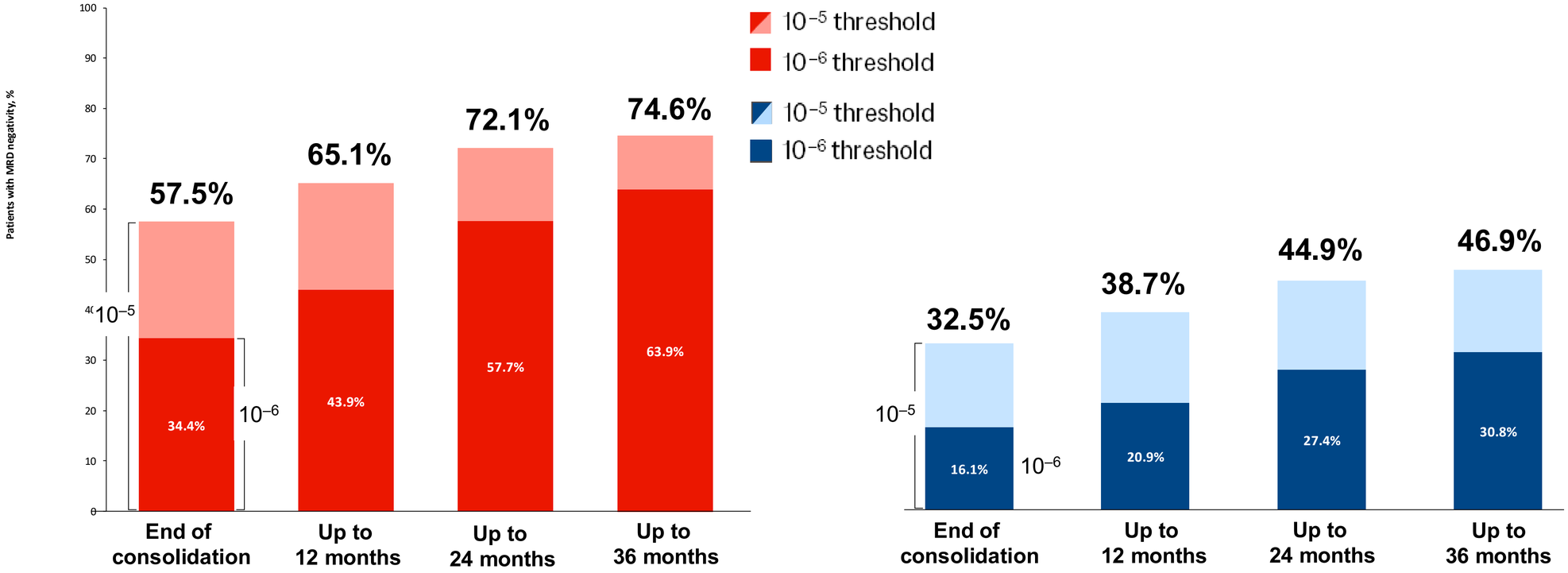


- 207 of 322 (64.3%) patients receiving maintenance in the D-VRd group discontinued DARA per protocol after receiving ≥24 months of maintenance therapy and achieving ≥CR and sustained MRD negativity for ≥12 months

CR, complete response; DARA, daratumumab; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; MRD, minimal residual disease; VRd, bortezomib/lenalidomide/ dexamethasone. [a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via next generation sequencing (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA). MRD was evaluated post-consolidation in patients with ≥VGPR or at the time of suspected ≥CR. For patients who achieved ≥CR, did not progress, and remained on study, an additional aspirate was obtained at 12, 18, 24, 30, and 36 months after cycle 1 day 1 and yearly thereafter. [b]P value was calculated with the stratified Cochran–Mantel–Haenszel chi-squared test. [c]P value was calculated with the Fisher's exact test. Figures adapted with permission from Sonneveld P et al. Presented at: The 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA.
Sonneveld P et al. Presented at: The 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA.

Minimal Residual Disease–negativity Rates 10^{-5} and 10^{-6} (ITT)

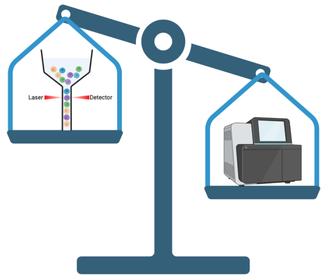
Cumulative MRD-negativity rates (%) measured from first treatment dose



- D-VRd + D-R doubled the rates of deeper MRD negativity at 10–6 versus VRd + R
- MRD negativity at 10–6 increased by approximately 30% during maintenance with D-R

D-R, daratumumab plus lenalidomide; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; ITT, intent-to-treat; MRD, minimal residual disease; R, lenalidomide; VRd, bortezomib/lenalidomide/dexamethasone.
MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. *P* values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. *P* <0.0001 for all comparisons of D-VRd versus VRd.
Figures from Rodriguez-Otero P, et al. Presented at The ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA.

Cost considerations

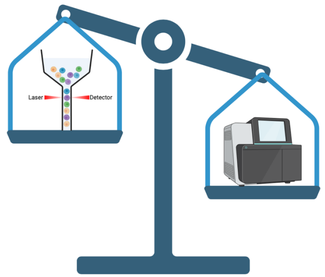


How much does an MRD test cost?
How much does NGS and NGF costs?

QUANTO POTREMMO RISPARMIARE?

MRD:
NGF: **200€**
NGS: **800-900€**

Cost considerations



QUANTO POTREMMO RISPARMIARE?

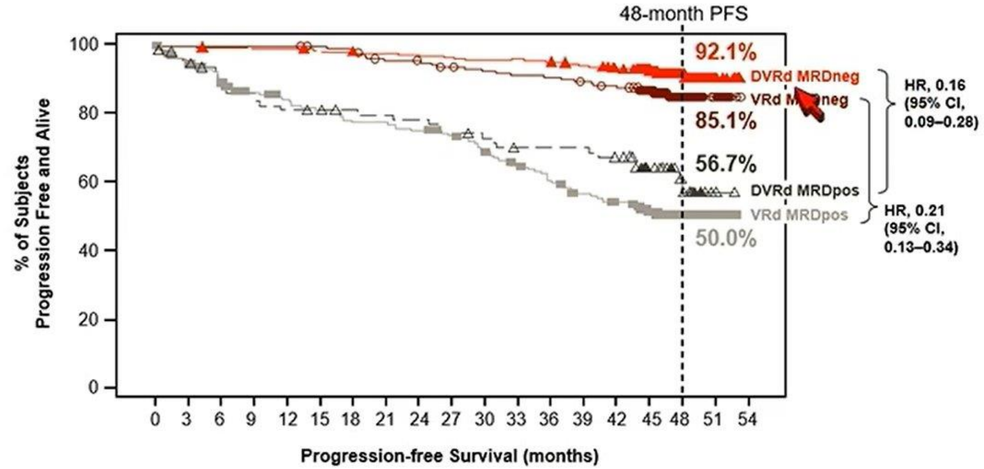
65% uMRD

35% pMRD

MRD e i nuovi trattamenti: quanto risparmiamo davvero?

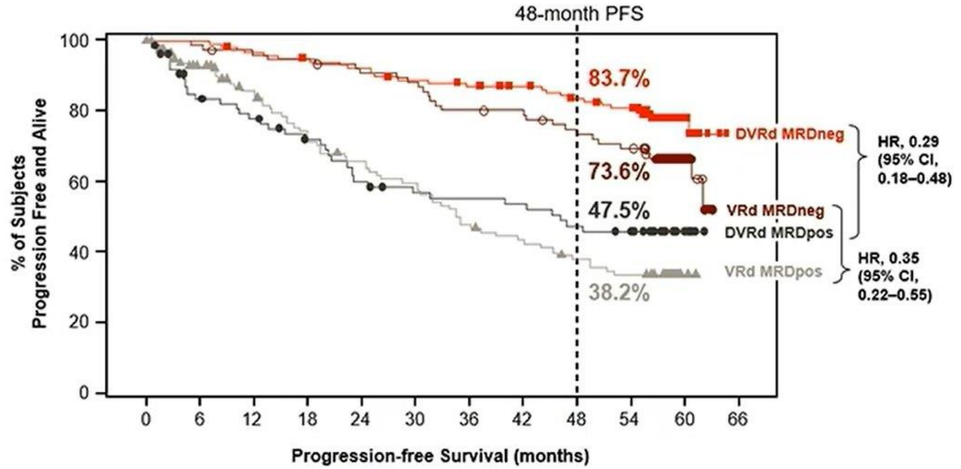
Achievement of MRD Negativity (10^{-5} and ≥CR) and Impact on PFS in PERSEUS and CEPHEUS

PERSEUS



Subjects at risk																			
DVRd MRD Negative	267	267	265	264	264	260	259	258	256	255	253	253	250	246	240	194	76	10	0
DVRd MRD Positive	88	78	70	65	63	62	59	58	57	54	52	49	49	49	46	32	14	1	0
VRd MRD Negative	168	168	168	168	168	166	165	157	156	152	149	147	146	143	139	115	44	10	0
VRd MRD Positive	186	167	153	143	136	131	126	126	122	118	109	100	92	85	80	60	23	3	0

CEPHEUS



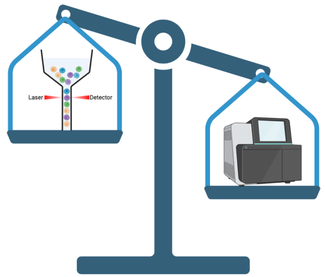
Subjects at risk												
DVRd MRD Negative	120	120	115	112	109	104	101	98	92	88	24	0
DVRd MRD Positive	77	60	55	48	40	36	35	34	30	27	9	0
VRd MRD Negative	78	77	74	73	69	67	61	59	54	51	18	0
VRd MRD Positive	120	97	83	70	62	56	44	39	34	30	3	0

Patients achieving MRD negativity had improved PFS vs those who remained MRD positive

CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; MRD, minimal residual disease; neg, negative; PFS, progression-free survival; pos, positive; VRd, bortezomib, lenalidomide, and dexamethasone.

Presented by J San Miguel at the 22nd International Myeloma Society (IMS) Annual Meeting & Exposition; September 17–20, 2025; Toronto, ON, Canada

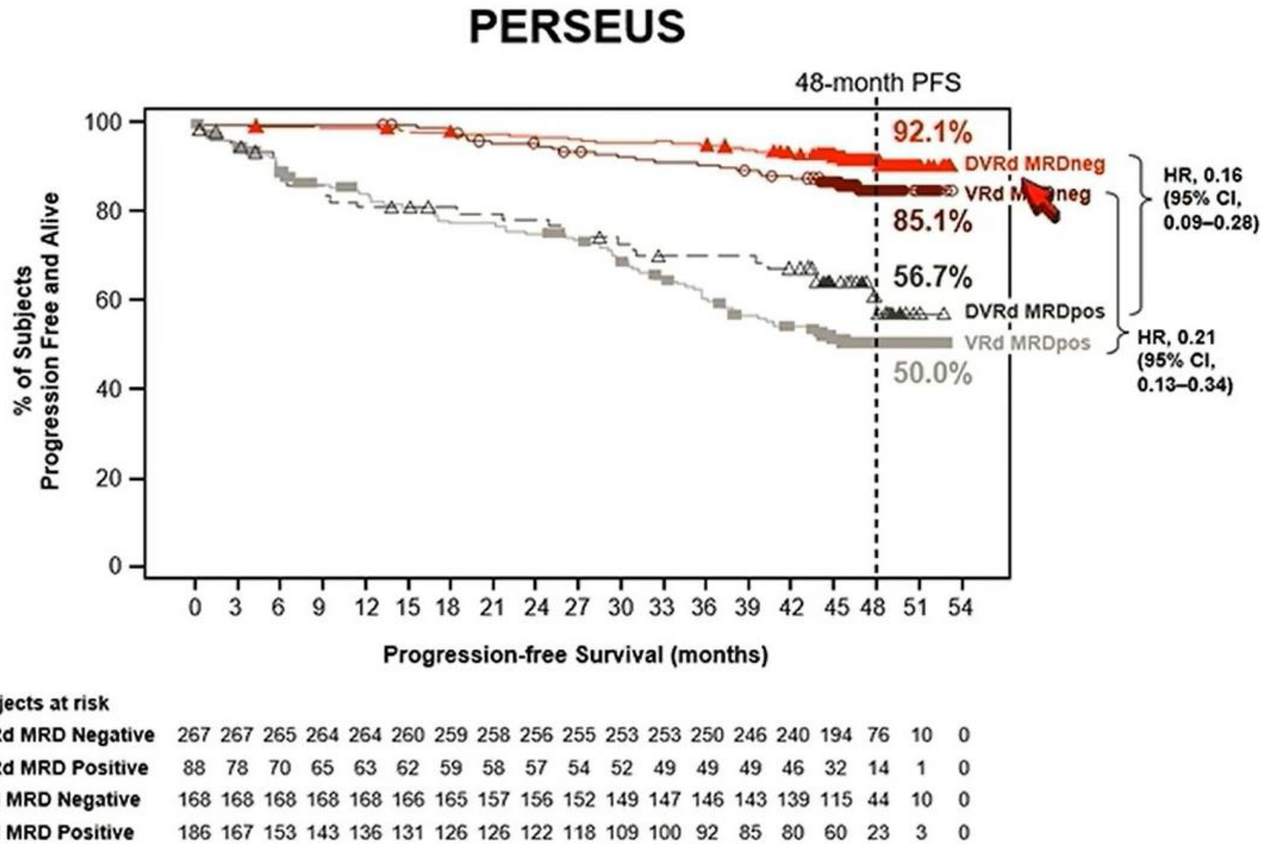
Cost considerations: scenario



QUANTO POTREMMO RISPARMIARE?

65% uMRD

35% pMRD

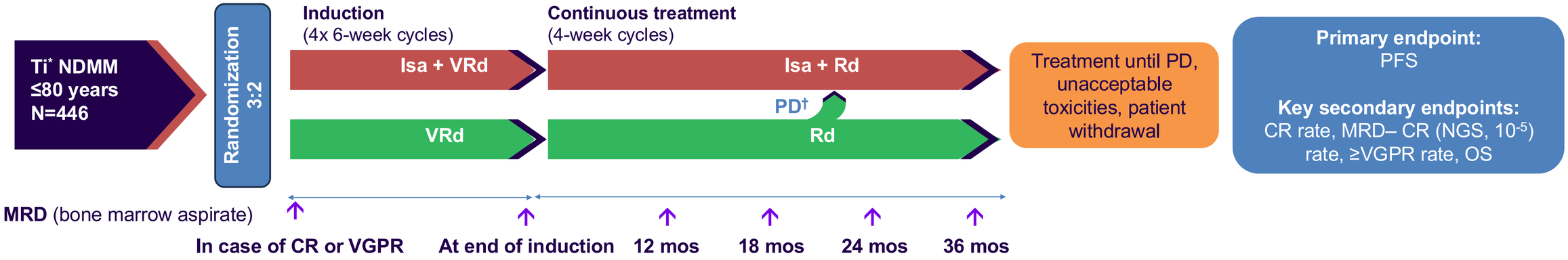


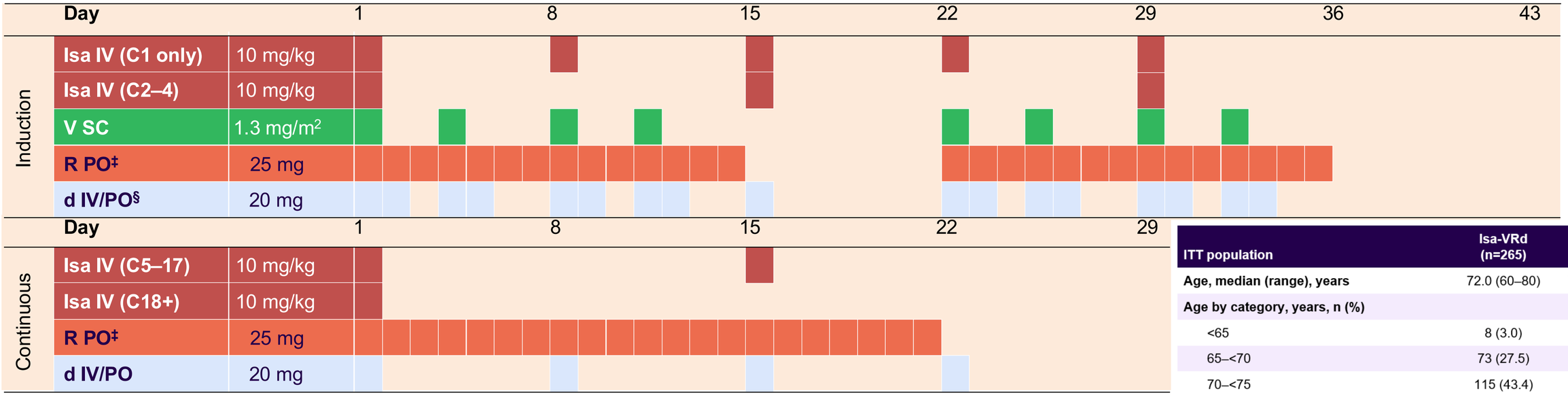
pMRD ➔ 50% 42k €/y per almeno 5 anni (gli altri meno…)
uMRD ➔ 92% 0 € per almeno 4 anni

E se il paziente è NTE?

Age >70 years ➔ Induction + Maintenance

IMROZ: I-VRD





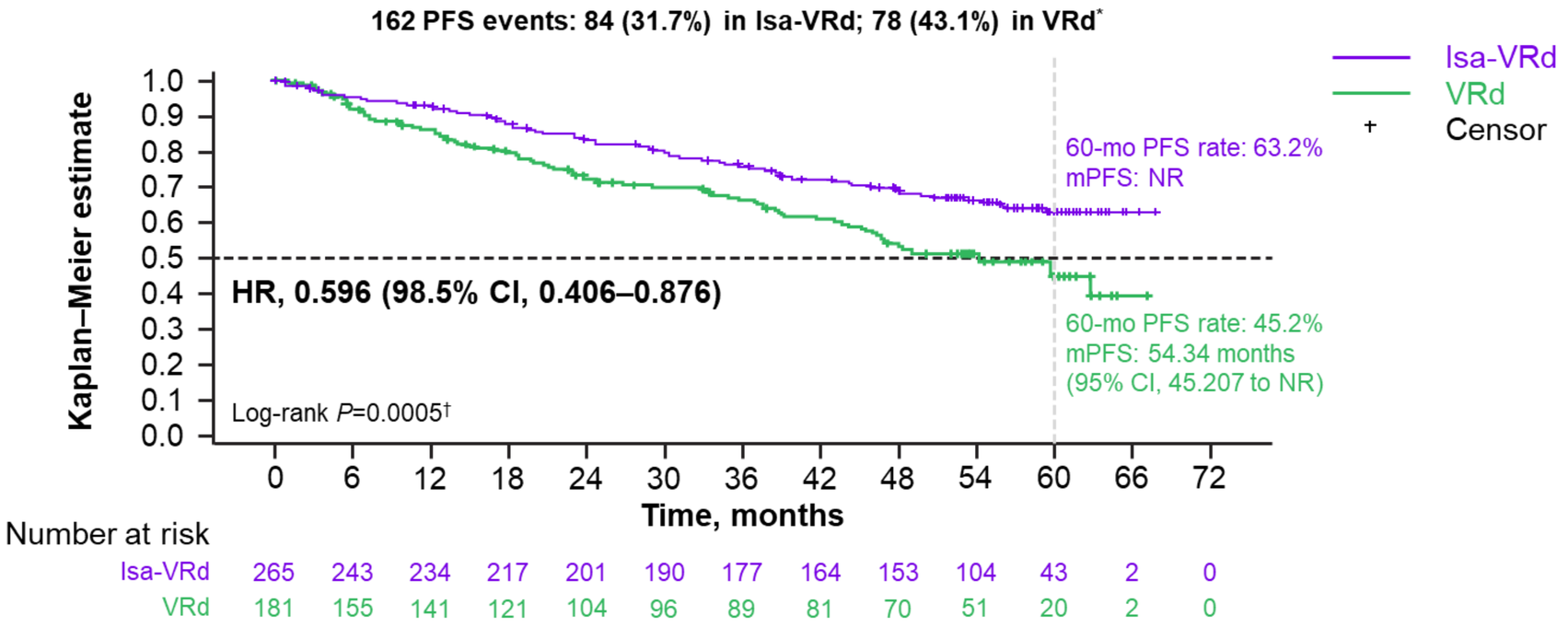
ITT population	Isa-VRd (n=265)	VRd (n=181)
Age, median (range), years	72.0 (60–80)	72.0 (55–80)
Age by category, years, n (%)		
<65	8 (3.0)	9 (5.0)
65–<70	73 (27.5)	47 (26.0)
70–<75	115 (43.4)	68 (37.6)
75–80	69 (26.0)	57 (31.5)

C, cycle; d, dexamethasone; Isa, isatuximab; R, lenalidomide; SC, subcutaneous; V, bortezomib.
Orlowski RZ, et al. ASCO 2018.

*Patients considered Ti due to age or comorbidities.

Age >70 years ➔ Induction + Maintenance

IMROZ: I-VRD

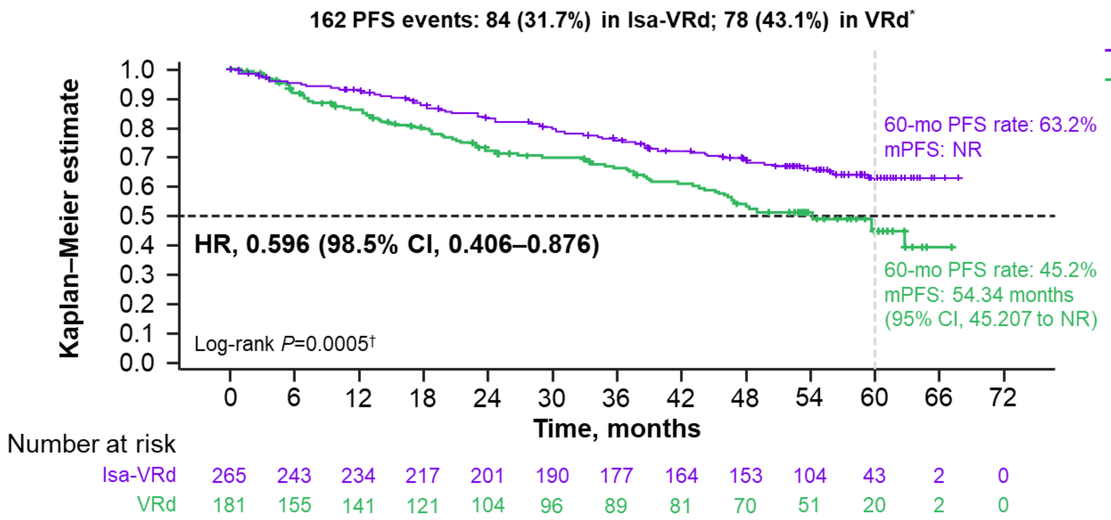


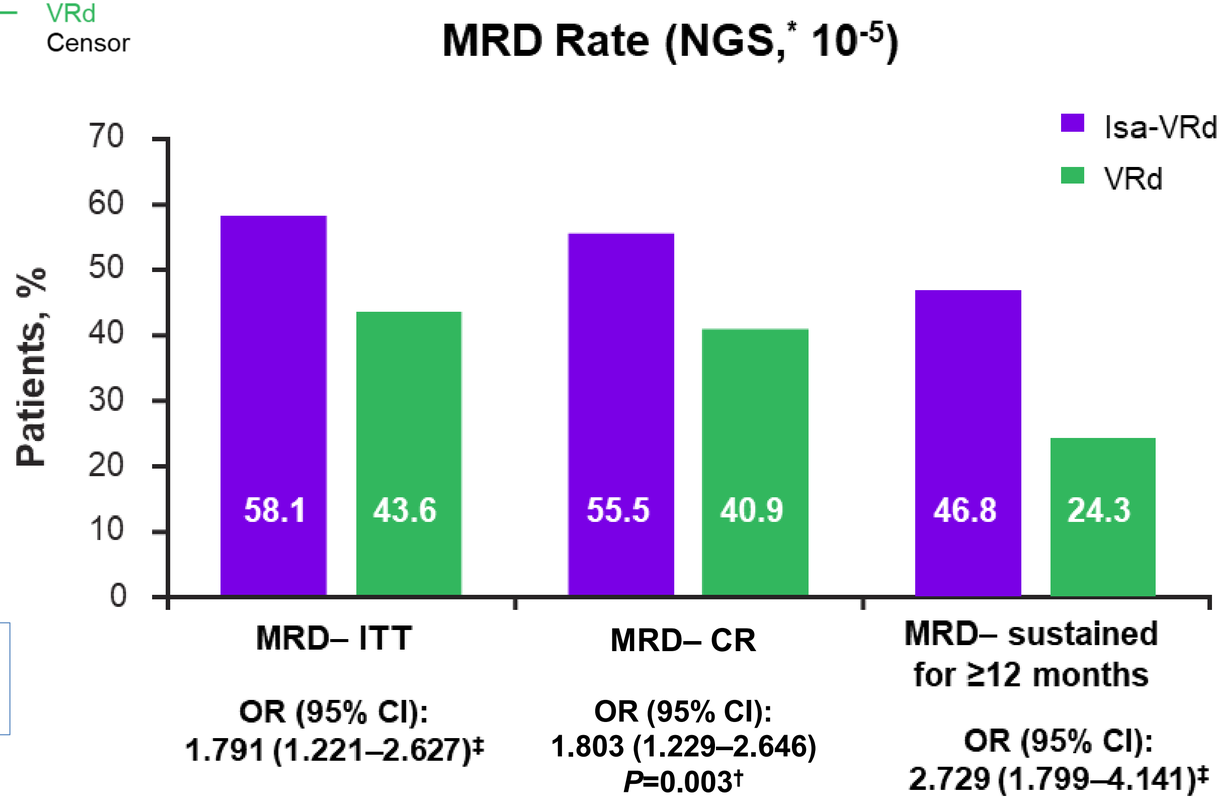
At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

*Cutoff date for PFS analysis: September 26, 2023 (median follow-up, ~5 years). †Nominal one-sided *P* value.
NR, not reached.

Facon T, ASCO 2024

Age >70 years ➔ Induction + Maintenance
IMROZ: I-VRD





Time to MRD–, median (95% CI)
Isa-VRd: 14.72 (11.53–24.08) months
VRd: 32.79 (17.51–45.11) months

Isa-VRd followed by Isa-Rd resulted in deep response rates, with a significant improvement in the MRD– CR rate, as well as higher rates of MRD– and sustained MRD– for ≥12 months

Facon T, ASCO 2024

Age >70 years ➔ Induction + Maintenance

CEPHEUS: D-VRD

Key eligibility criteria:

- NDMM (TIE or transplant deferred)
- ECOG PS ≤2
- **IMWG frailty score of 0–1**

1:1 randomization (N=395)

	Cycles 1–8	Cycles 9+
VRd	**V**: 1.3 mg/m^2 SC days 1, 4, 8, 11 **R**: 25 mg PO days 1–14 **d**: 20 mg PO days 1, 2, 4, 5, 8, 9, 11, 12	**R**: 25 mg PO days 1–21 **d**: 40 mg PO days 1, 8, 15, 22
DVRd	**Dara**: 1800 mg SC[a] QW cycles 1–2, Q3W cycles 3–8 **VRd**: schedule as above	**Dara**: 1800 mg SC[a] Q4W **Rd**: schedule as above
	21-day cycles	28-day cycles until disease progression or unacceptable toxicity

Primary endpoint:

- Overall MRD (≥CR) negativity

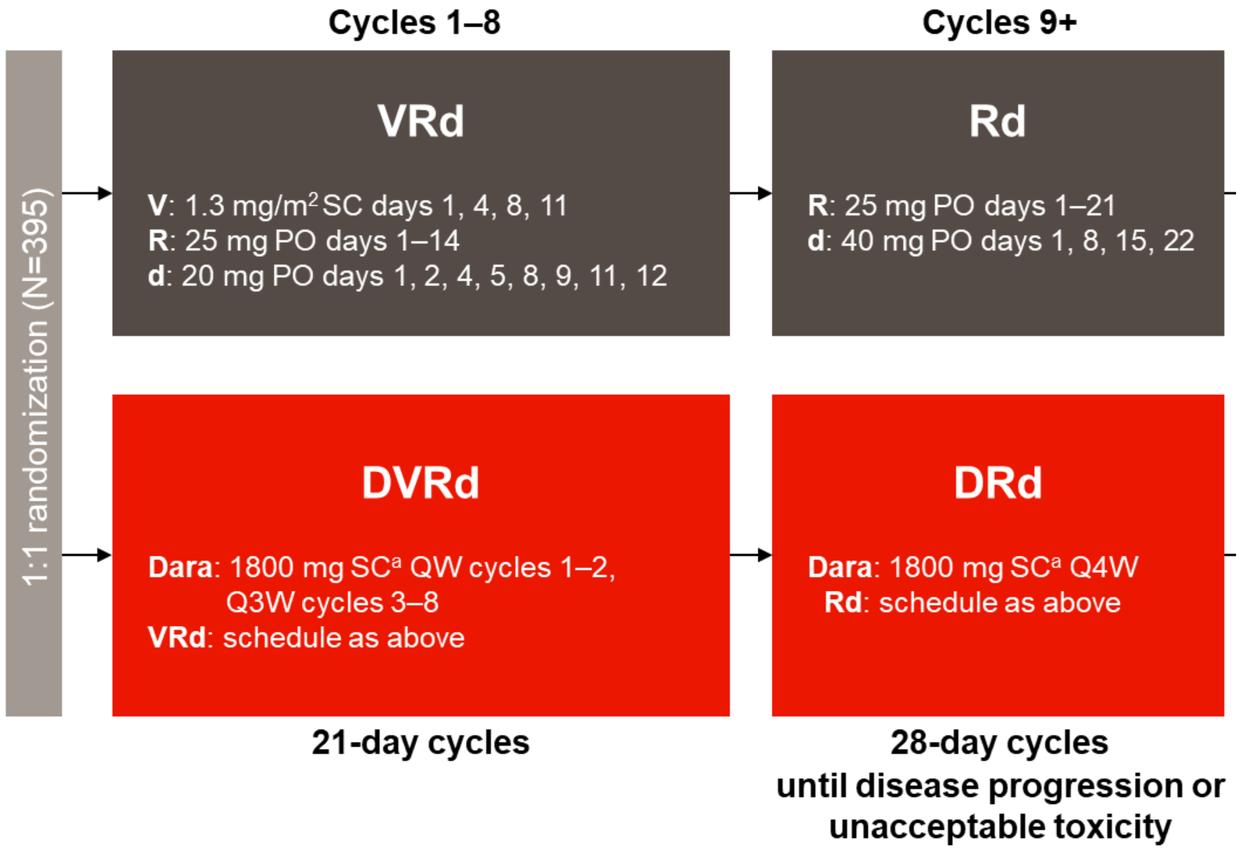
Key secondary endpoints:

- PFS
- Sustained MRD (≥CR) negativity (≥12 months)
- ≥CR

Presented by S Zweegman at the 6th European Myeloma Network (EMN) Meeting; April 10–12, 2025; Athens, Greece

Age >70 years ➔ Induction + Maintenance

CEPHEUS: D-VRD



Characteristic	D-VRd (*n*=197)	VRd (*n*=198)
Age		
Median (range) (years)	70 (42–79)	70 (31–80)
Distribution, no. (%)		
<65 years	36 (18.3)	35 (17.7)
65 to <70 years	52 (26.4)	53 (26.8)
≥70 years	109 (55.3)	110 (55.6)
Age/transplant eligibility, no. (%)		
<70 years and transplant ineligible	35 (17.8)	35 (17.7)
<70 years and transplant deferred	53 (26.9)	53 (26.8)
≥70 years	109 (55.3)	110 (55.6)

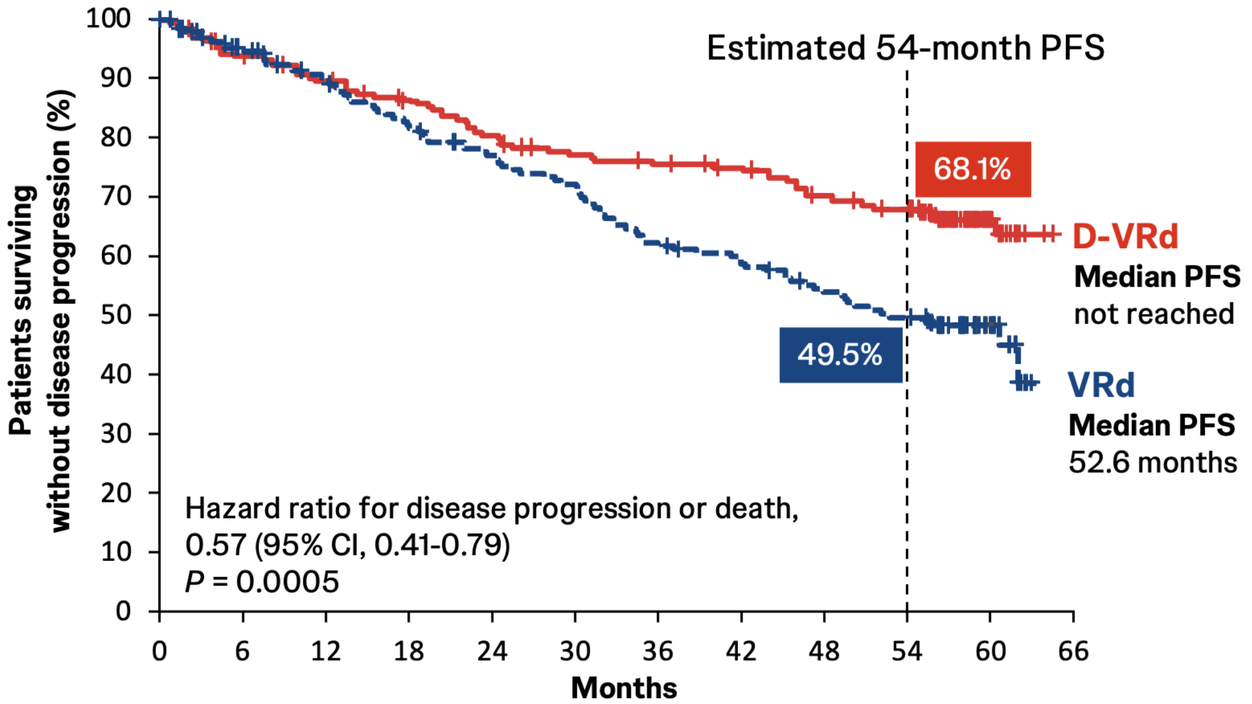
Usmani SZ, Nat Med, 2025

CEPHEUS: D-VRD

PFS in ITT population

Median follow-up was 58.7 months

Daratumumab significantly improved PFS, with a 43% reduction in the risk of progression or death



No. at risk:

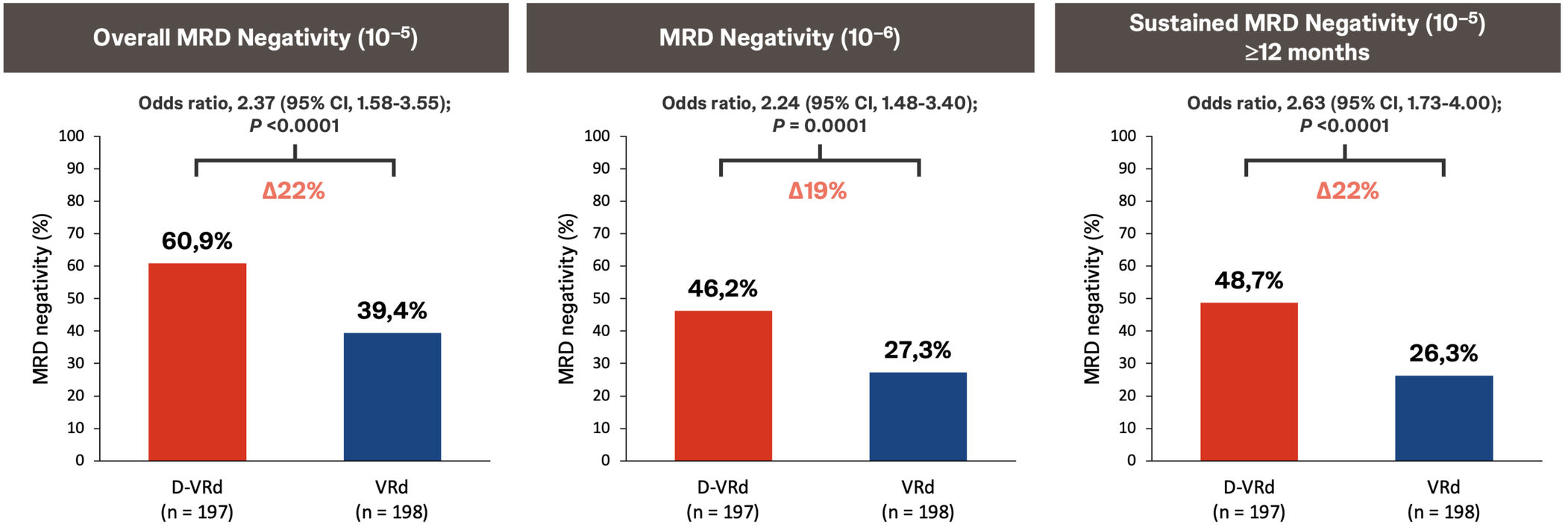
D-VRd	197	180	170	160	149	140	136	132	122	115	33	0
VRd	198	174	157	143	131	123	105	98	88	81	21	0

PFS, progression-free survival; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; CI, confidence interval.

Usmani SZ, et al. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil.

CEPHEUS: D-VRD

Overall and Sustained MRD-negativity[a] Rates



Daratumumab led to deeper MRD responses and a higher sustained MRD-negativity rate

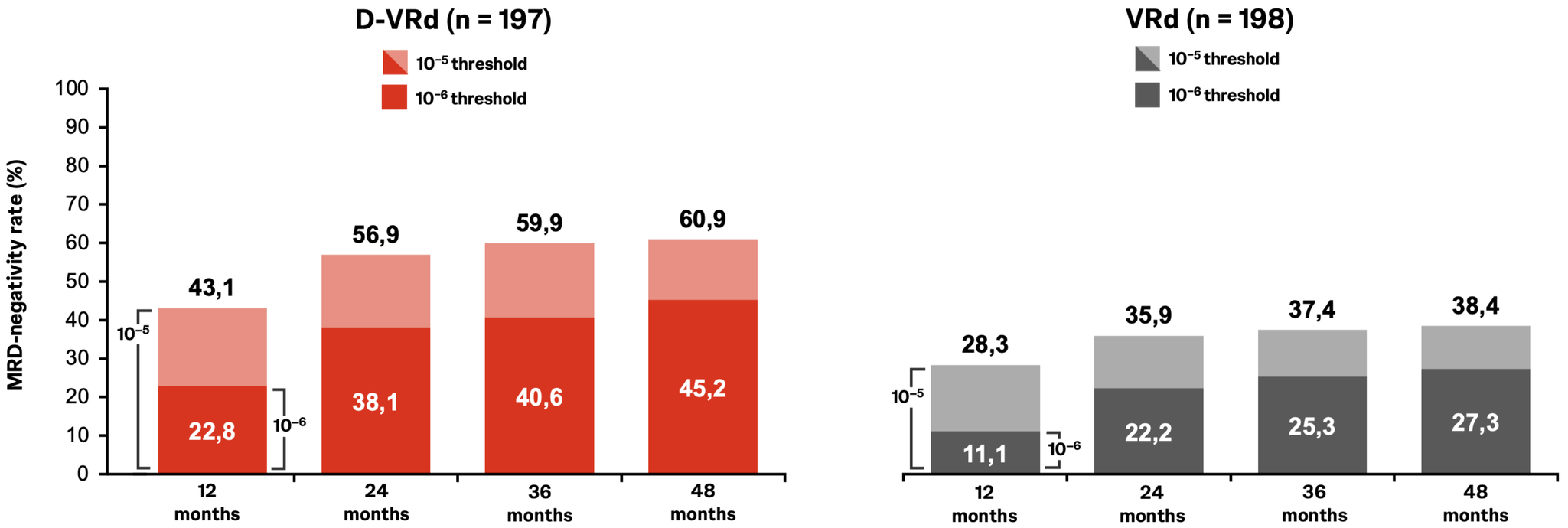
MRD, minimal residual disease; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; CR, complete response. [a]Overall MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (at or below a sensitivity threshold of 10^{-5}) and ≥CR.

Usmani SZ, et al. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil.

- CP-579177

CEPHEUS: D-VRD

Overall and Sustained MRD-negativity[a] Rates



The addition of daratumumab to VRd improved accumulative MRD-negativity rates versus VRd at all prespecified timepoints at both 10^{-5} and 10^{-6}

A window of ±3 months at each time point was applied to complete the bone marrow aspiration.

MRD, minimal residual disease; CI, confidence interval; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; CR, complete response. [a]Overall MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (at or below a sensitivity threshold of 10^{-5}) and ≥CR.

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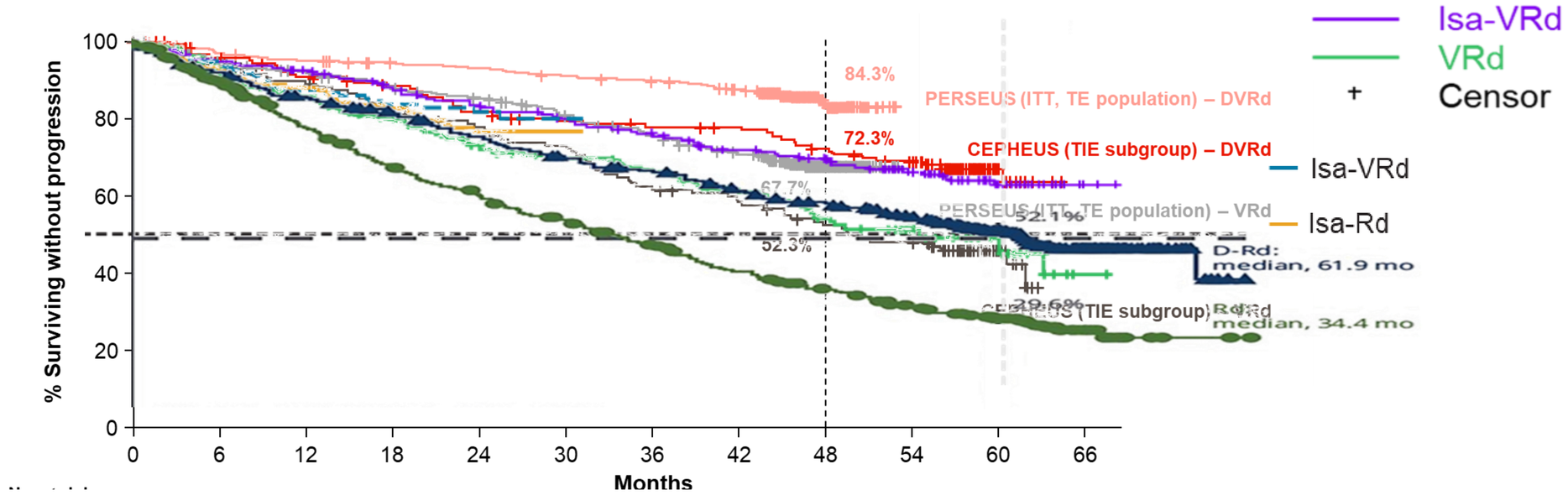
- CP-579177

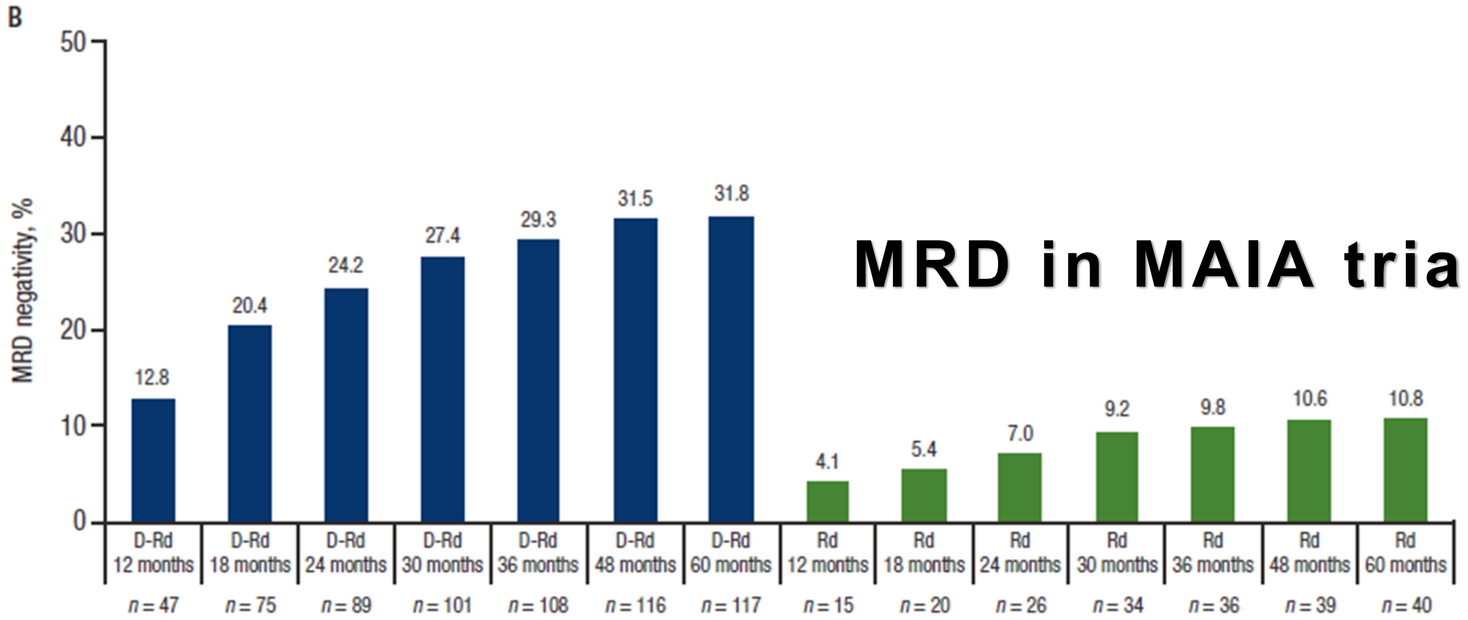
TIE-MM: best option? ➔ PFS

	MAIA		CEPHEUS		IMROZ		BENEFIT	
	D-RD	*RD*	*D-VRD*	*VRD*	*I-VRD*	*VRD*	*I-VRD*	*I-RD*
<65	78	77	36	35	8	9	28	25
65-70			52	53	73	47		
70-75	130	131	109	110	115	68	65	62
75-80	94	90			69	57	42	48
>80	66	71			0	0		



TIE-MM: best option? ➔ PFS

	MAIA		CEPHEUS		IMROZ		BENEFIT	
	D-RD	*RD*	*D-VRD*	*VRD*	*I-VRD*	*VRD*	*I-VRD*	*I-RD*
<65	78	77	36	35	8	9	28	25
65-70			52	53	73	47		
70-75	130	131	109	110	115	68	65	62
75-80	94	90			69	57	42	48
>80	66	71			0	0		



MRD in MAIA trial!

Key messages:

1) **La valutazione delle risposte non è più sufficiente per valutare andamento terapia**

2) **La MRD è ad oggi il più forte predittore di PFS e OS (marker surrogato)**

3) **Su può valutare in NGS o in NGF ➔ metodiche equivalenti dal punto di vista regolatorio**

4) **Il costo non è un problema, entrambe recuperabili risparmiando un mese di Daratumumab**

5) **La determinazione dell'MRD è raggiungibile nella pratica clinica con una metodica standardizzata e DEVE essere il nuovo standard per la valutazione delle risposte nei pazienti con MM**

6) **Le quadruplette sono oggi lo standard terapeutico di prima linea per tutti I pazienti in grado di sostenerle ➔ DaraRD resta lo standard per i pazienti frail**