Highlights nel Mieloma Multiplo in prima linea

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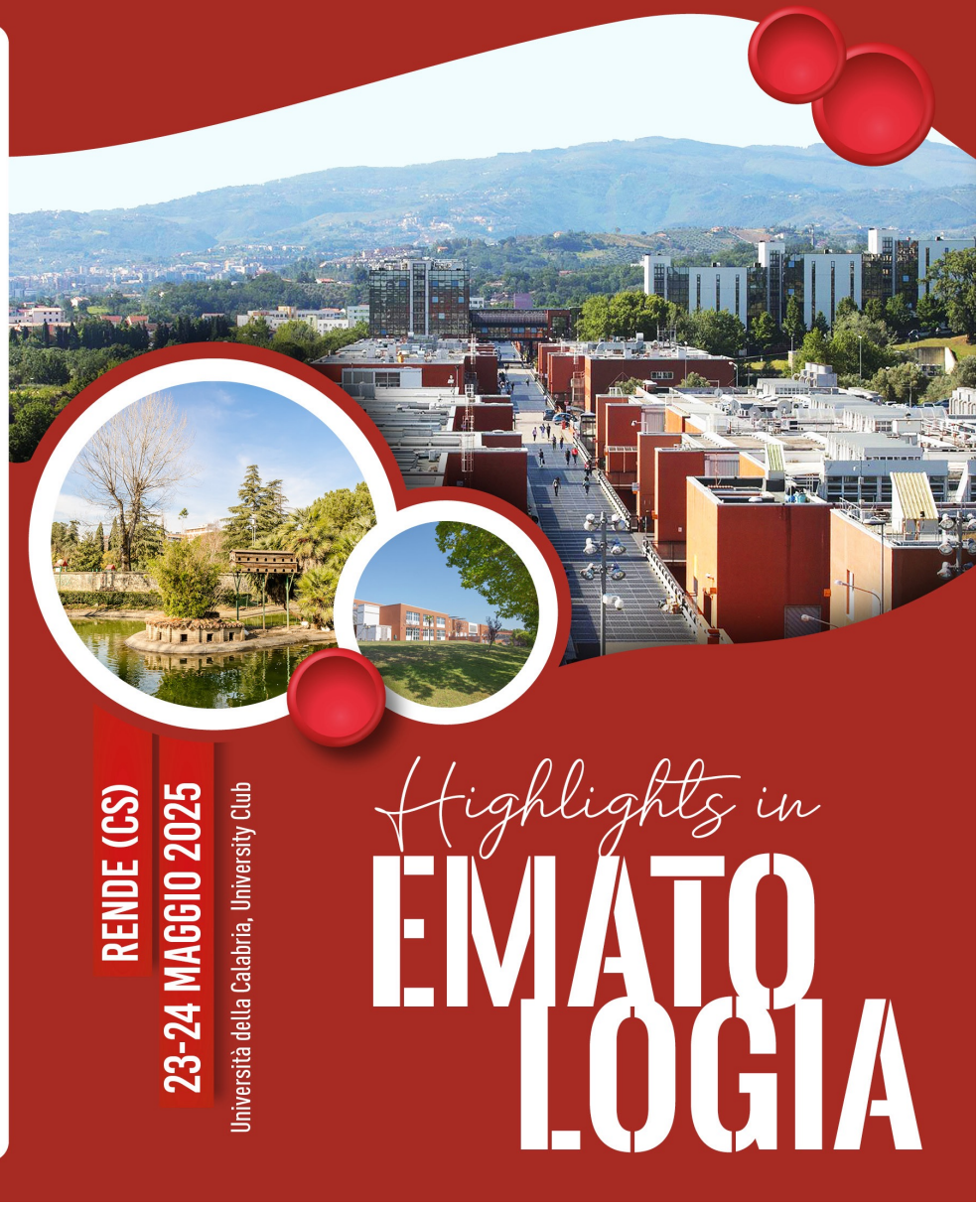
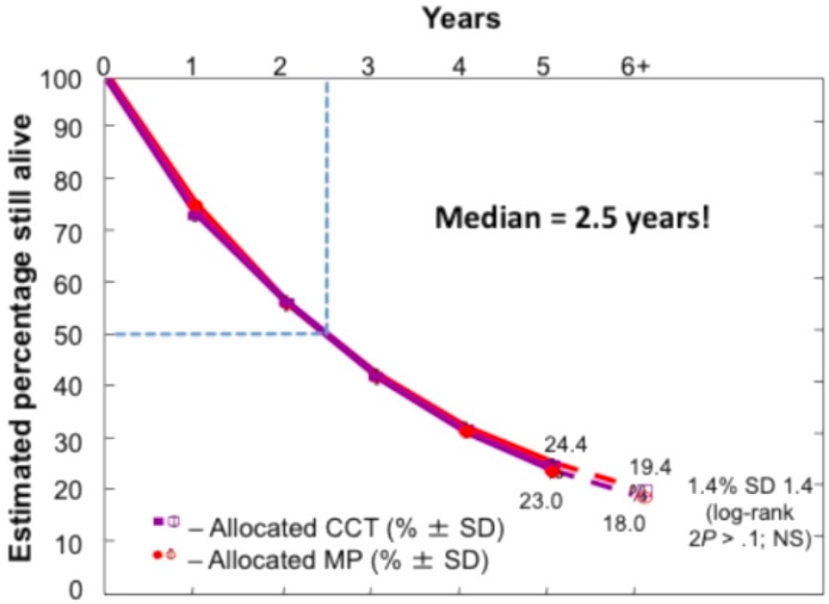


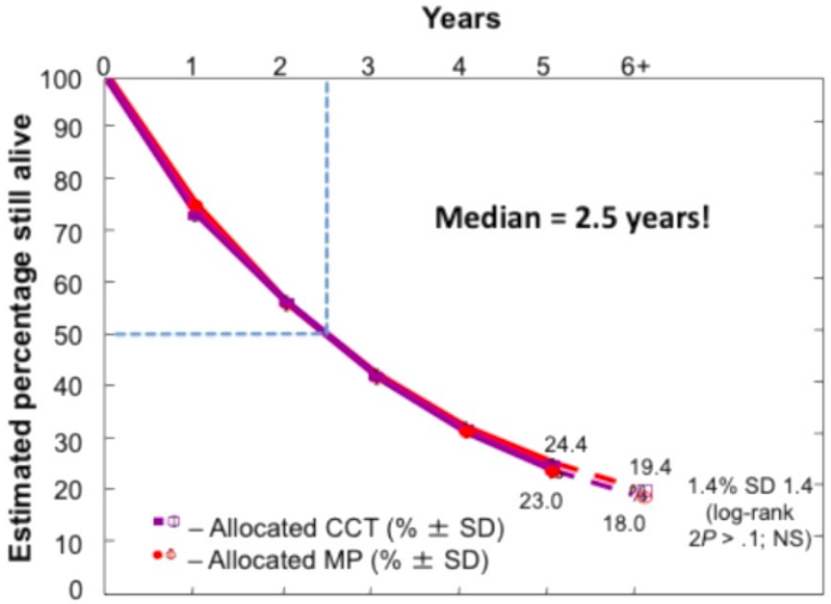
Myeloma outcomes…over 3 decades



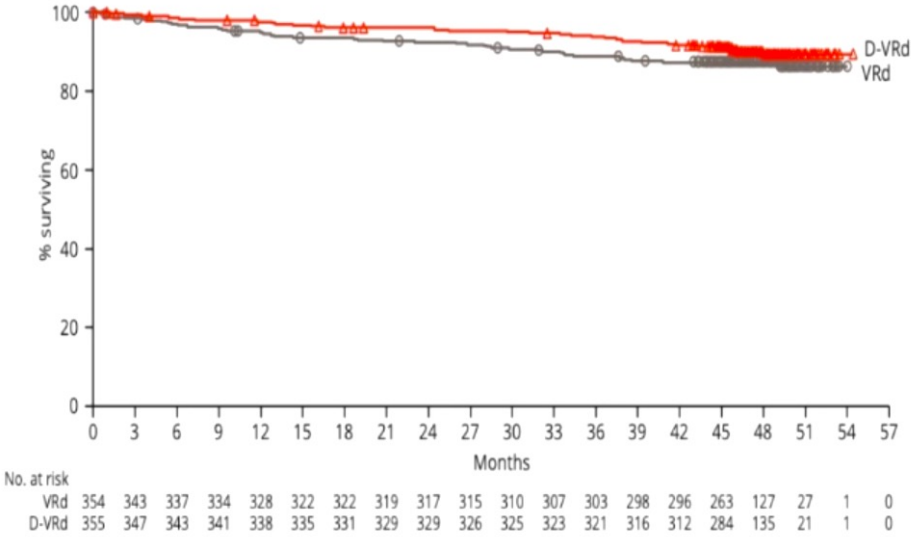
Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;12:3832


PEARL JAM
LONG ROAD

Myeloma outcomes…over 3 decades



Myeloma Trialists' Collaborative Group. *J Clin Oncol.* 1998;16;12:3832



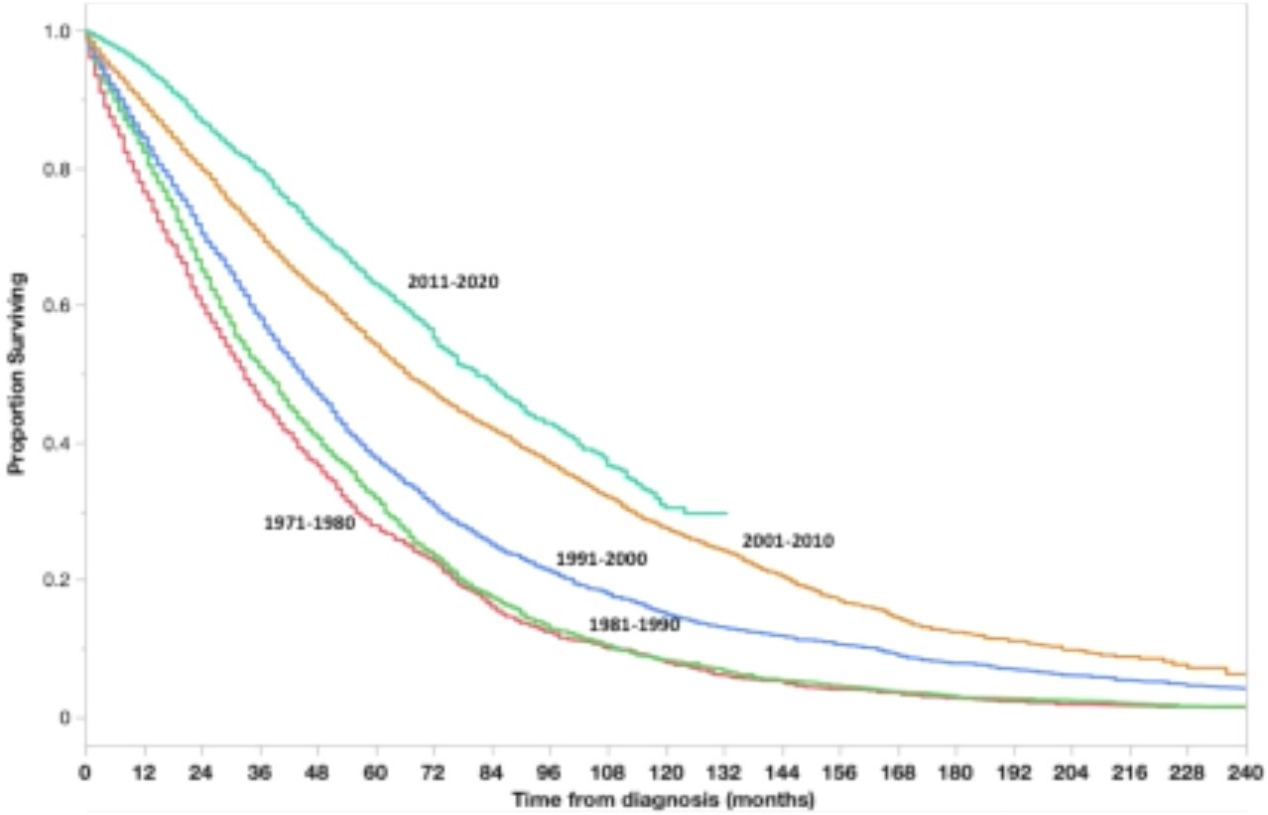
Sonneveld P et al. N Engl J Med2024;390:301-313

How did we get here?

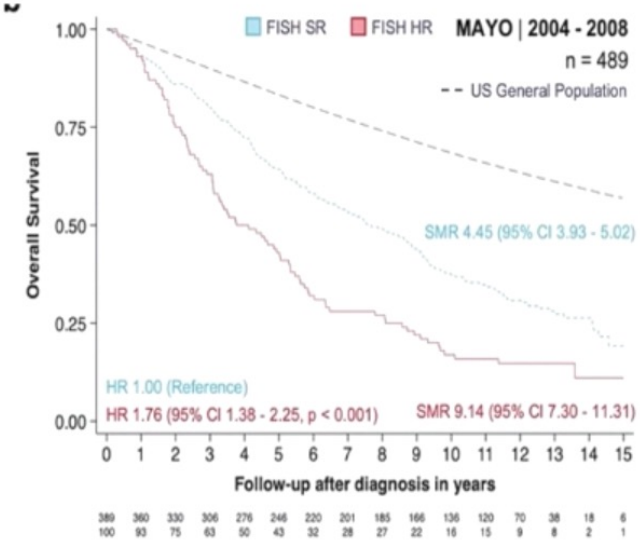
- **Better understanding of disease biology**
  - Unraveling the drivers of heterogeneity in the disease
- **Development of new drugs with distinct mechanisms of action**
  - Deriving novel, effective combinations from these
- **Appropriate use of autologous stem cell transplant as consolidation**
  - Consistent use of maintenance/long-term therapy for disease control
- **Timely and effective management of disease and treatment-related complications through supportive care measures**
  - Infections, bone disease, renal insufficiency, neuropathy etc.

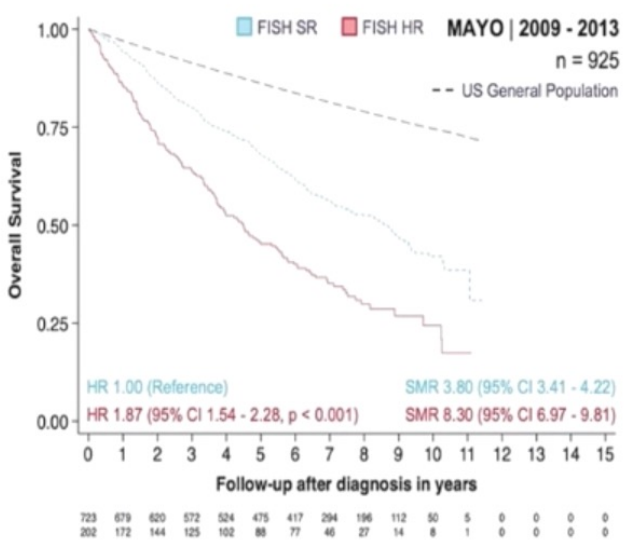
Kumar S. ASH 2024

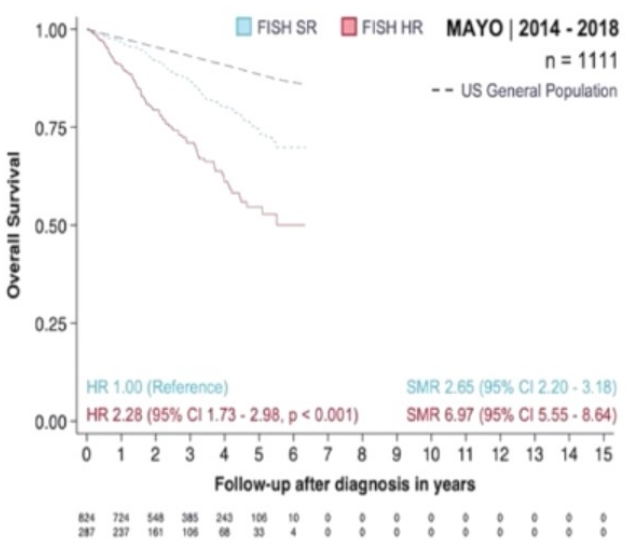
Survival is improving…but much work remains



Progress …. But not same for all

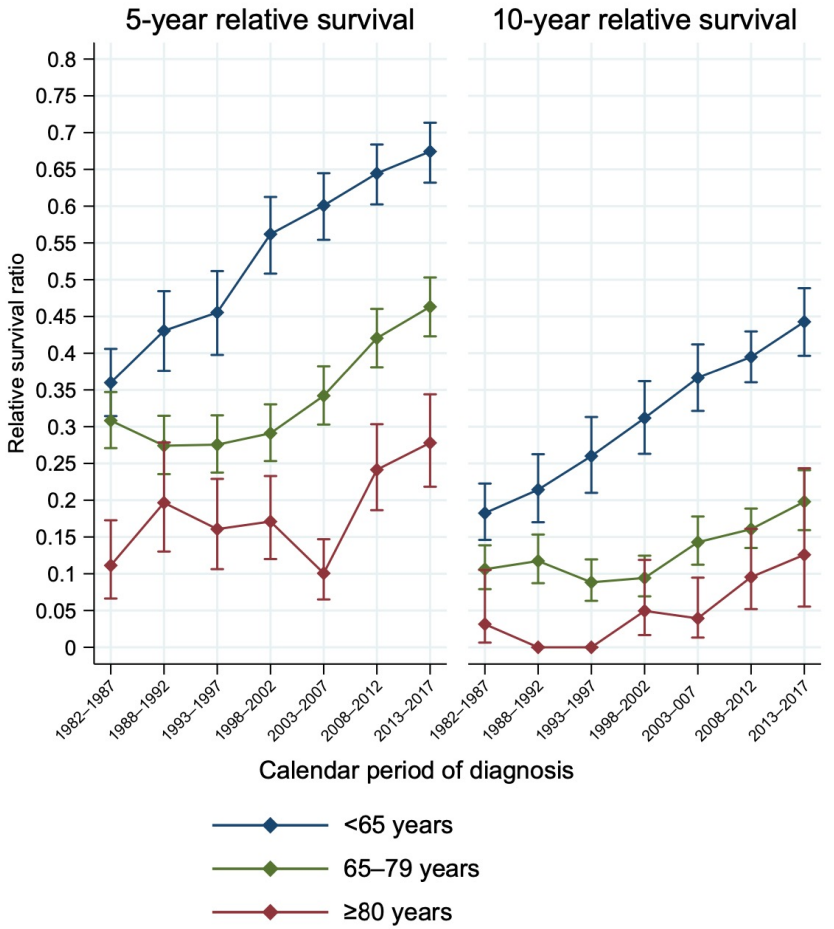






bjh research paper

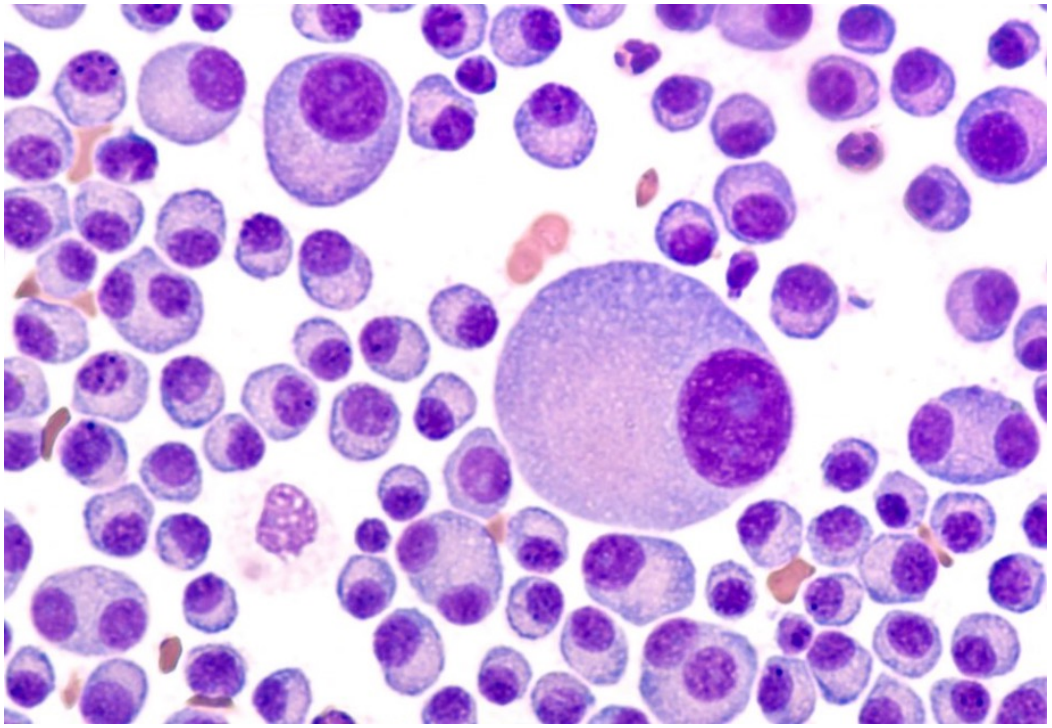
Incidence and survival of multiple myeloma: a population-based study of 10 524 patients diagnosed 1982–2017



Five- and 10-year relative survival ratios with 95% confidence intervals by age group and calendar period of diagnosis.

Langseth O. et al, British Journal of Haematology, 2020, 191, 418–425

What about new EHA/EMN guidelines?



Dimopoulos M.A et. al
Nat Clin Oncol Rev 2025 *in press*

2021 Guidelines

Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up

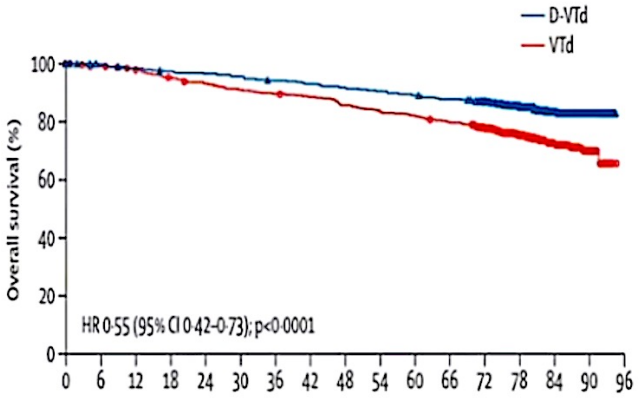
Meletios A. Dimopoulos[1], Philippe Moreau[2], Evangelos Terpos[1], María-Victoria Mateos[3], Sonja Zweegman[4], Gordon Cook[5], Michel Delforge[6], Roman Hájek[7], Fredrik Schjesvold[8,9], Michele Cavo[10], Hartmut Goldschmidt[11], Thierry Facon[12], Hermann Einsele[13], Mario Boccadoro[14], Jesús San-Miguel[15], Pieter Sonneveld[16], Ulrich Mey[17], on behalf of the EHA Guidelines Committee and the ESMO Guidelines Committee

Correspondence: EHA Executive Office/EHA Guidelines Committee (guidelines@ehaweb.org), or ESMO Head Office/ESMO Guidelines Committee (clinicalguidelines@esmo.org).

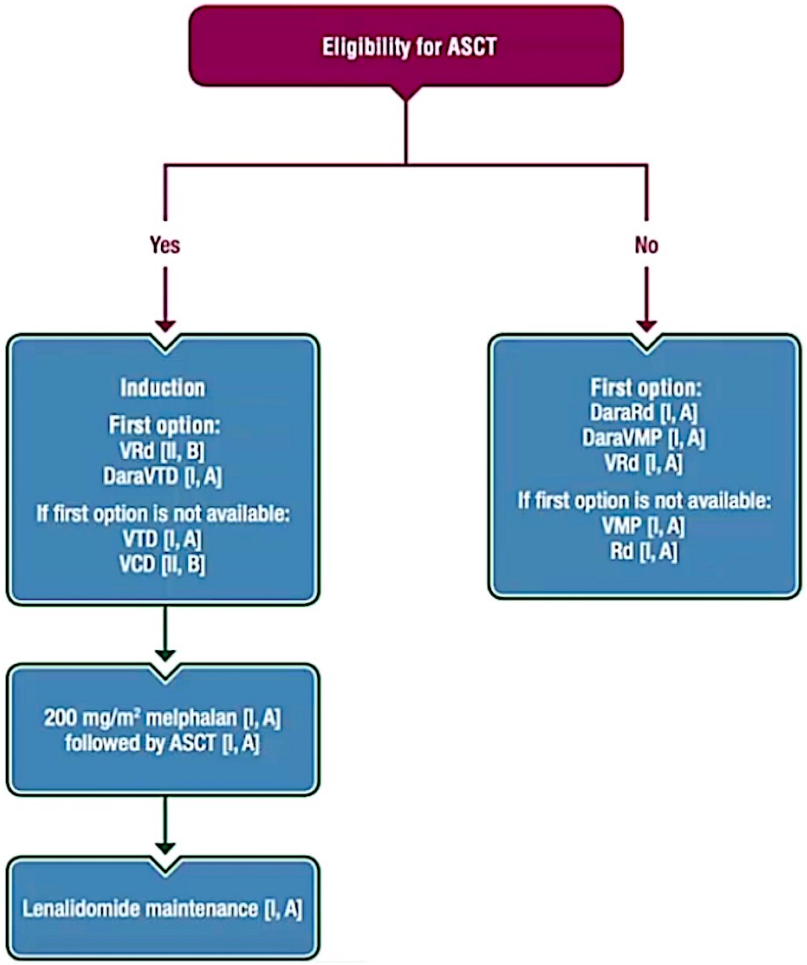
Dimopoulos MA et al. Hemasphere 2021
Dimopoulos MA er al. Ann Oncol 2021

Cassiopeia update (D-VTD arm)

mPFS = 84 months
mOS NR, (72m-OS = 87%)

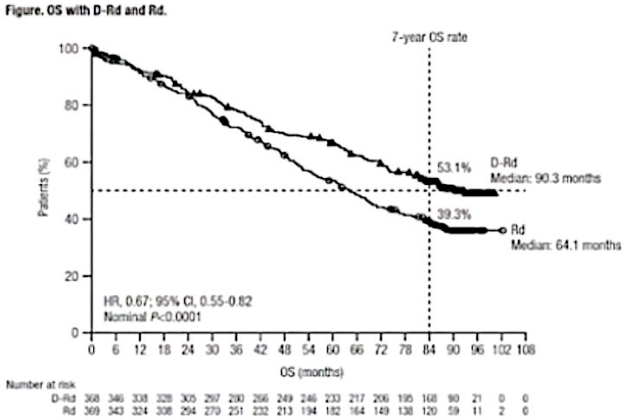


Moreau P et al, Lancet Oncol 2024



Maia update (D-RD arm)

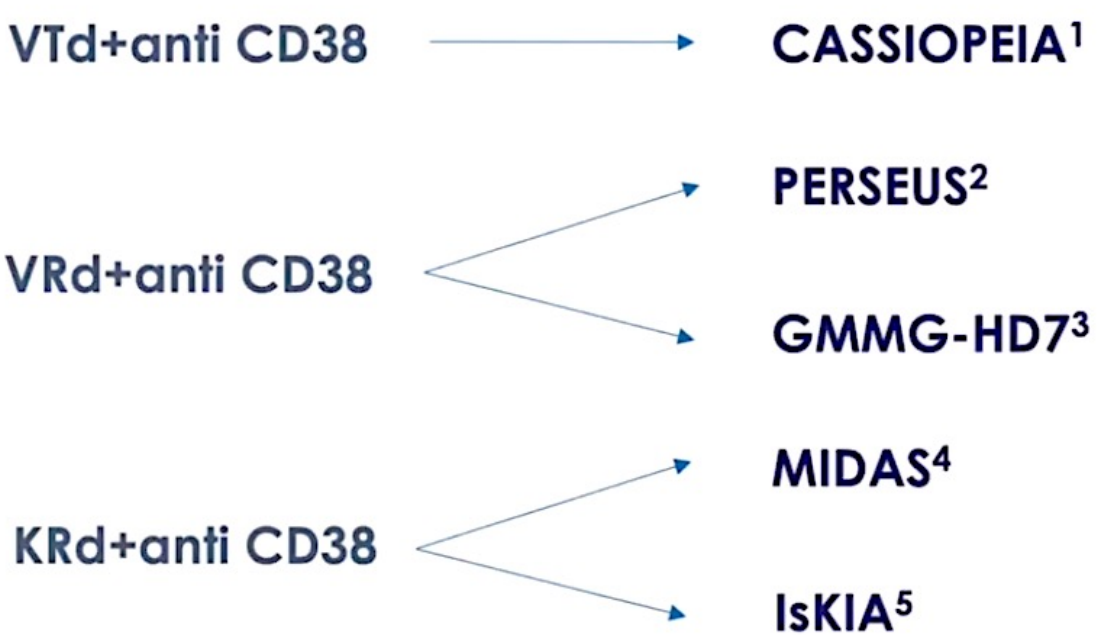
mPFS = 62 months
mOS = 90 months



Facon T et al, EHA 2024

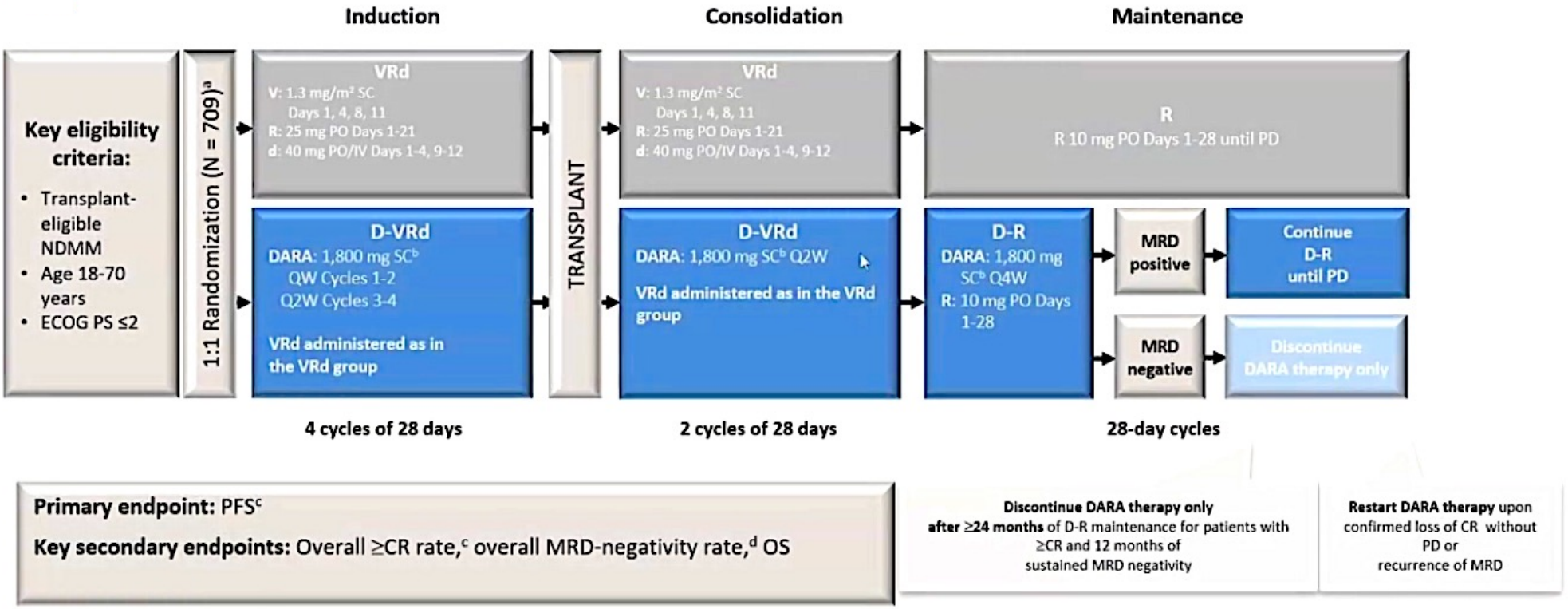
Triplet or quadruplet regimen in transplant eligible NDMM

Data from 5 phase III randomized trials



1. Moreau P *et al. Lancet* 2019394:29-38 / *Lancet Oncol*. 2024;25:1003-14 ; **2.** Sonneveld P et *al. N Engl J Med.* 2023;390:301-13 ;
3. Mai EK *et al. J Clin Oncol*. 2024:JCO2402266. ; **4.** Perrot A *et al. Blood* 2025 **5.** Gay F *et al. Blood* 2023;142 (suppl 1-ASH):4

Dara-VRD approval in 2024 according on the results of PERSEUS trial



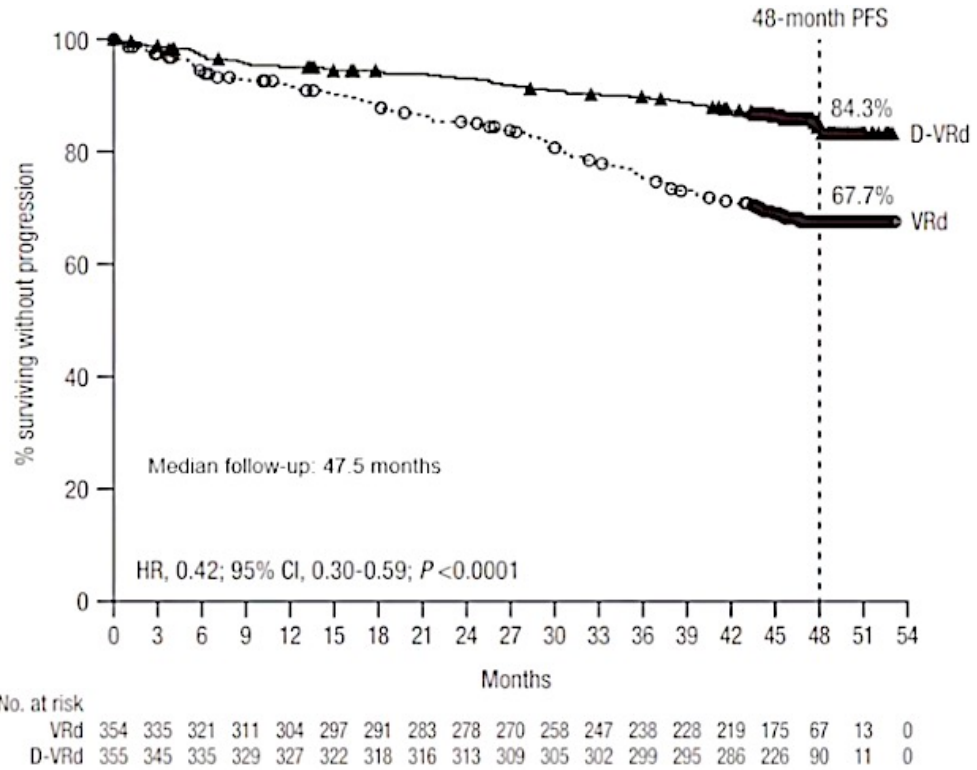
Primary endpoint: PFS[c]

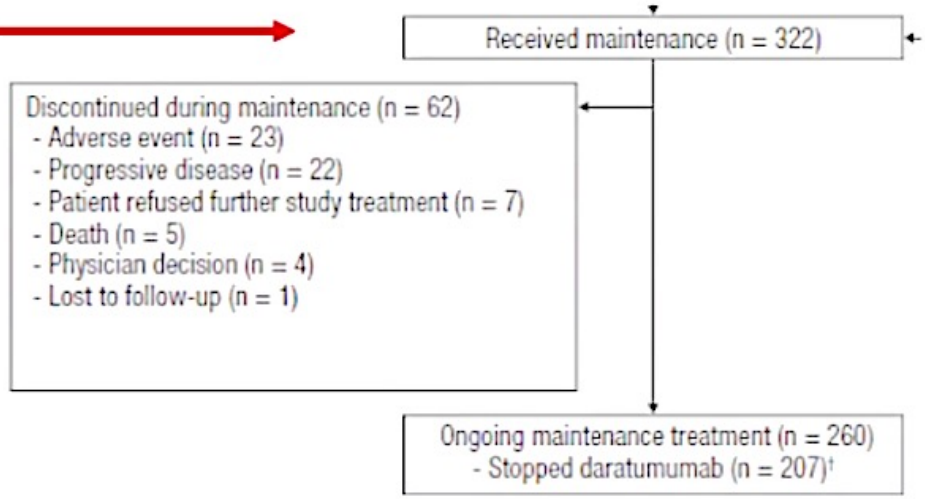
Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

Dara-VRD approval in 2024 according on the results of PERSEUS trial





P Sonneveld et al, N Engl J Med 2024

Modeling Long-Term Progression-Free Survival in Transplant-Eligible and Transplant-Ineligible Newly Diagnosed Multiple Myeloma Treated With Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone

Pieter Sonneveld[1], Sonja Zweegman[2], Thierry Facon[3], Vania Hungria[4], Nizar J Bahlis[5], Philippe Moreau[6], Hermann Einsele[7], Mario Boccadoro[8], Fredrik Borgsten[9], Annette Lam[9], Marjorie Nobrega[9], Viktor Kovács[10], Jianping Wang[11], Melissa Rowe[12], Anna Sitthi-Amorn[11], Robin L Carson[11], Meletios A Dimopoulos[13], Paula Rodriguez-Otero[14], Saad Z Usmani[15]

[1]Erasmus MC Cancer Institute, Rotterdam, Netherlands. [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands. [3]University of Lille, CHU de Lille, Lille, France. [4]Clínica Médica São Germano, São Paulo, Brazil. [5]Arne Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada. [6]Laboratoire d'anatomo-pathologie, CHU de Nantes, Nantes, France. [7]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Wurzburg, Germany. [8]University of Turin, Turin, Italy. [9]Johnson & Johnson, Raritan, NJ, USA. [10]Evidera, Budapest, Hungary. [11]Johnson & Johnson, Spring House, PA, USA. [12]Johnson & Johnson, High Wycombe, UK. [13]National and Kapodistrian University of Athens, Athens, Greece. [14]Department of Hematology, Cancer Center Clínica Universidad de Navarra, Cena, Pamplona, Spain. [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA.

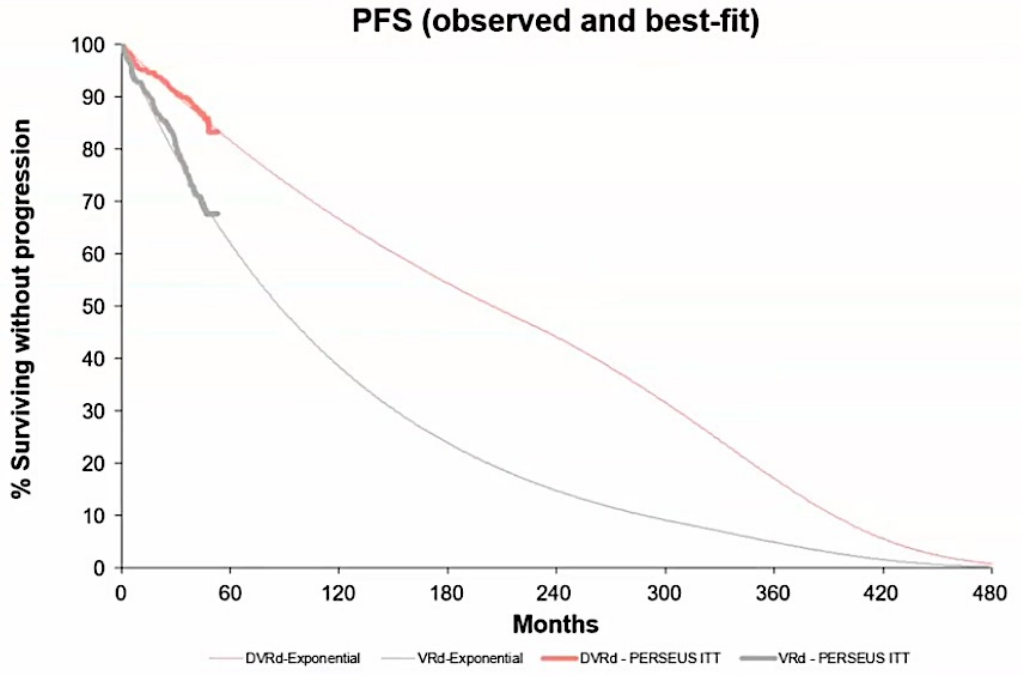
Presented by P Sonneveld at the 6th European Myeloma Network (EMN) meeting; April 10–12, 2025; Athens, Greece

PERSEUS: Significantly Longer Projected PFS With DVRd

TE NDMM

- **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

The best-fit projection estimates a 118-month longer PFS benefit with DVRd vs VRd



DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TE, transplant-eligible; VRd, bortezomib, lenalidomide, and dexamethasone.

Presented by P Sonneveld at the 6th European Myeloma Network (EMN) meeting; April 10–12, 2025; Athens, Greece

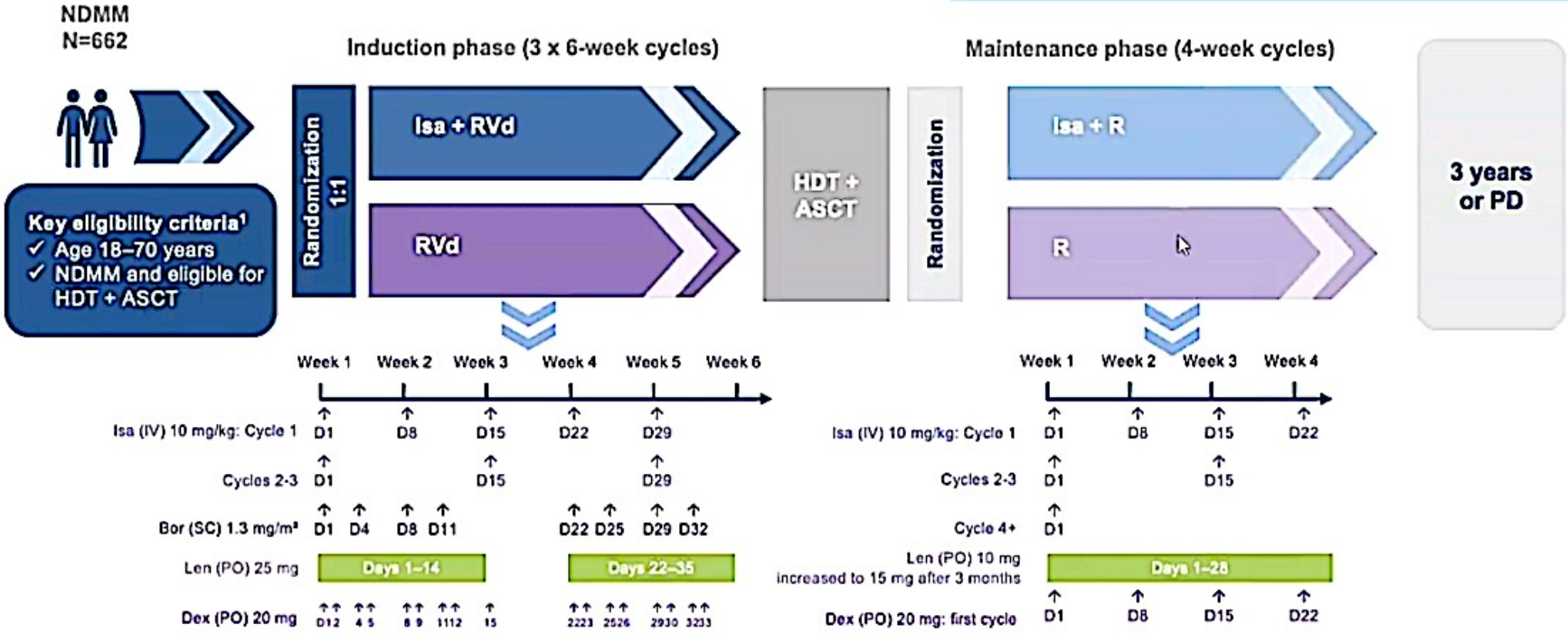
Results of the phase 3 GMMG HD 7 trial

Primary endpoint
- MRD negativity at the end of induction treatment (NGF, sensitivity 10^{-5}) stratified according to R-ISS

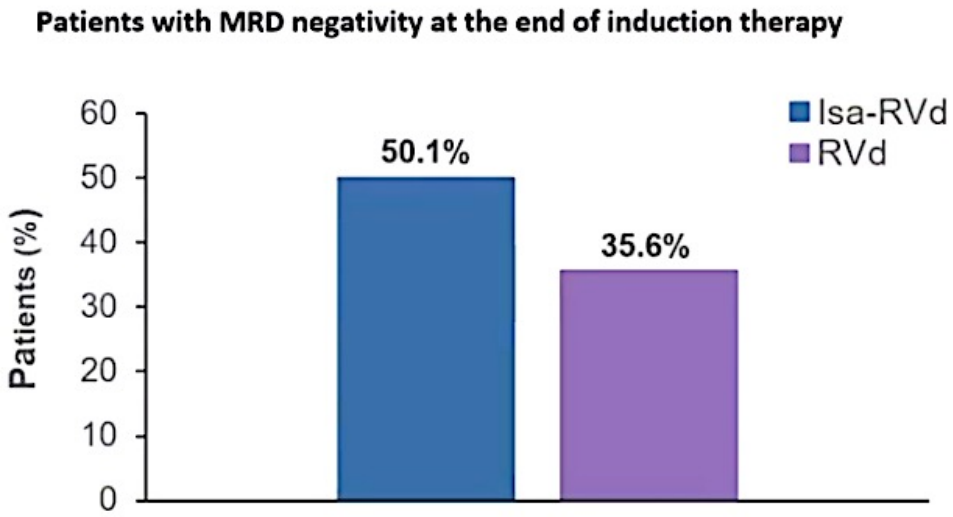
Secondary endpoints
- CR rate
- MRD negativity after intensification

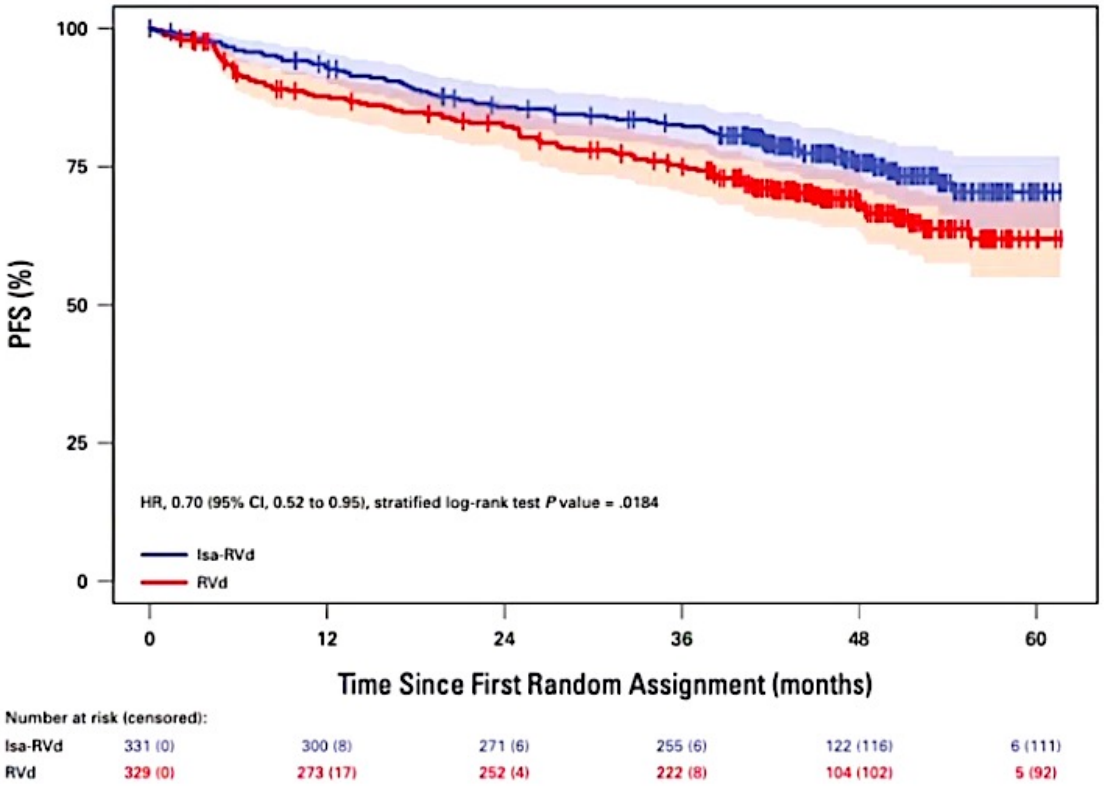
Data cutoff
- Oct 2023

Exploratory endpoints
- ORR
- MRD negativity/VGPR and MRD negativity/CR rates after intensification



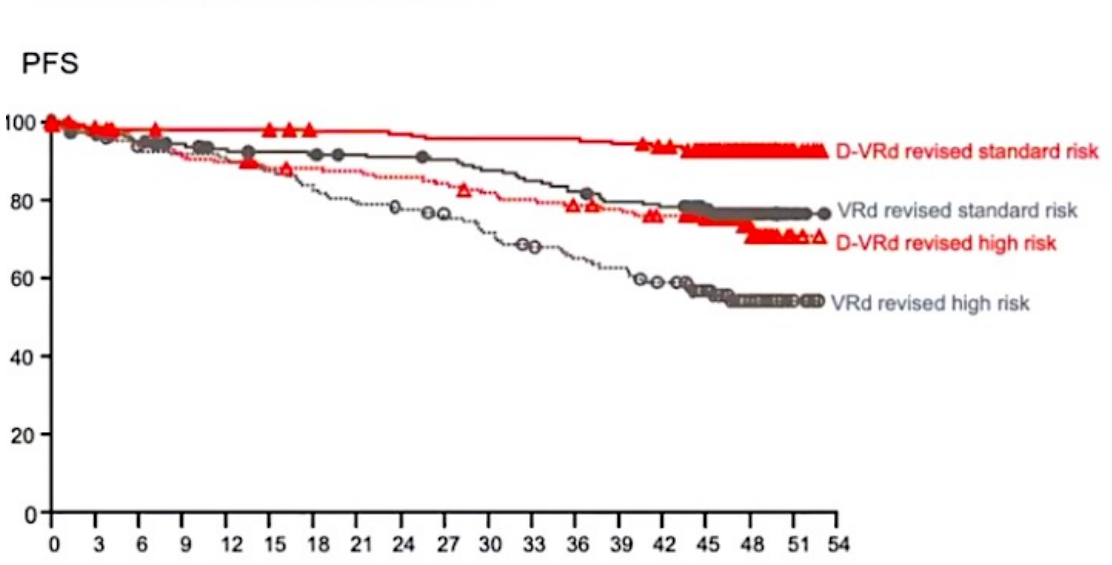
Results of the phase 3 GMMG HD 7 trial



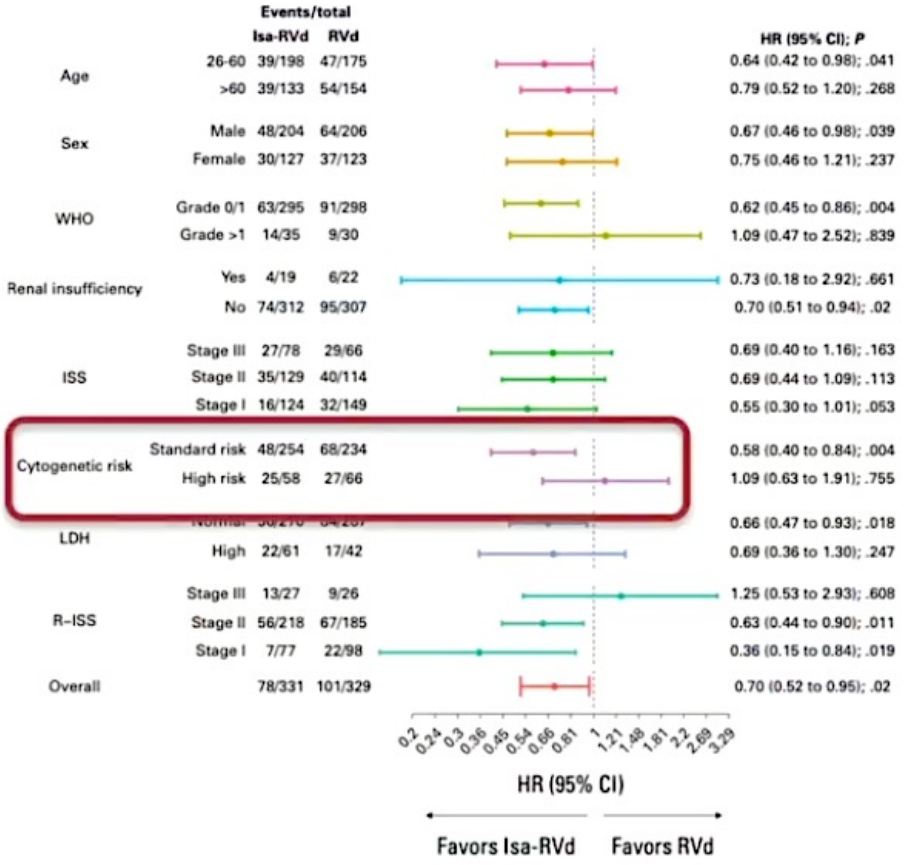


Mai EK et al, J Clin Oncol 2025

Risk-adapted consolidation

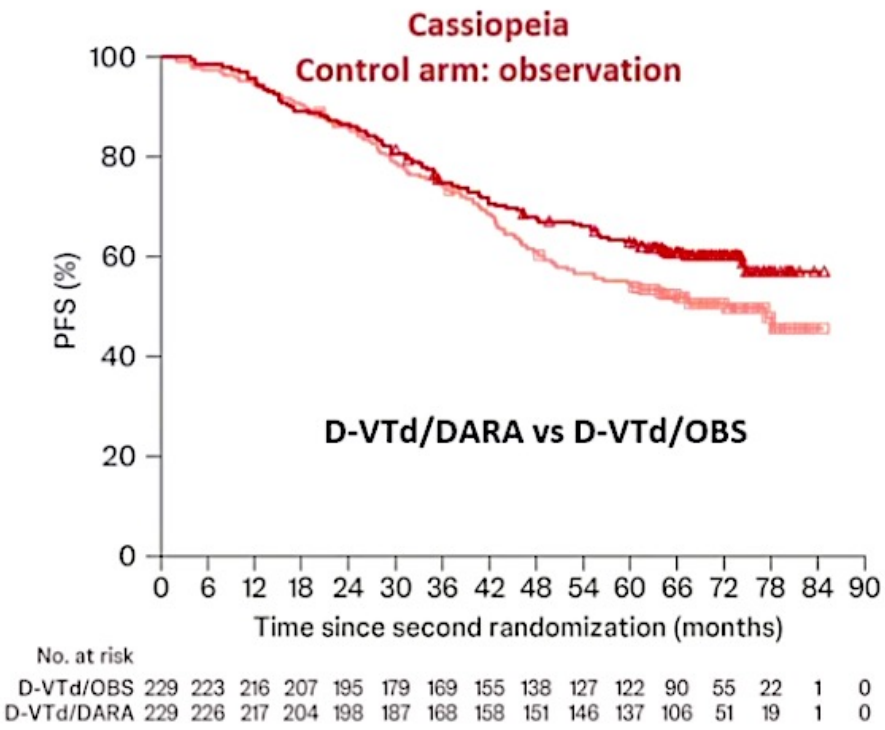


Dimopoulos MA et al, IMS 2024



Mai EK et al, J Clin Oncol 2025

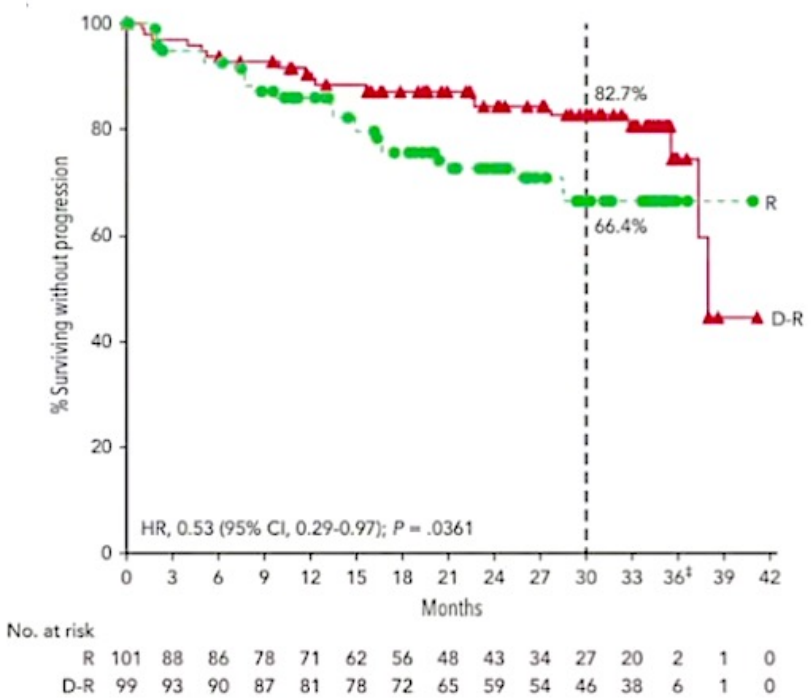
Maintenance with Daratumumab



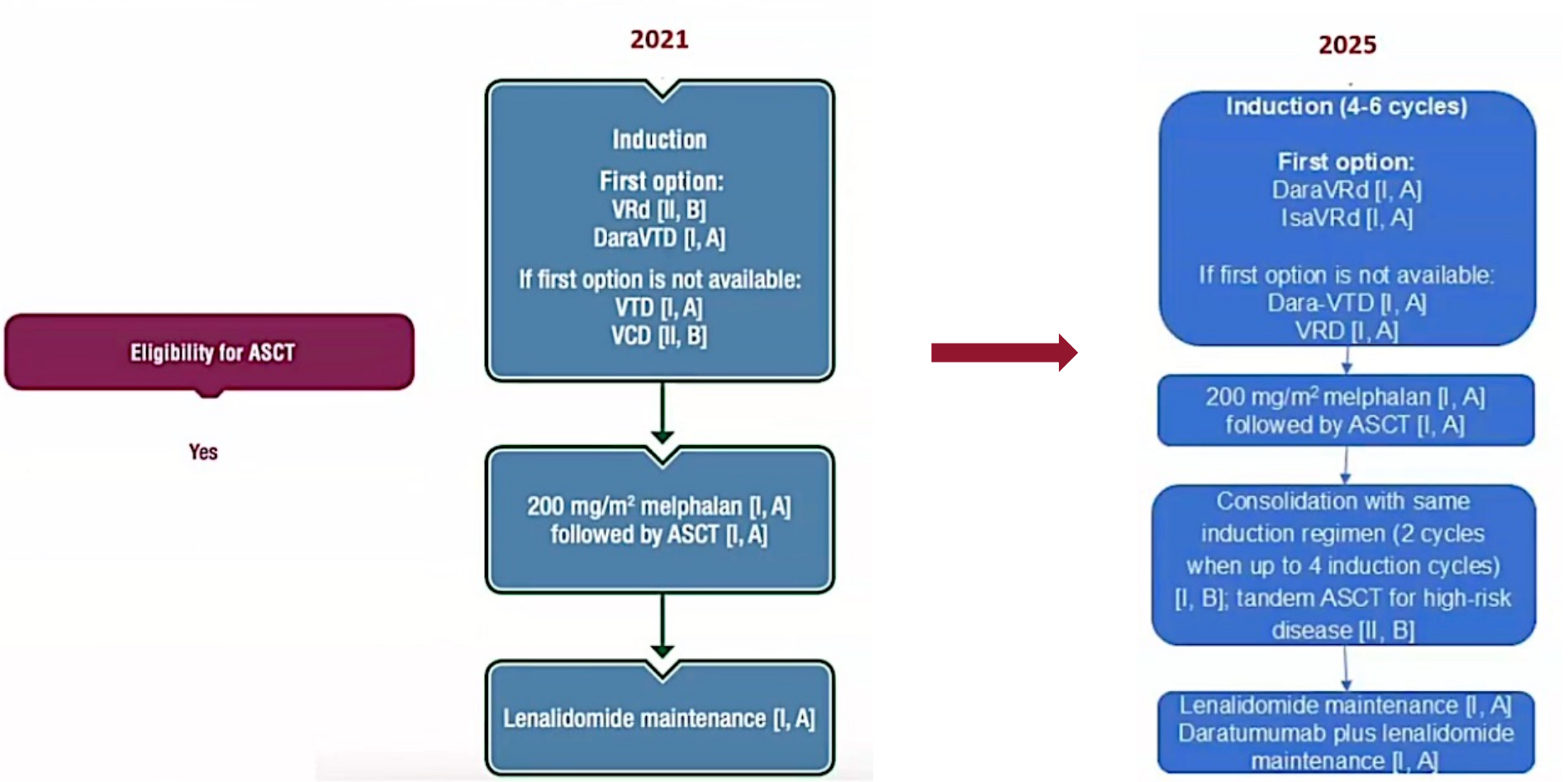
Moreau P et al, Lancet Oncol 2024

Perseus
No second randomisation

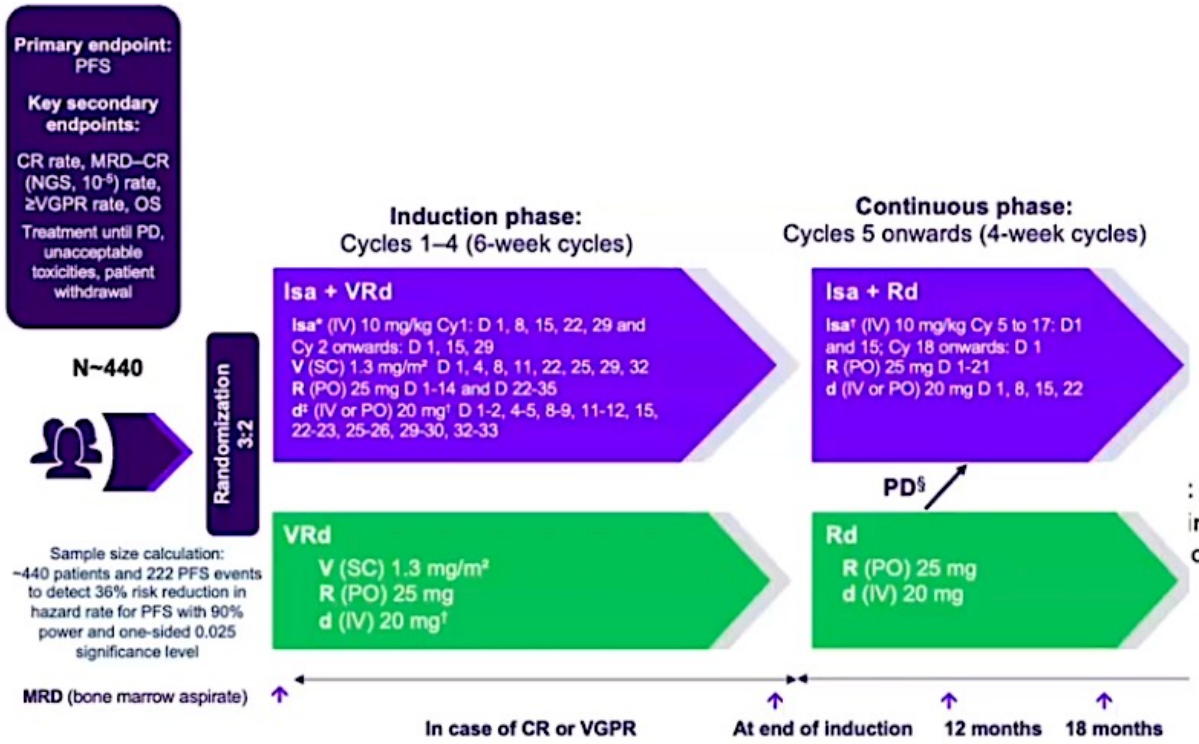
Auriga trial
VRD induction, MRD+

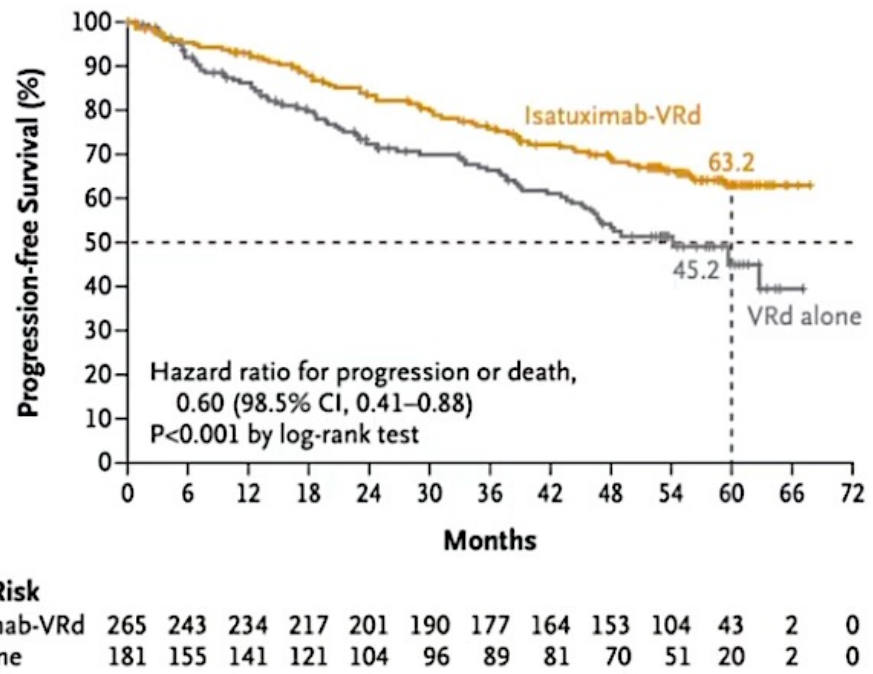


Badros A et al, Blood 2025


2021
Induction
First option:
VRd [II, B]
DaraVTD [I, A]
If first option is not available:
VTD [I, A]
VCD [II, B]
Eligibility for ASCT
Yes
200 mg/m² melphalan [I, A] followed by ASCT [I, A]
Lenalidomide maintenance [I, A]
2025
Induction (4-6 cycles)
First option:
DaraVRd [I, A]
IsaVRd [I, A]
If first option is not available:
Dara-VTD [I, A]
VRD [I, A]
200 mg/m² melphalan [I, A] followed by ASCT [I, A]
Consolidation with same induction regimen (2 cycles when up to 4 induction cycles) [I, B]; tandem ASCT for high-risk disease [II, B]
Lenalidomide maintenance [I, A]
Daratumumab plus lenalidomide maintenance [I, A]

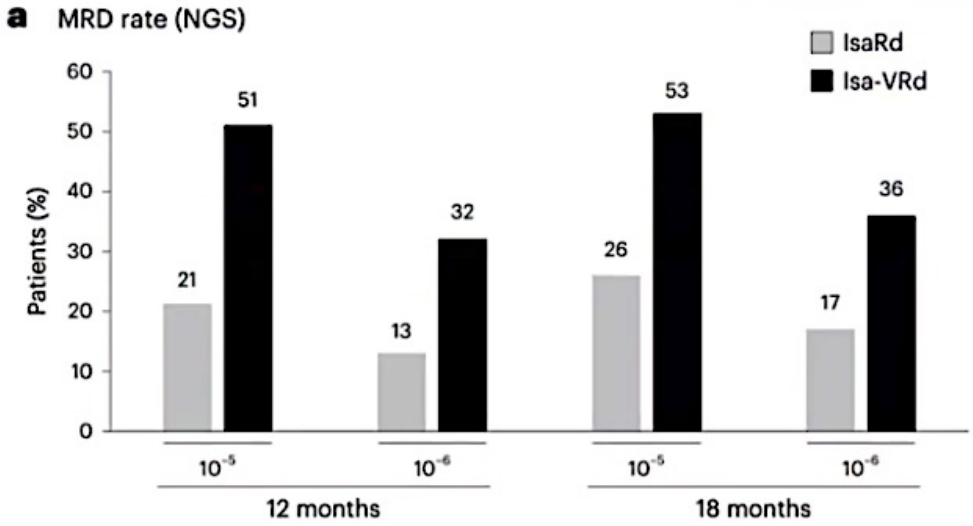
Results of the phase 3 IMROZ registration trial





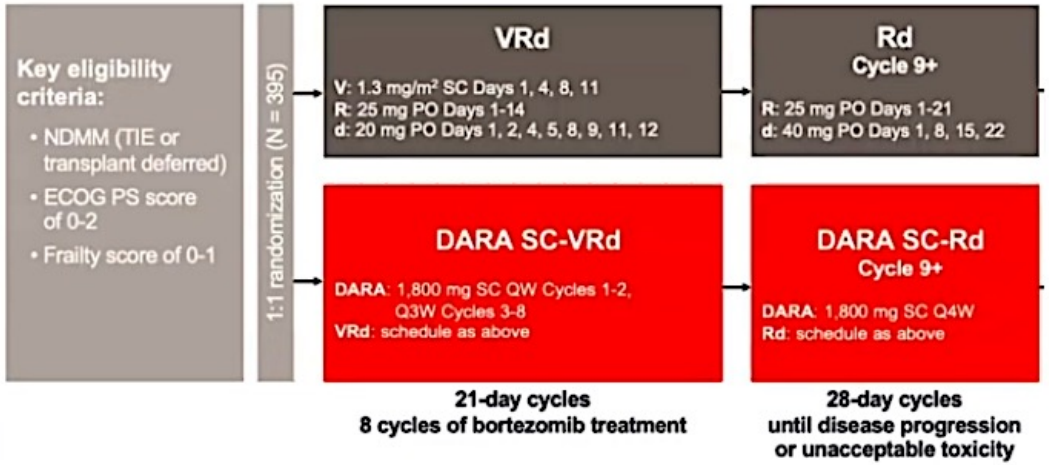
Facon Tet al, N Engl J Med 2024

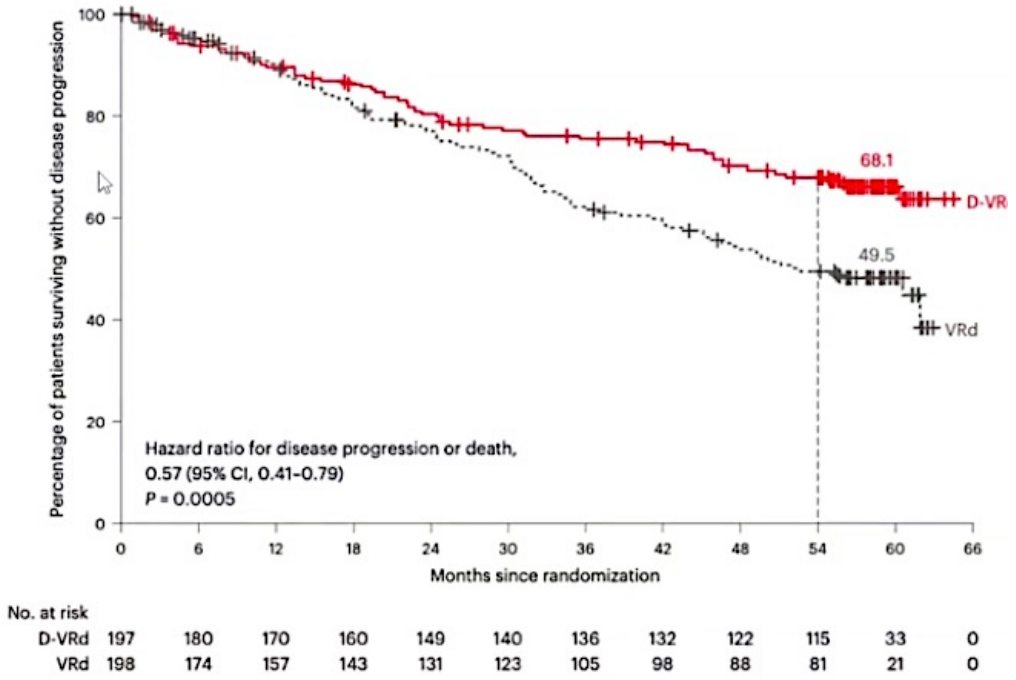
Results of the phase 3 BENEFIT registration trial



Leleu X et al, Nat Med 2024

Results of the phase 3 CEPHEUS registration trial





Usmani S et al, Nat Med 2025

Modeling Long-Term Progression-Free Survival in Transplant-Eligible and Transplant-Ineligible Newly Diagnosed Multiple Myeloma Treated With Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone

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[1]Erasmus MC Cancer Institute, Rotterdam, Netherlands, [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [3]University of Lille, CHU de Lille, Lille, France, [4]Clínica Médica São Germano, São Paulo, Brazil, [5]Arne Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada, [6]Laboratoire d'anatomo-pathologie, CHU de Nantes, Nantes, France, [7]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Wurzburg, Germany, [8]University of Turin, Turin, Italy, [9]Johnson & Johnson, Raritan, NJ, USA, [10]Evidera, Budapest, Hungary, [11]Johnson & Johnson, Spring House, PA, USA, [12]Johnson & Johnson, High Wycombe, UK, [13]National and Kapodistrian University of Athens, Athens, Greece, [14]Department of Hematology, Cancer Center Clínica Universidad de Navarra, Cima, Pamplona, Spain, [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA

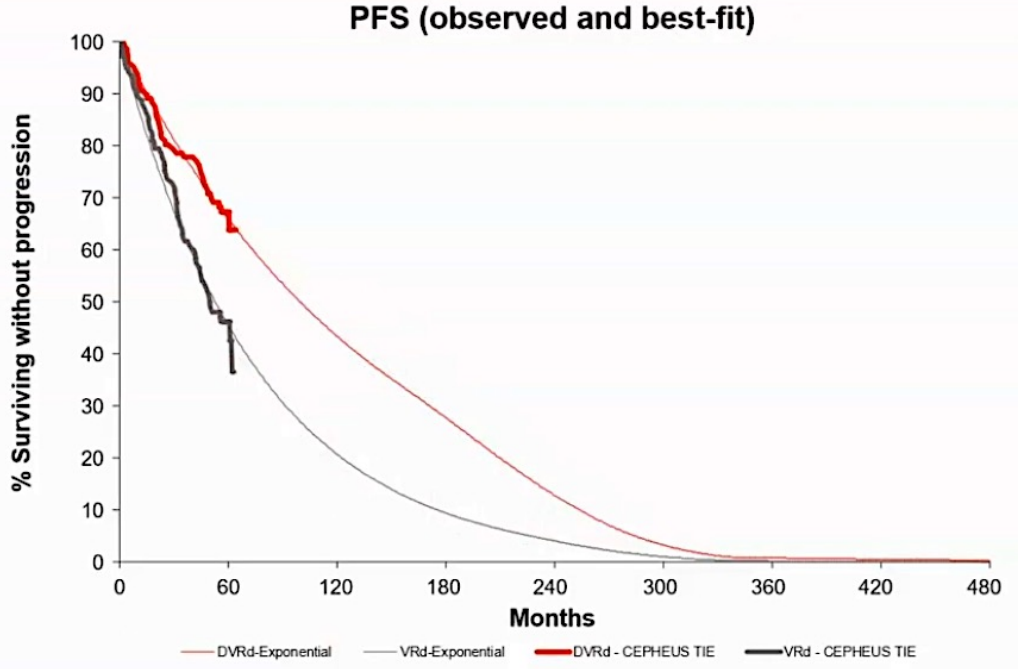
Presented by P Sonneveld at the 6th European Myeloma Network (EMN) meeting; April 10–12, 2025; Athens, Greece

CEPHEUS: Significantly Longer Projected PFS With DVRd

TIE NDMM

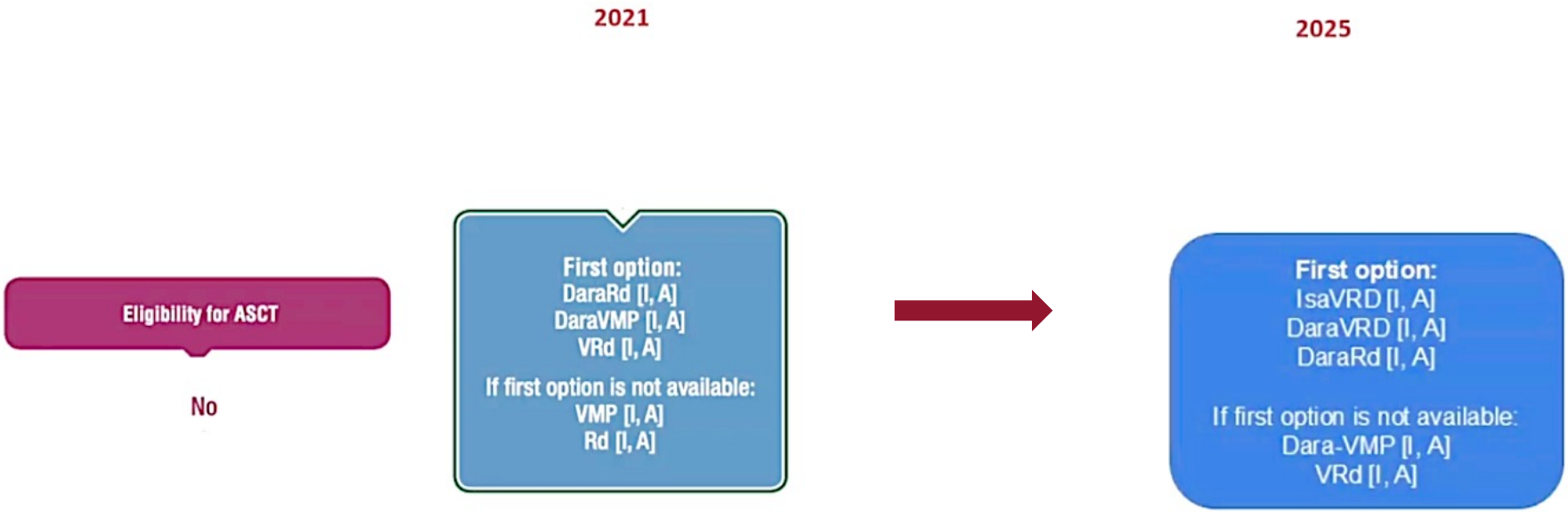
- **Median PFS not reached with DVRd in the TIE population**
- **Estimated median PFS**
  - Range across **all** distributions:
    - **DVRd: 96–118 months**
    - VRd: 52–54 months
  - **Best-fit:**
    - **DVRd: 100 months**
    - VRd: 53 months

The best-fit projection estimates a 47-month longer PFS benefit with DVRd vs VRd



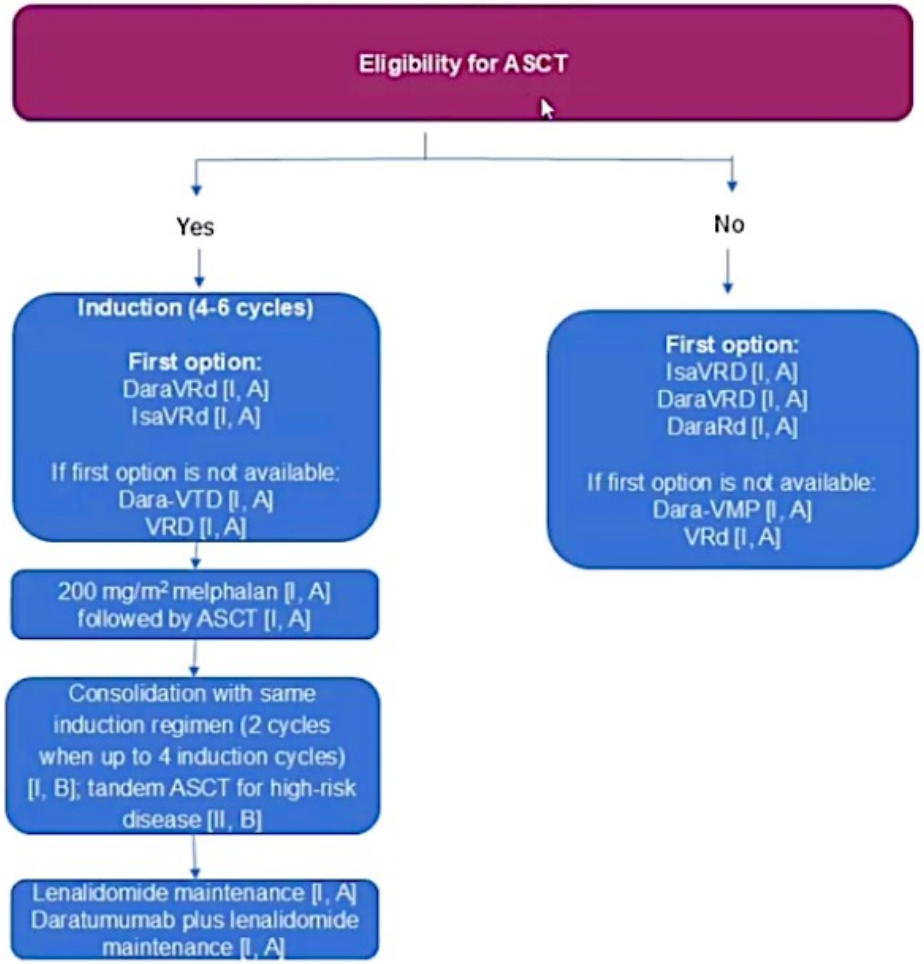
DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TIE, transplant-ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

Presented by P Sonneveld at the 6th European Myeloma Network (EMN) meeting; April 10–12, 2025; Athens, Greece


2021
2025
Eligibility for ASCT
No
First option:
DaraRd [I, A]
DaraVMP [I, A]
VRd [I, A]
If first option is not available:
VMP [I, A]
Rd [I, A]
First option:
IsaVRD [I, A]
DaraVRD [I, A]
DaraRd [I, A]
If first option is not available:
Dara-VMP [I, A]
VRd [I, A]

TE- NDMM

a. Quadruplets induction for (almost) all
b. Transplant upfront
c. Consolidation risk adapted strategy
d. Double maintenance (for all?)



TNE- NDMM

a. Quadruplet induction Continuous anti-CD38+Len
b. Anti-CD38+Len +/- Dex for frails

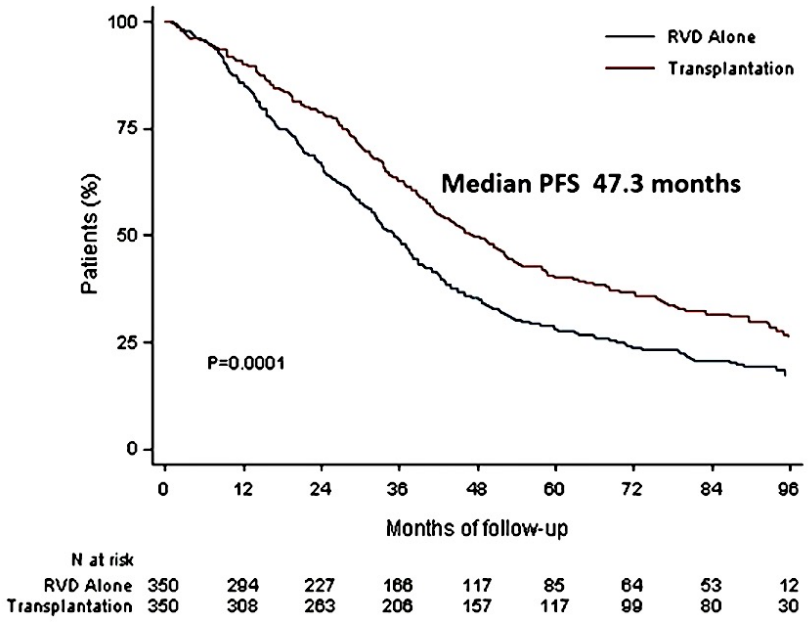
What next?

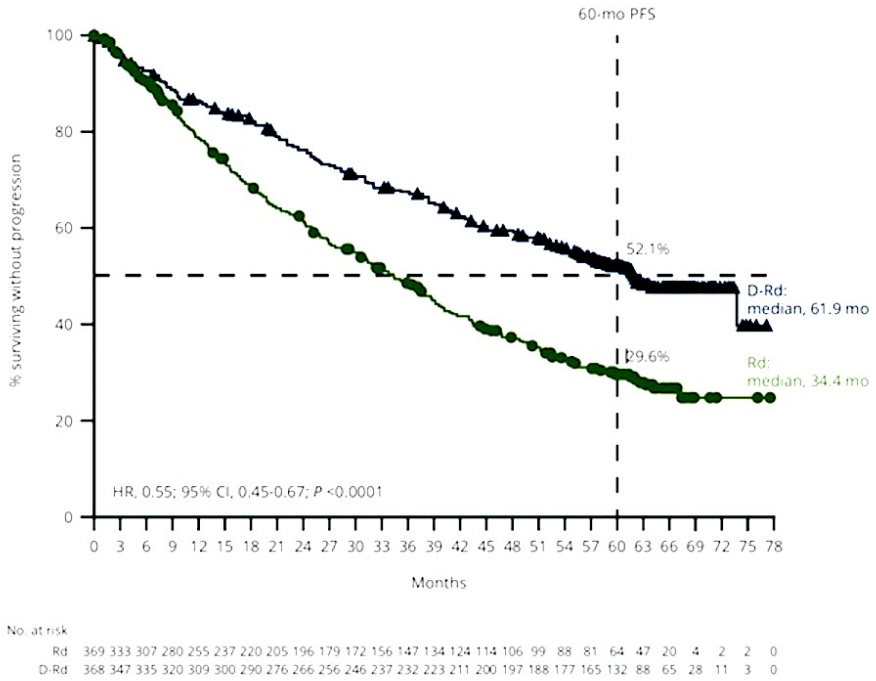
- **Optimize** the tools we have to provide the maximum duration of disease control with minimum toxicity
- **Limit the duration** of treatment – more treatment-free interval
- Requires **individualization** of therapeutic approach
  - Dynamic and ongoing risk stratification
  - Response adapted approaches
  - Account for individual functional status
- Explore options to reach a **cure** – at the minimum, a functional cure

What next?

- **Optimize** the tools we have to provide the maximum duration of disease control with minimum toxicity
- **Limit the duration** of treatment – more treatment-free interval

Improving PFS



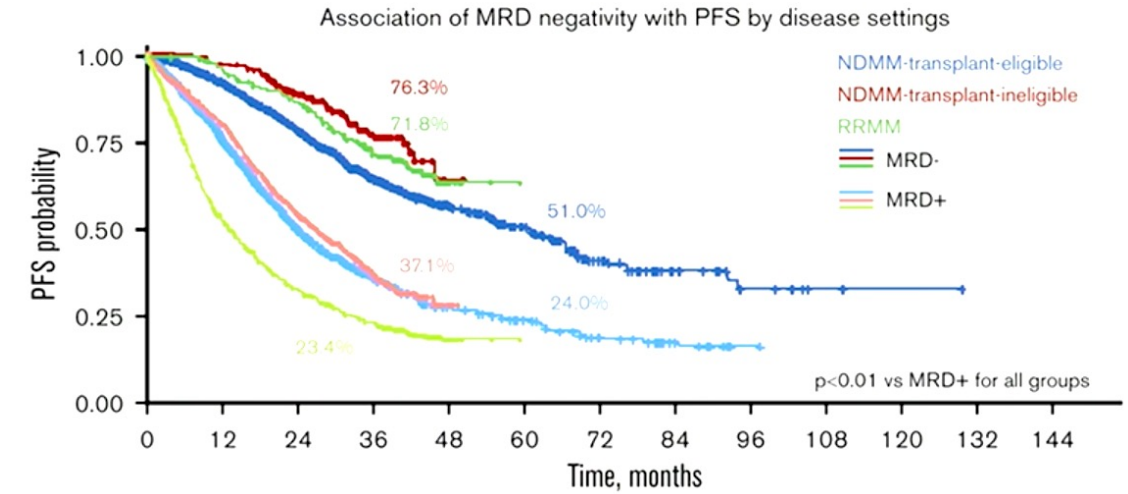


International Myeloma Society

The price of progress

- ✓ Design a phase 3 trial with control arm PFS of 60 months
- ✓ Experimental arm exploring an improvement to 72 months
- ✓ Such a trial would require over 1,500 patients followed for >
- ✓ Increasingly impossible to do this in the setting of newly diagnosed MM
- ✓ Will increasingly be a problem in relapsed trials too.... Recent phase 3 trials of triplets with PFS>3.5 years
- ✓ How can we get over this problem?

MRD as a surrogate



Number at risk

MRD-	1515	1055	589	332	164	95	47	22	10	3	1	0	0
MRD+	1180	719	317	153	72	50	30	13	2	0	0	0	0
MRD-	291	283	217	93	4	0							
MRD+	1328	983	516	133	5	0							
MRD-	164	155	135	97	10	0							
MRD+	960	456	269	179	11	0							

Blood Adv, 2020,

21st International Myeloma Society Annual Meeting

ODAC - Oncology Drug Advisory Committee

- The Committee advises the Commissioner of Food and Drugs in discharging responsibilities as they relate to helping to ensure safe and effective drugs for human use and as required, ***any other product*** for which the Food and Drug Administration (FDA) has regulatory responsibility.
- It reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer and makes appropriate recommendations to the Commissioner

ODAC Voting

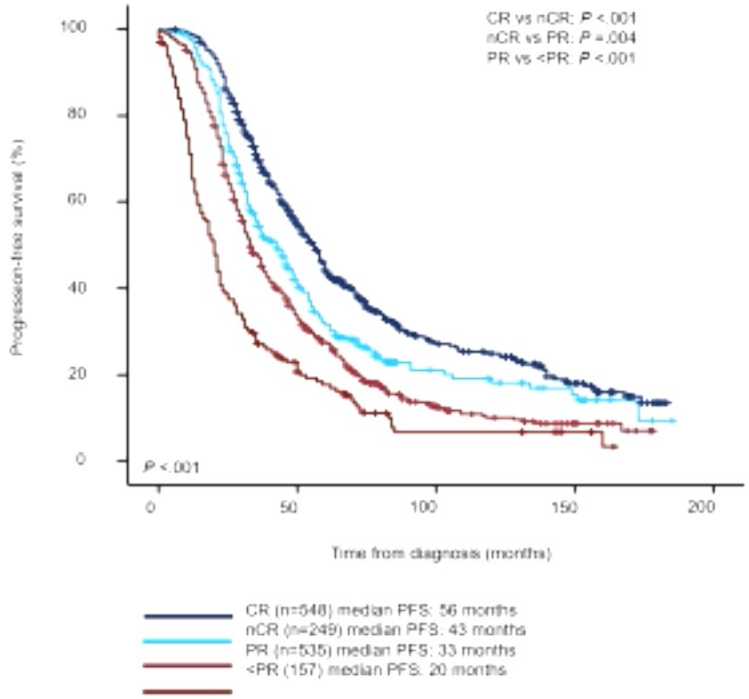
VOTE: Does the evidence support the use of MRD as an accelerated approval endpoint in MM clinical trials?

Vote Result: Yes: 12 No: 0 Abstain: 0

"The Committee unanimously agreed that the evidence does support the use of MRD as an accelerated approval endpoint in MM clinical trials. A few Committee members acknowledged that MRD negativity may not correlate perfectly with clinical efficacy and overall survival. However, members agreed that the use of MRD in MM clinical trials to support accelerated approval is a reasonable approach"

Critical analysis on the value of *MRD versus CR*

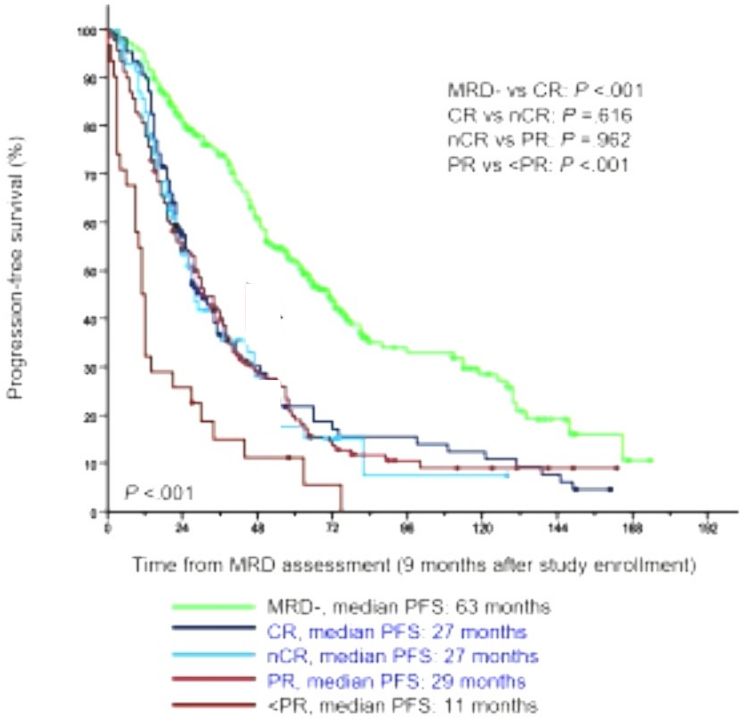
Patients attaining CR experience prolonged survival...but...



GEM trials: CR (n=1.230) and MRD (n=797)

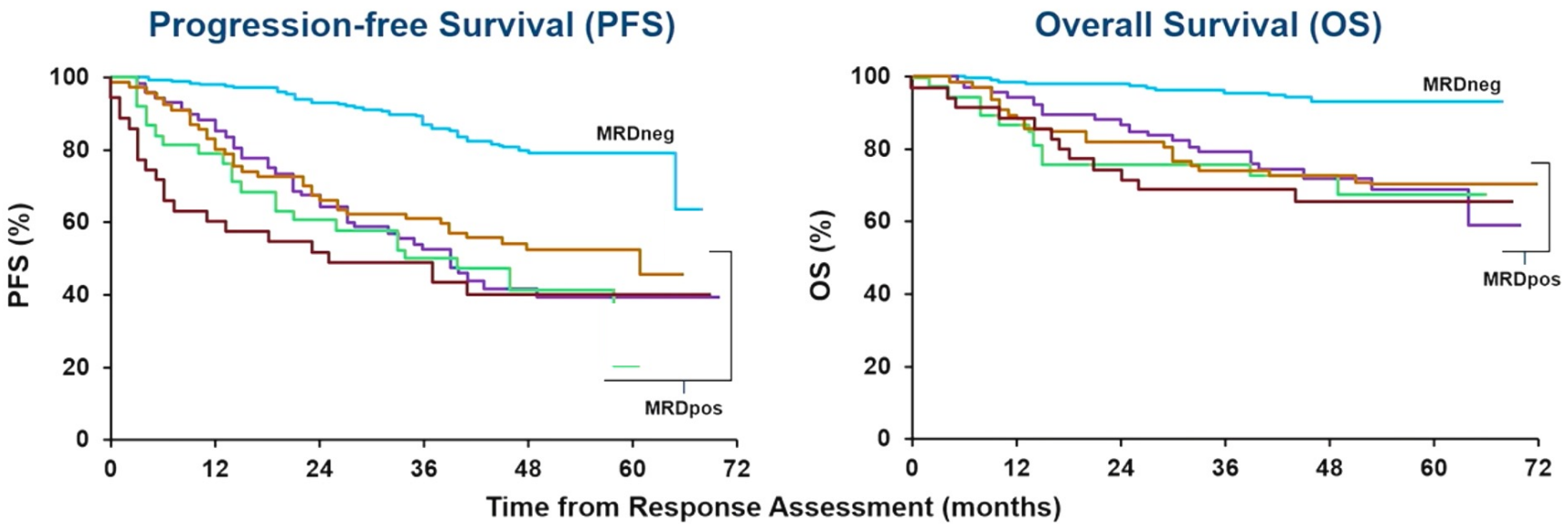
GEM2000, GEM2006MENO66, GEM2006MA66, GEMD10MA65

but... this is due to the impact of MRD-ve cases



Lahuerta JJ, Paiva B, et al. J Clin Oncol 2017; doi: *10.1200/JCO.2016.69.2517*

MRD is the Most Accurate Response Criterion to Measure Treatment Efficacy and Predict Longer Survival[1]



MRD negativity is the new CR

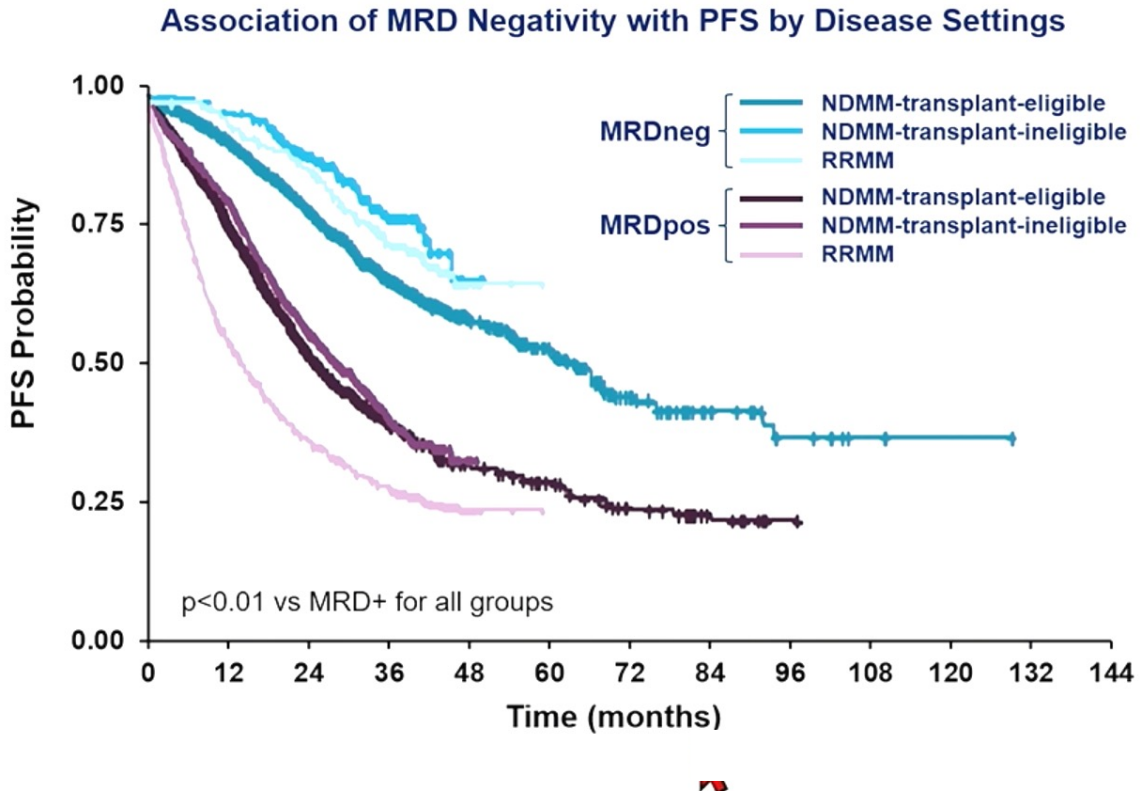
. Jimenez-Ubieto A & Paiva B, et al. *Blood*. 2021;138(19):1901-1905.

Is MRD a Key Prognostic Factor in All Disease Settings?

Large Meta-analysis Using Published Data

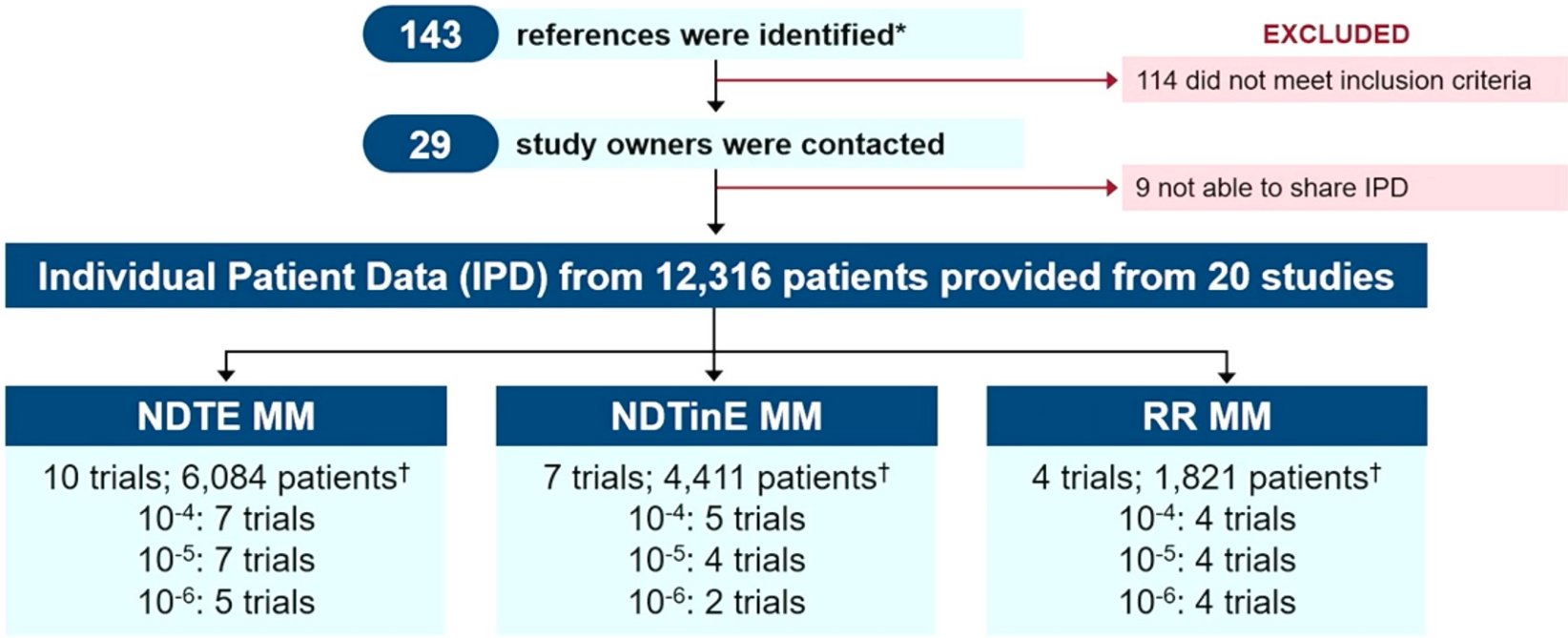
93 publications

8098 patients



Munshi NC, et al. *Blood Adv*. 2020 Dec 8;4(23):5988-5999.

Unprecedented Data Sharing in Multiple Myeloma



Note: one trial enrolled patients in both NDTE and NDTinE populations

*Identified March 2020, Medline database search for publications and conference abstracts using the strategy of the MeSH terms "multiple myeloma" AND "neoplasm, residual" AND the nonMeSH terms "MRD", "myeloma", AND "minimal residual disease".
†Unique patients indicated in the transferred datasets who were randomized.

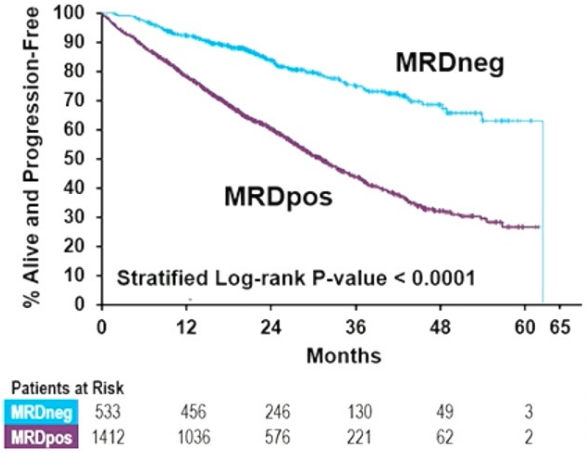
CC-14

MRD Negativity Strongly Associated with Longer PFS in all 3 Populations

9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

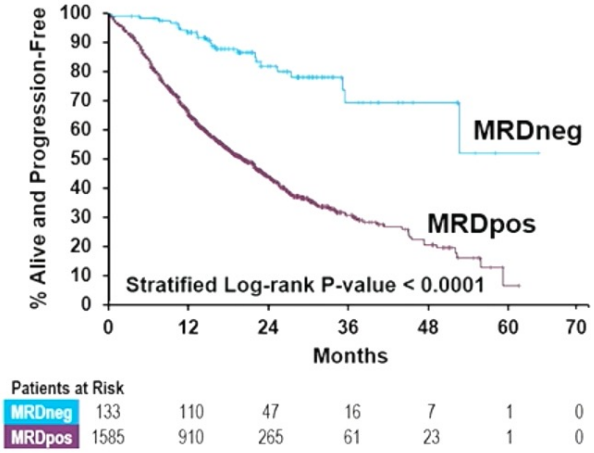
NDTE MM



Patients at Risk							
MRDneg	533	456	246	130	49	3	
MRDpos	1412	1036	576	221	62	2	

HR=0.29 (0.24-0.37)

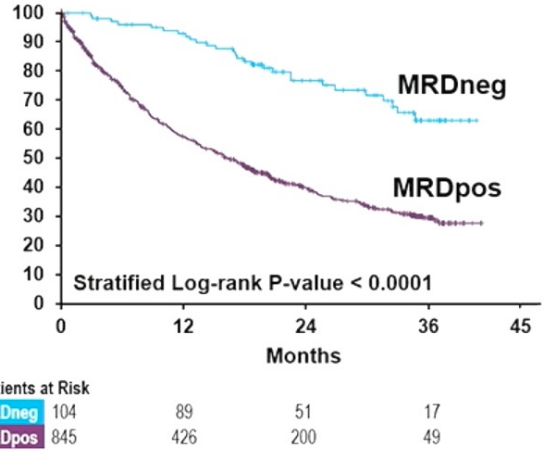
NDTinE MM



Patients at Risk							
MRDneg	133	110	47	16	7	1	0
MRDpos	1585	910	265	61	23	1	0

HR=0.24 (0.16-0.36)

RR MM



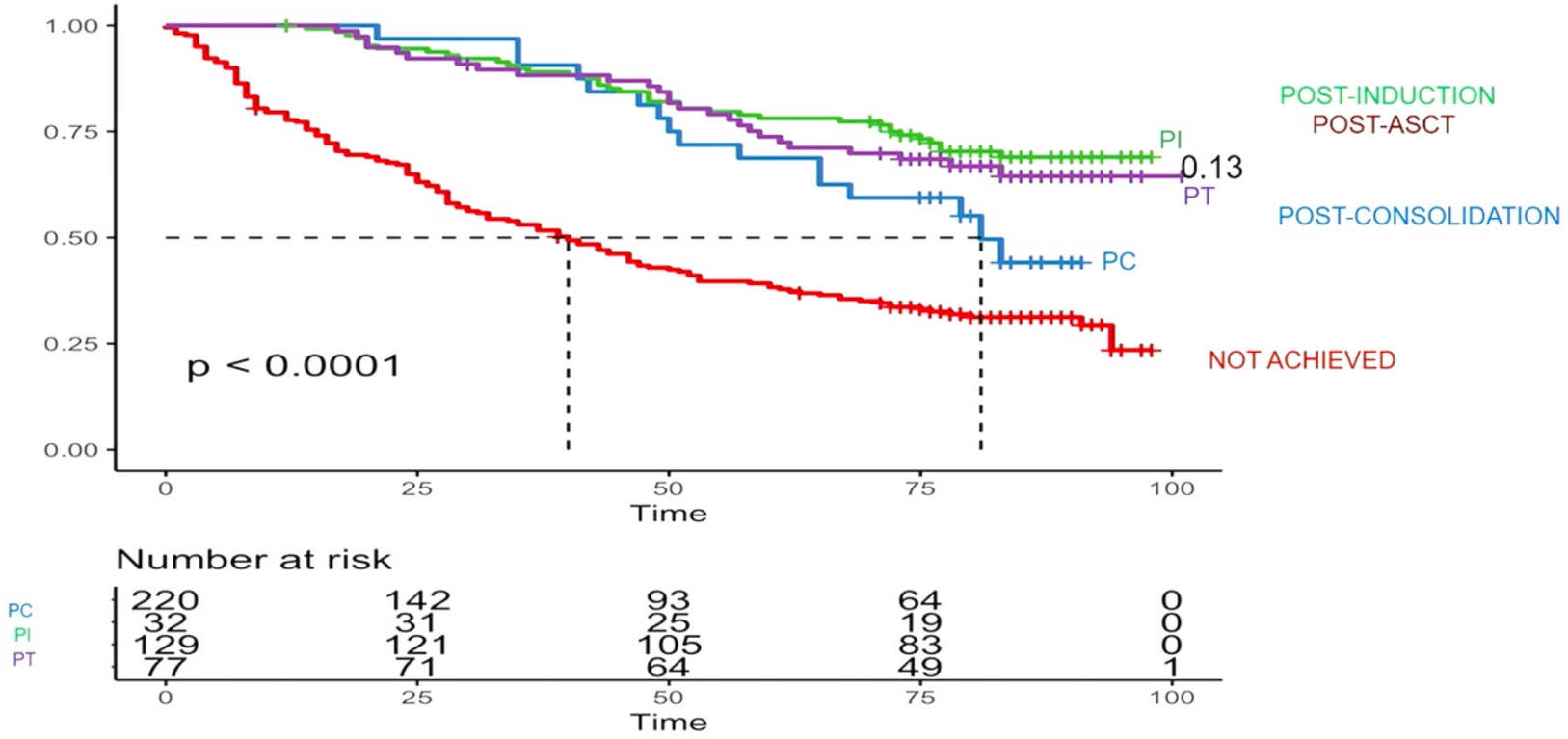
Patients at Risk				
MRDneg	104	89	51	17
MRDpos	845	426	200	49

HR=0.31 (0.20-0.46)

CC-17

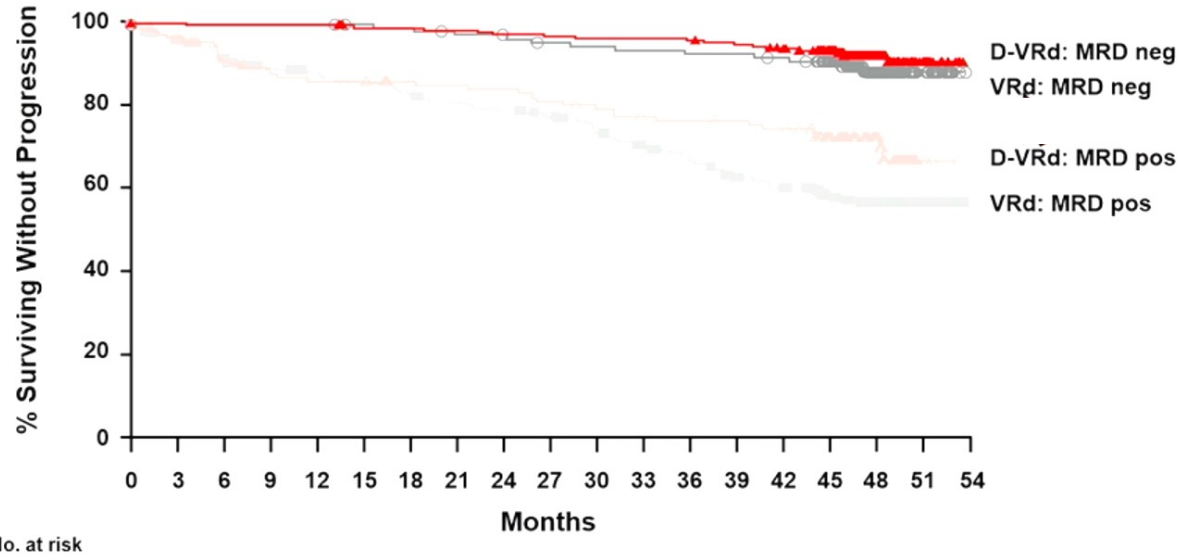
Stratified by studies

Does the Time to achievement of MRDneg matters?



Does The Prognostic Value of MRD Depends on the Regimen Patients Receive?

PERSEUS Phase 3 Trial: PFS according to MRD status



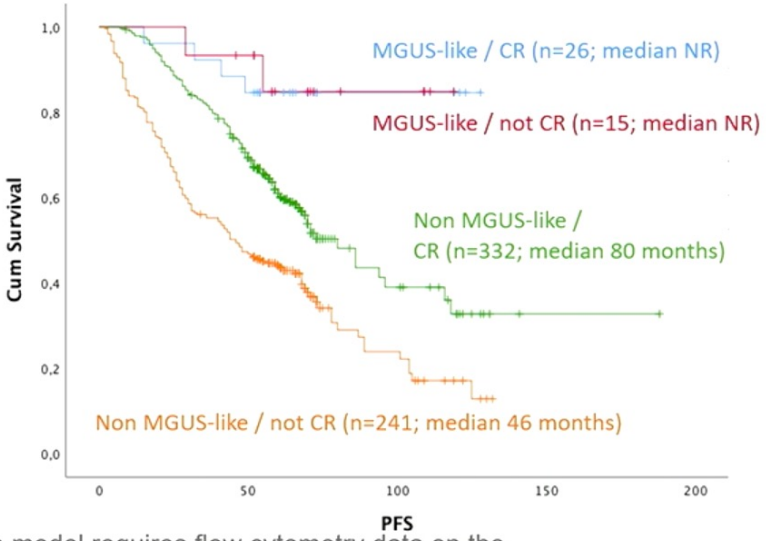
No. at risk																		
VRd: MRD neg	114	114	114	114	114	112	111	108	107	104	103	102	101	101	98	87	34	9	0
D-VRd: MRD neg	231	231	230	230	230	226	226	225	223	222	221	221	219	216	210	169	70	10	0
VRd: MRD pos	240	221	207	197	190	185	180	175	171	166	155	145	137	127	121	88	33	4	0
D-VRd: MRD pos	124	114	105	99	97	96	92	91	90	87	84	81	80	79	76	57	20	1	0

Rodriguez-Otero P, et al. *ASCO* 2024. Abstract 7502
Sonneveld P, et al. *EHA*. 2024. Abstract S201
Sonneveld P, et al. *N Engl J Med*. 2024 Jan 25;390(4):301-313.

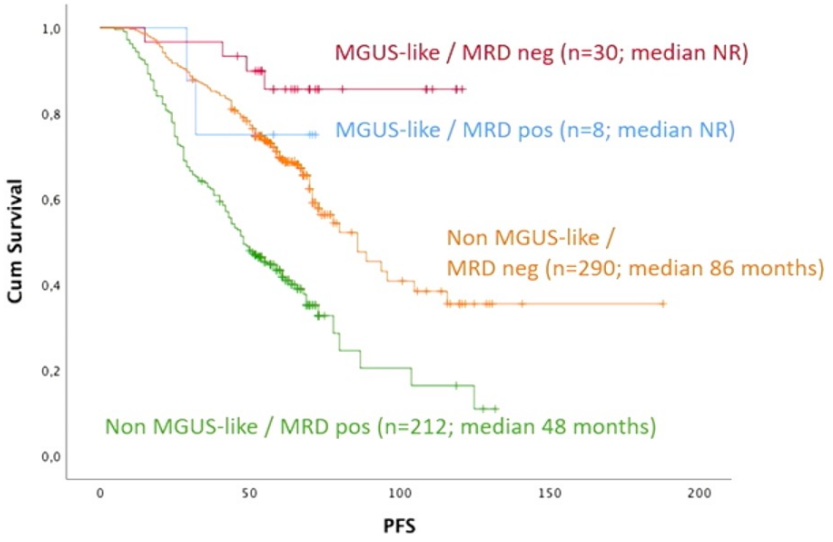
Some patients in spite of an MRD+ve status do not relapse ….have long PFS

Long-term survival in transplant-eligible pts with an MGUS-like immunophenotypic profile regardless of CR and MRD status

Combination of CR and MGUS-Like profiles



Combination of MRD and MGUS-Like profiles



The model requires flow cytometry data on the frequency of bone marrow (BM) plasma cells (PC) and the percentage of clonal PC within the BM compartment, at diagnosis ***Web-based calculator. MGUS-like.com***

Absence of CTC: 8% of patients

Burgos L, et al. *J Clin Oncol 2023*

Where in clinical study do you suggest using MRD?

- ✓ **To evaluate treatment efficacy .... NDMM, RRMM, high & standard Risks**
- ✓ **To compare two treatment approaches**
- ✓ Adapted therapy according to MRD follow-up
- ✓ To adapt Maintenance Intensity and Duration
- ✓ To introduce Early Rescue Intervetion (ERI)

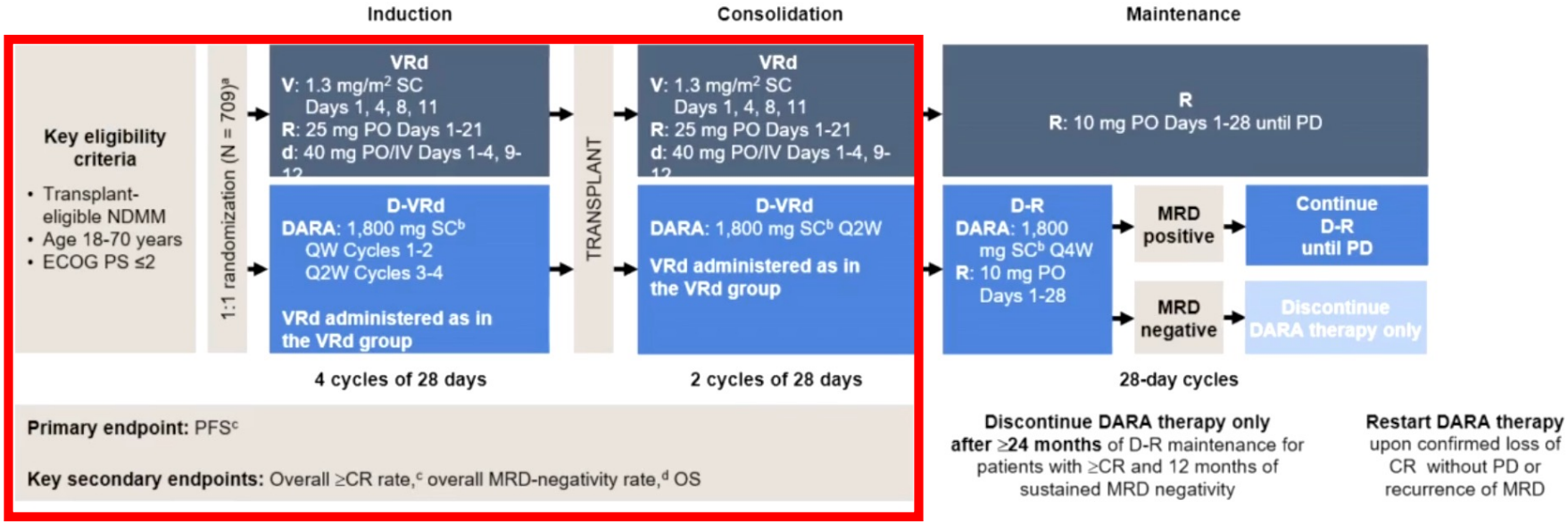
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 25, 2024 VOL. 390 NO. 4

Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Sonneveld, M.A. Dimopoulos, M. Boccadoro, H. Quach, P.J. Ho, M. Beksac, C. Hulin, E. Antonioli, X. Leleu, S. Mangiacavalli, A. Perrot, M. Cavo, A. Belotti, A. Broijl, F. Gay, R. Mina, I.S. Nijhof, N.W.C.J. van de Donk, E. Katodritou, F. Schjesvold, A. Sureda Balari, L. Rosiñol, M. Delforge, W. Roeloffzen, T. Silzle, A. Vangsted, H. Einsele, A. Spencer, R. Hajek, A. Jurczyszyn, S. Lonergan, T. Ahmadi, Y. Liu, J. Wang, D. Vieyra, E.M.J. van Brummelen, V. Vanquickelberghe, A. Sitthi-Amorn, C.J. de Boer, R. Carson, P. Rodriguez-Otero, J. Bladé, and P. Moreau, for the PERSEUS Trial Investigators*

PERSEUS: the new Standard of Care for NDMM TE

SOC = Induction DVRd x4 - HDM200 / ASCTx1 - Consolidation DVRd x2 – Maintenance Len until PD



ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. aStratified by ISS stage and cytogenetic risk. bDARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA). cResponse and disease progression were assessed using a computerized algorithm based on IMWG response criteria. dMRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

P Sonneveld et al, N Engl J Med 2023

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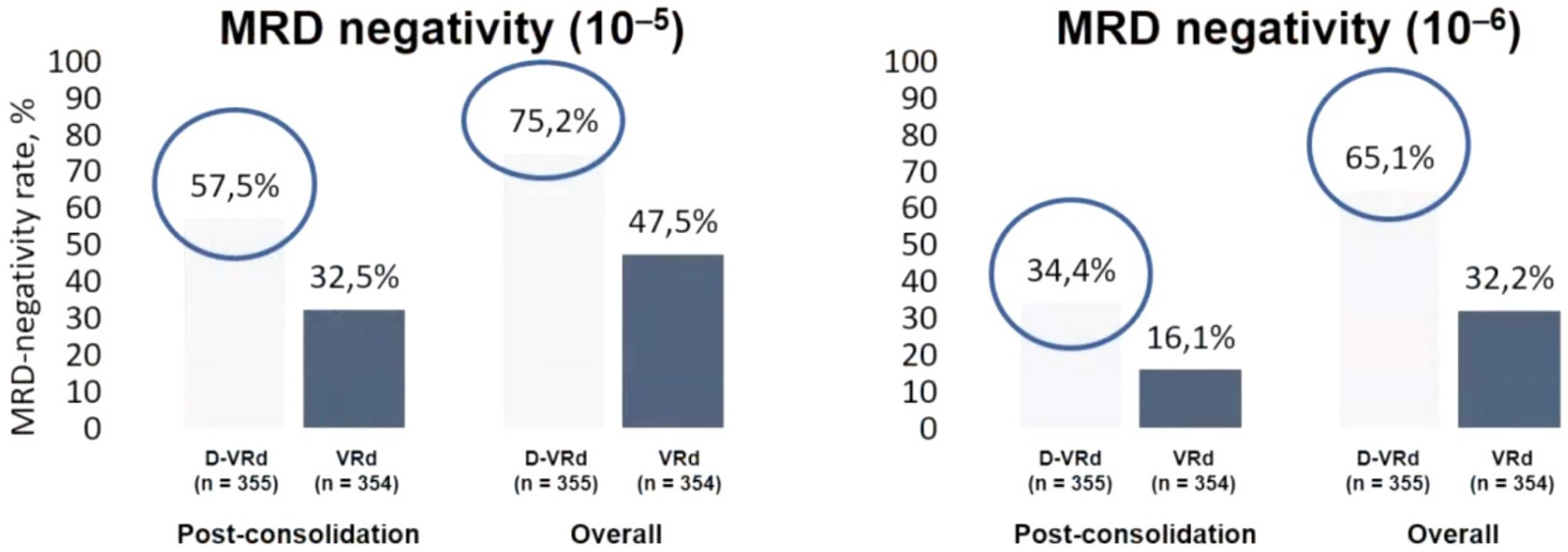
PERSEUS: MRD-negativity Ratesa Over Time



- Rates of MRD negativity improved during maintenance
- The absolute difference between D-VRd and VRd widened over time and is most evident at the deeper threshold of 10^{-6}

[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).

P Sonneveld et al, N Engl J Med 2023

Ongoing studies in Ti NDMM will help elucidate the patient populations that can benefit from quadruplets over triplets

IMROZ[1]

- ✓ Age 18–80 years
- ✓ Not eligible for transplant due to age (≥65) or <65 with comorbidities impacting transplant
- x ECOG PS >2

Frail patients were not excluded

3:2

Induction phase (4 x 6-week cycles)	Continuous phase (4-week cycles)
Isa-VRd	Isa-Rd
VRd	Rd

Optional cross over at PD

Primary endpoint
PFS

Treatment until PD, unacceptable toxicities, or patient withdrawal

BENEFIT – IFM 2020-05[2]

- ✓ Age ≥65–<80 years
- ✓ Not eligible for transplant
- x ECOG PS >2

1:1

Induction phase (12 x 4-week cycles)	Cycles 13–18	Cycles 19 → PD
Isa-VRd†	Isa-VR†	Isa-R
Isa-Rd	Isa-R	Isa-R

Primary endpoint
MRD– rate at 18months

Treatment until PD, unacceptable toxicities, or patient withdrawal

CEPHEUS[2]

- ✓ Age ≥18 years
- ✓ No intent for transplant: ≥65 or <65 with comorbidities impacting transplant
- x ECOG PS >2
- x Frailty index ≥2*

1:1

Induction phase (8 x 3-week cycles)	Maintenance phase (4-week cycles)
DVRd	DRd
VRd	Rd

Primary endpoint
MRD– rate

Treatment until PD or unacceptable toxicities

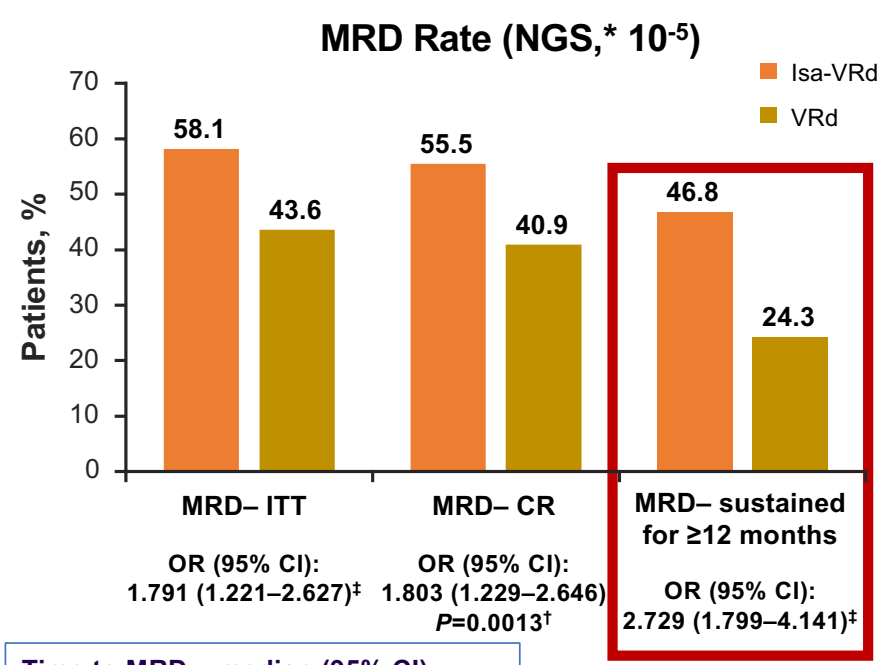
Off label

*Myeloma Geriatric Assessment score; †V given QW (C1–13) and Q2W (C13–18)

MRD, minimal residual disease; PFS, progression-free survival; D, daratumumab, d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; Isa, isatuximab;

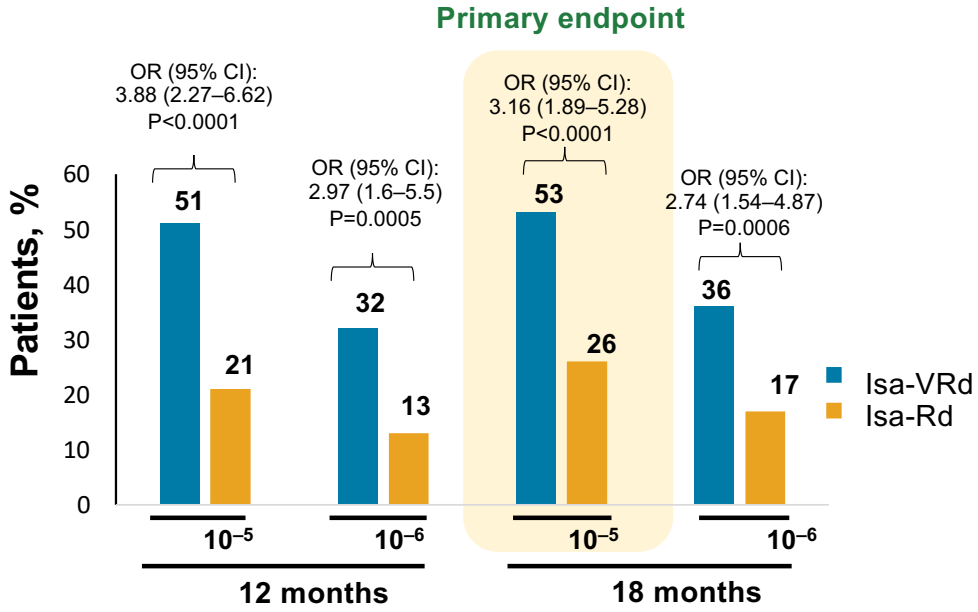
1.Orlowski RZ, et al. ASCO 2018; Abstract TPS8055;
2.Clinialtrials.gov NCT04751877
Clinialtrials.gov NCT03652064

IMROZ



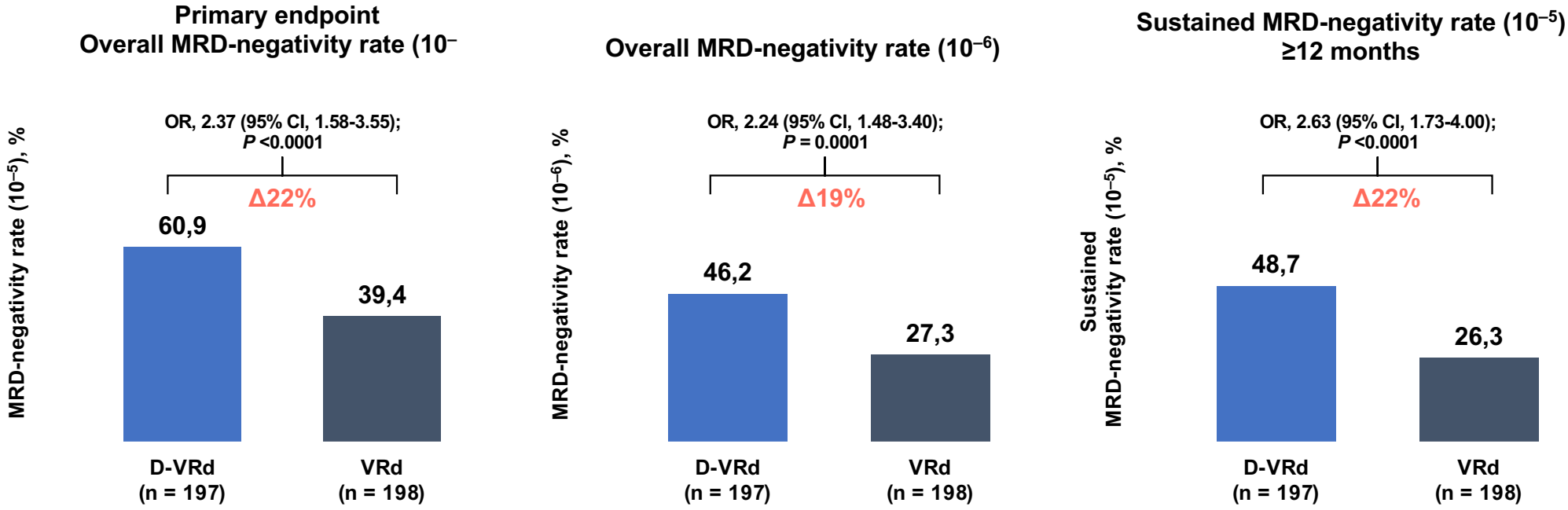
Time to MRD–, median (95% CI)
Isa-VRd: 14.72 (11.53–24.08) months
VRd: 32.79 (17.51–45.11) months

BENEFIT



Facon T, et al. ASCO 2024. Presentation 7500.
Facon T, et al. NEJM 2024
Gay F, et al. NatMed 2024.

CEPHEUS: Overall and Sustained MRD-negativity Rates[a] (ITT Population)



Daratumumab led to deeper MRD responses at 10^{-6} and a higher sustained MRD-negativity rate

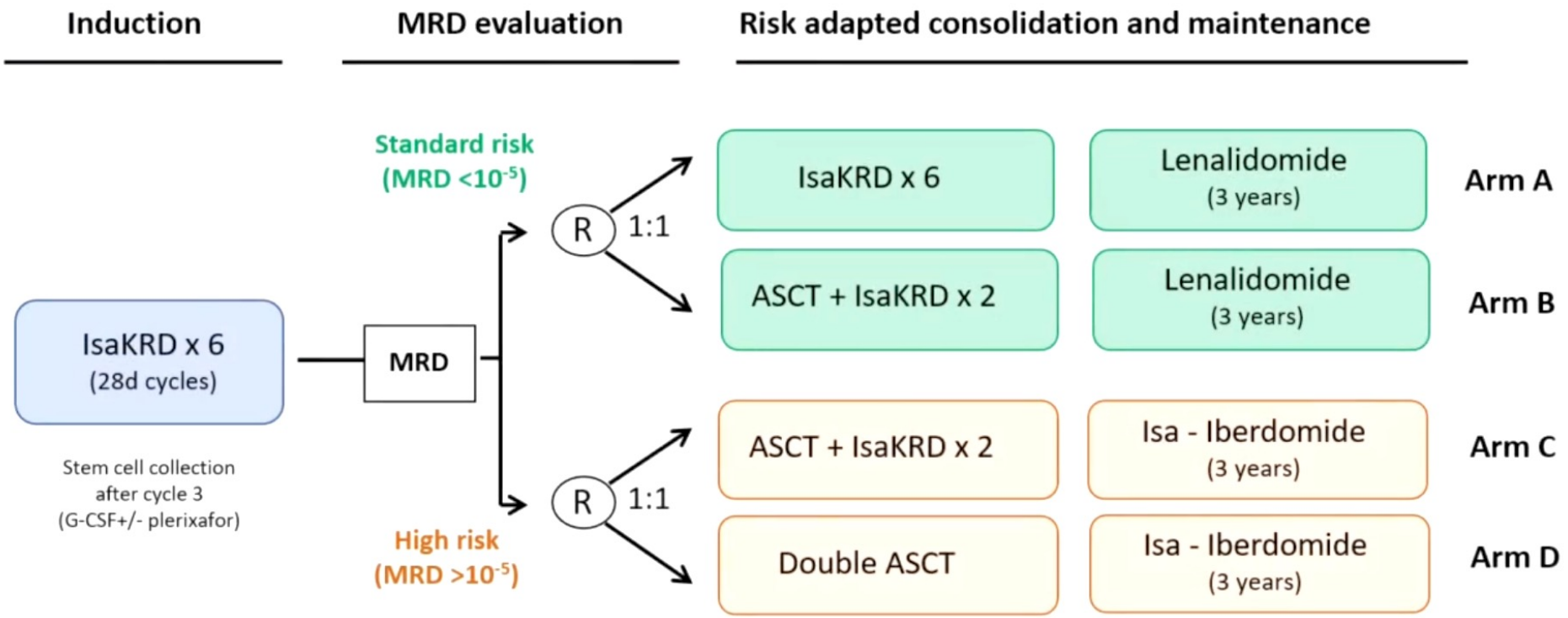
[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5}) and ≥CR.

Where in clinical study do you suggest using MRD?

- ✓ To evaluate treatment efficacy .... NDMM, RRMM, high & standard Risks
- ✓ To compare two treatment approaches
- ✓ **Adapted therapy according to MRD follow-up**
- ✓ To adapt Maintenance Intensity and Duration
- ✓ To introduce Early Rescue Intervetion (ERI)

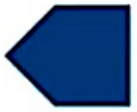
Response-Adapted Strategy?

MInimal residual Disease Adapted Strategy



Quadruple-based induction regimens: summary

	Schema	N patients	Induction	MRD post-induction
CASSIOPEIA	DaraVTD	543	4 cycles of 28 d	35 % (10^{-5})
GRIFFIN	DaraVRD	104	4 cycles of 21 d	22 % (10^{-5}) 1 % (10^{-6})
PERSEUS	DaraVRD	355	4 cycles of 28 d	ND
GMMG-HD7	IsaVRD	331	3 cycles of 42 d	50 % (10^{-5})
EMN24 IsKia	IsaKRD	151	4 cycles of 28 d	45 % (10^{-5}) 27 % (10^{-6})
MASTER	DaraKRD	123	4 cycles of 28 d	37 % (10^{-5}) 23 % (10^{-6})
IFM2020-02 MIDAS	IsaKRD	791	6 cycles of 28 d	63 % (10^{-5}) 47 % (10^{-6})



More is better…

Do we still need to think in terms of CYCLES ?

Induction + Consolidation

- ✓ 4 plus 2
- ✓ 6 plus 0
- ✓ 4 or 6 plus 2
- ✓ 4 or 6 plus x

or

MRD negativity drives CYCLES ?

Induction + Consolidation

- ✓ x 6 MRD - plus 0
- ✓ x 6 MRD + plus x

Where in clinical study do you suggest using MRD?

- ✓ To evaluate treatment efficacy .... NDMM, RRMM, high & standard Risks
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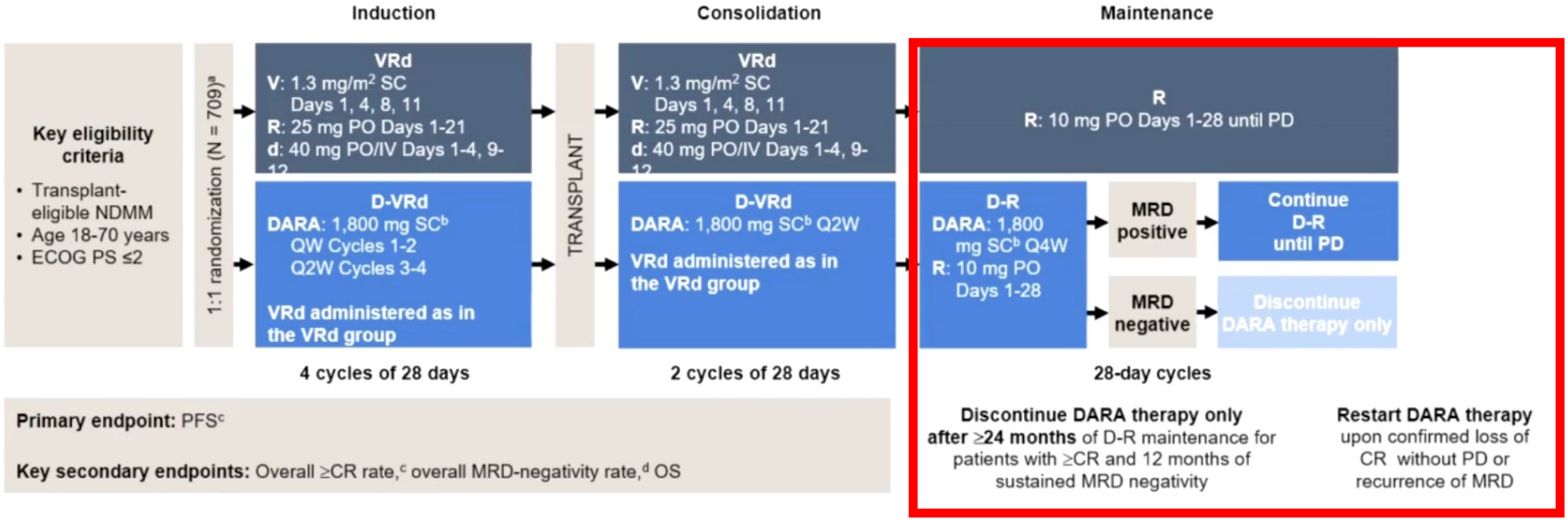


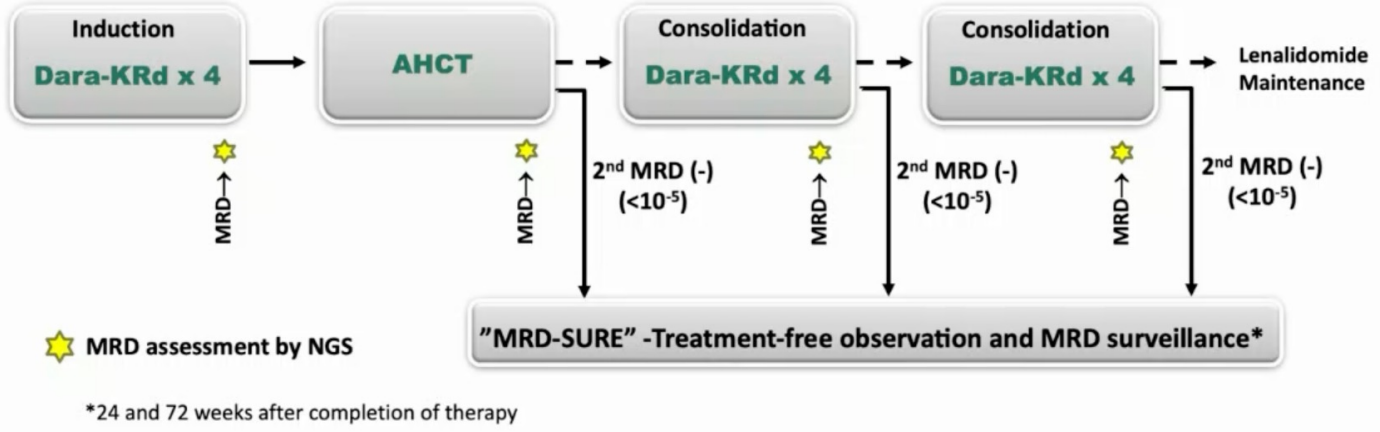
ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

P Sonneveld et al, N Engl J Med 2023

Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22

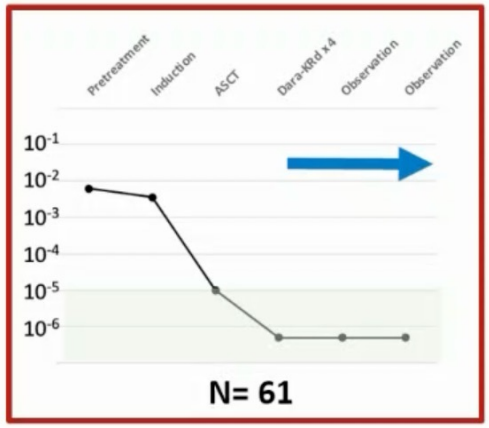


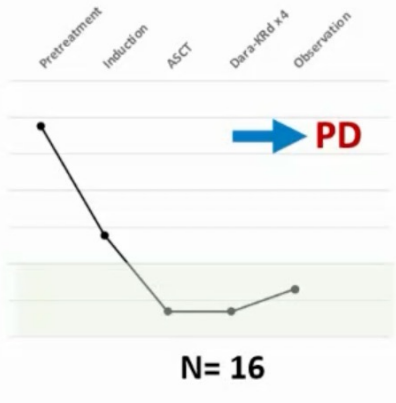
*24 and 72 weeks after completion of therapy

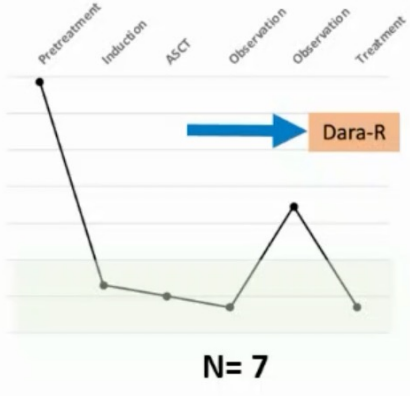
MRD tested on "first pull" and reported utilizing intent-to-treat principle according to International Harmonization

Costa LJ et al Leukemia 2021 35:18

Outcomes MRD-SURE





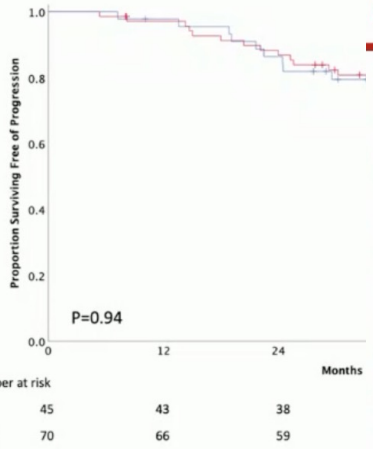


- Sixty-one patients (52% MRD evaluable patients; 73% MRD-SURE) remain free of therapy with sustained MRD negativity.

- Twenty-three patients (27%)resumed therapy:
  - 16 due to progression
  - 7 due to MRD resurgence without progression
  - OS 18-months from resuming therapy is 100%

Post Induction Landmark Analysis

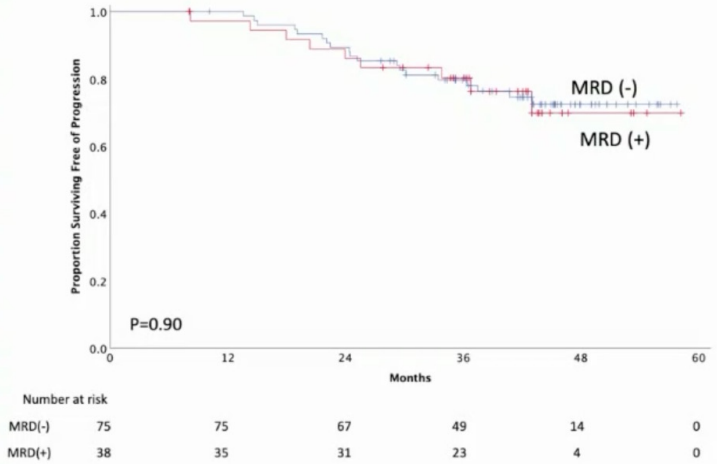
PFS



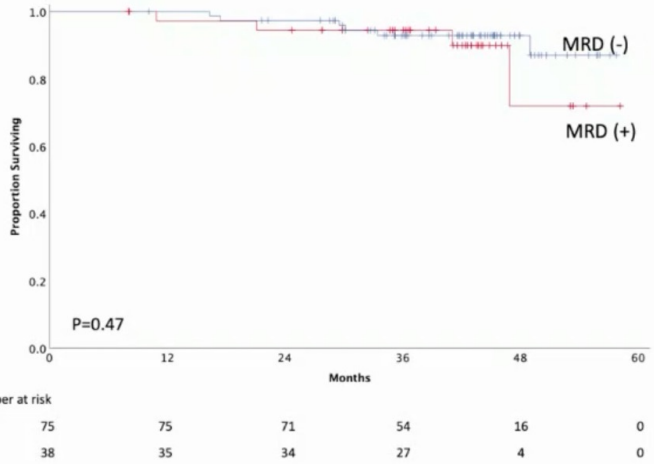
MRD-adapte

Post AHCT Landmark Analysis

PFS



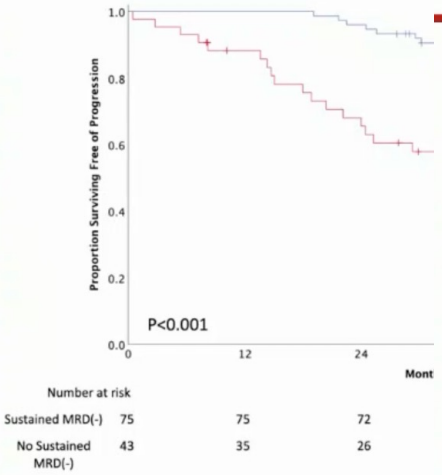
OS

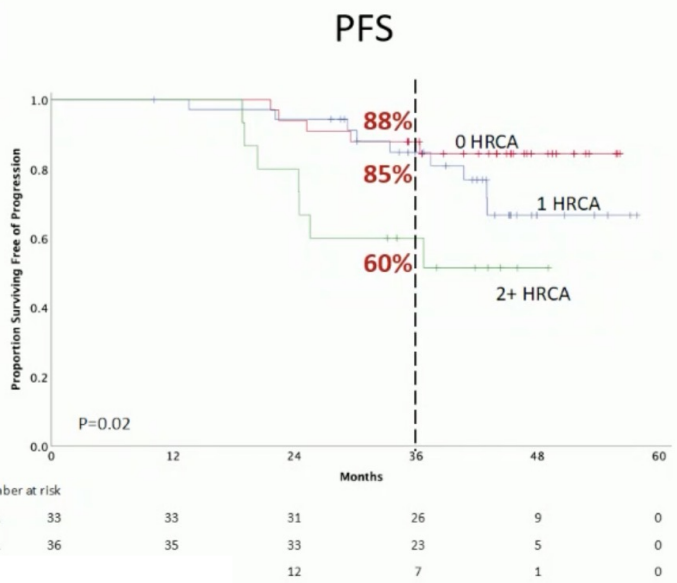


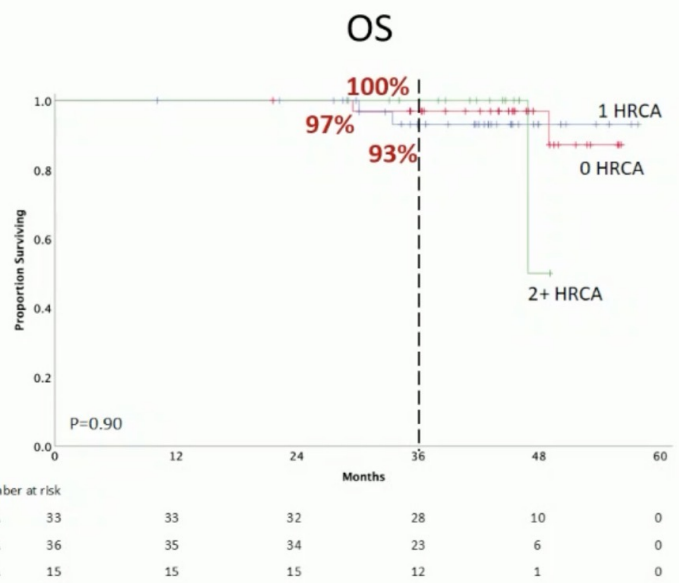
MRD-adapted therapy mitigates the impact of MRD(+) at end of post-AHCT

Sustained MRD(-)* and PFS

PFS-from Patients Reaching MRD-SURE (N=84)







*2 consecutive MRD<10-5 at least 1 year apart

Median follow up post cessation of therapy = 32.7 mo.

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Memorial Sloan Kettering Cancer Center

Best chance of curing MM is at diagnosis – achievable in < 10 years

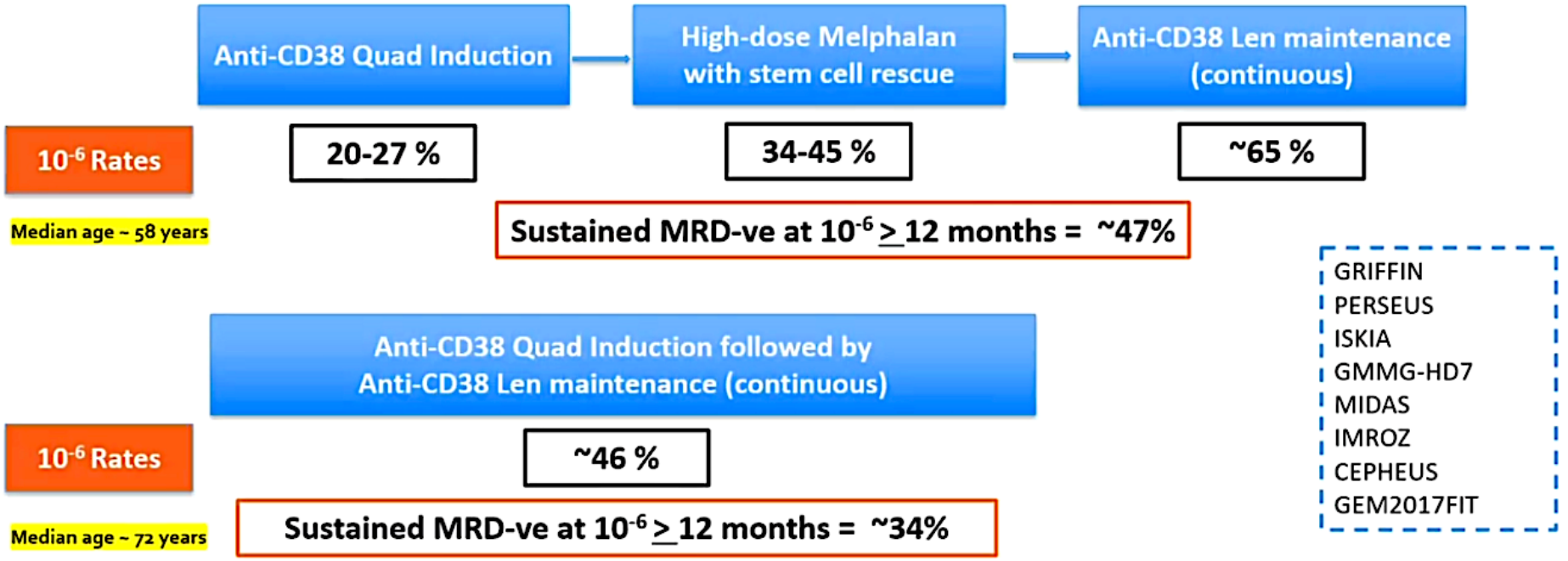
- Draw the line for treatment intervention somewhere between current definition of smoldering MM to active MM
  - Combined modeling of MM genomics, BM microenvironment and immune profiling.
- Pick the strategy that gives the highest likelihood of achieving sustained MRD negativity.
  - MRD 10^{-6} >> Sustained MRD 10^{-6}
- Optimize induction, consolidation and maintenance to increase sustained MRD negativity rates and define the duration of treatment.
  - Standard risk: 2-year sustained MRD 10^{-6} (including functional imaging)
  - High risk: at least 3-year sustained MRD 10^{-6} (including functional imaging)
- Increase the cure fraction without compromising on safety and quality of life.
  - Sustained MRD negativity ((including functional imaging) off therapy for at least 5 years
  - Achievable regardless of fitness level – need the right recipe to balance benefit vs risk.

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

Usmani S personal communication

Memorial Sloan Kettering Cancer Center

Sequential increment in MRD negativity rates



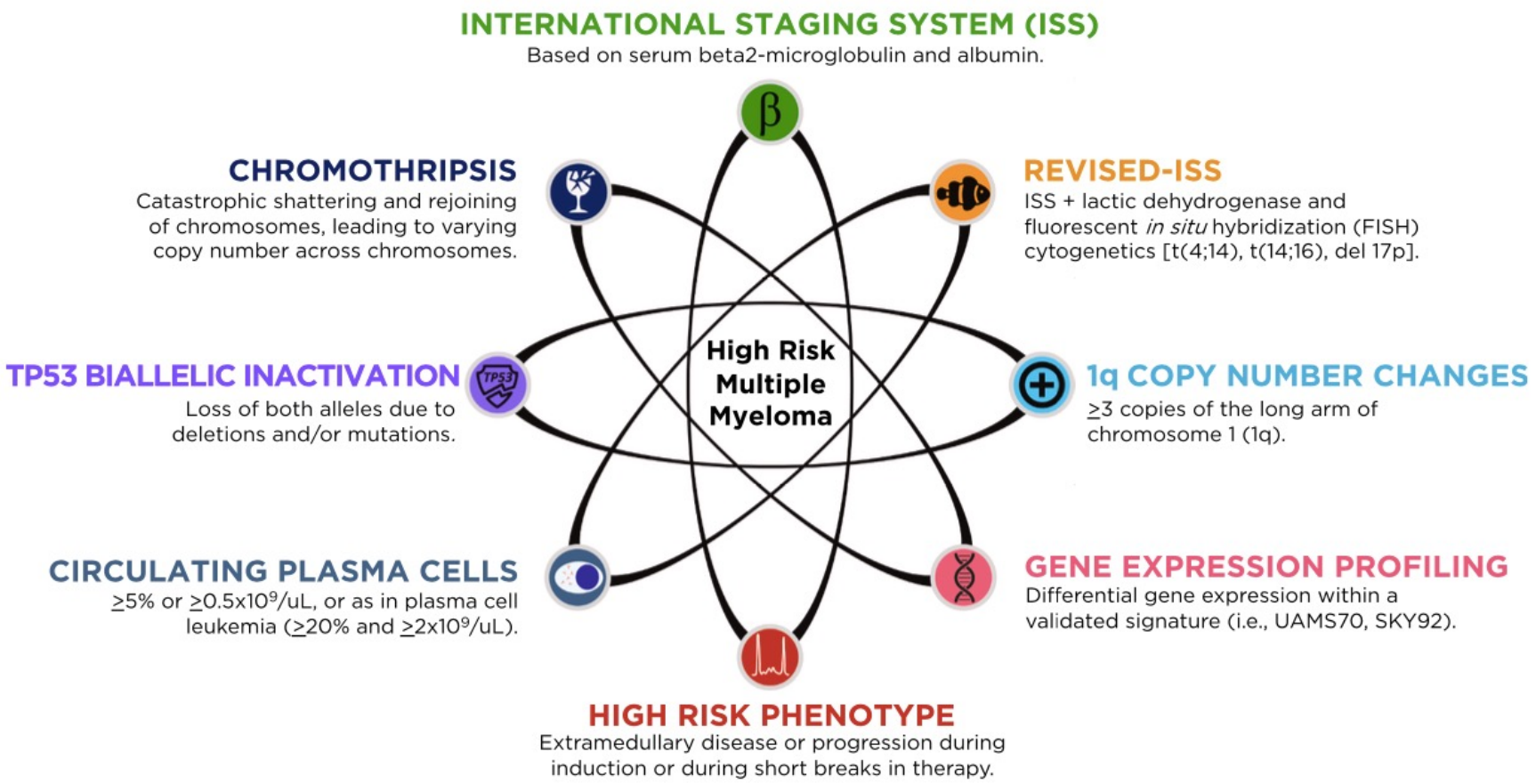
Presented by: Saad Z. Usmani, MD MBA, @szusmani

Usmani S personal communication

What next?

- Requires **individualization** of therapeutic approach
  - Dynamic and ongoing risk stratification
  - Response adapted approaches
  - Account for individual functional status
- Explore options to reach a **cure** – at the minimum, a functional cure

The Many Facets of High Risk Multiple Myeloma

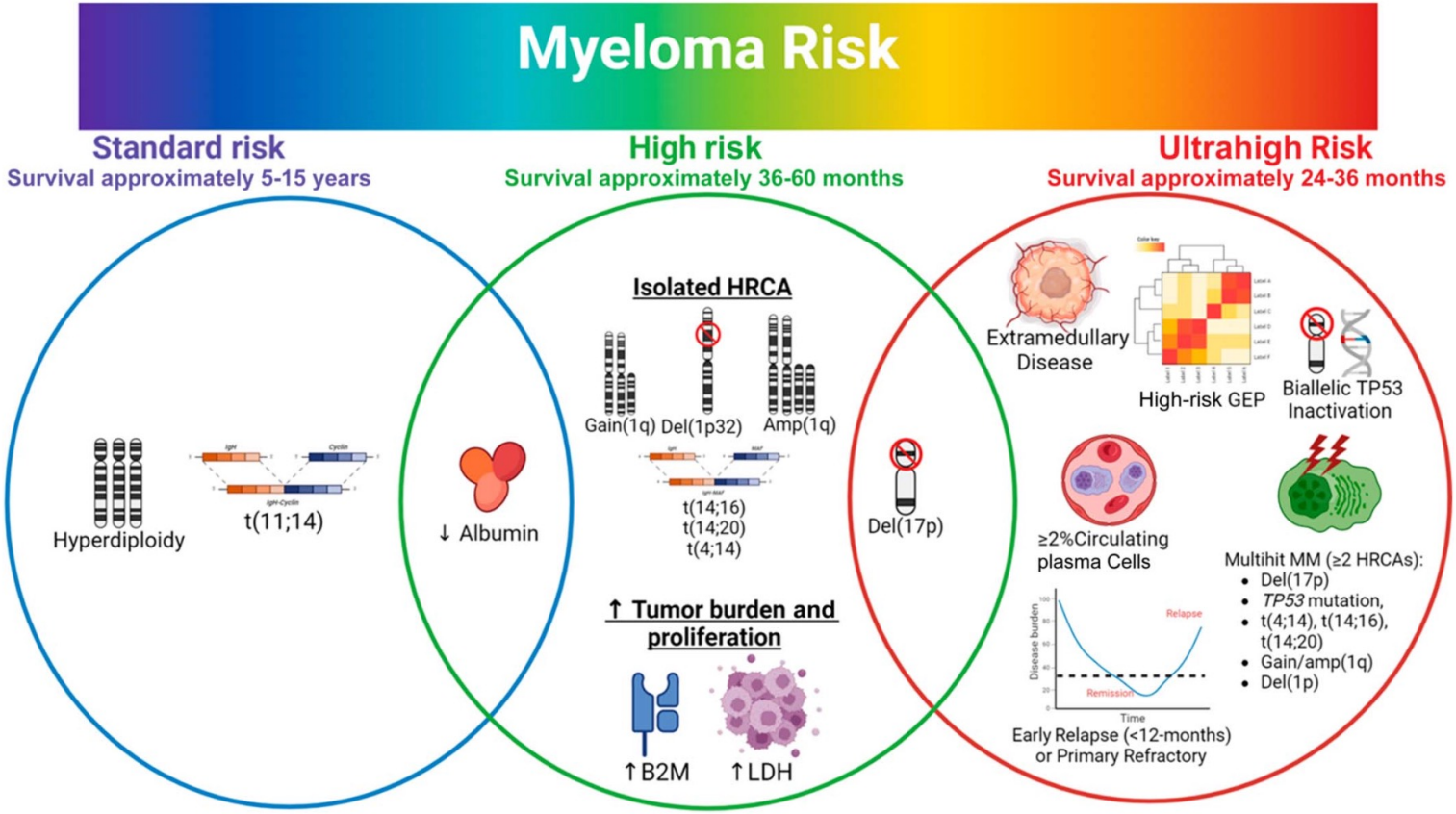


Hematologic Malignancies

Navigating High-Risk and Ultrahigh-Risk Multiple Myeloma: Challenges and Emerging Strategies

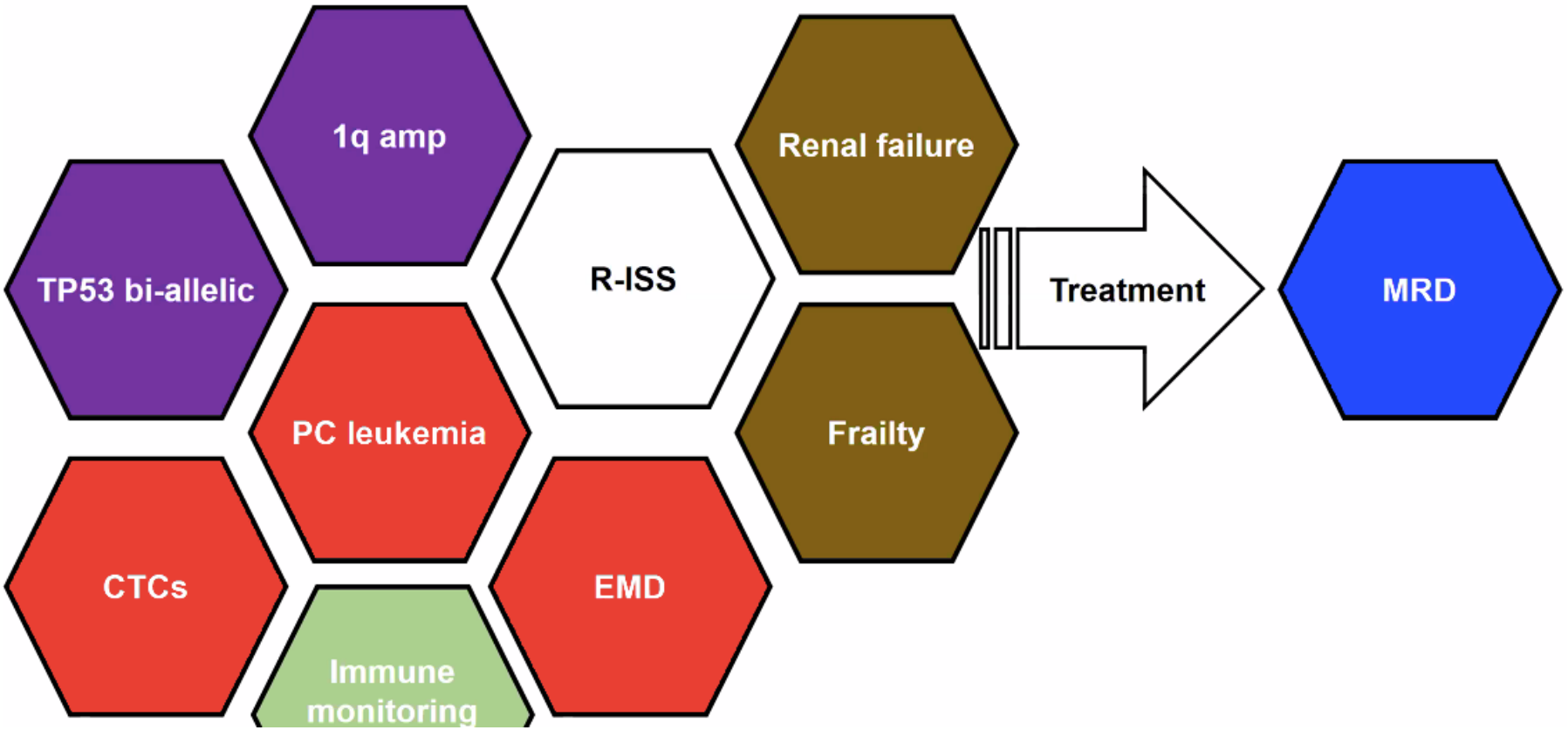
Matthew J. Rees, MD[1]; Mattia D'Agostino, MD[2]; Lisa B. Leypoldt, MD[3,4]; Shaji Kumar, MD[1]; Katja C. Weisel, MD[3]; and Francesca Gay, MD, PhD[2]

DOI https://doi.org/10.1200/EDBK_433520



The spectrum of myeloma risk and conceptual thresholds for high-risk and ultrahigh-risk myelomas. amp, amplification; B2M, beta-2-microglobulin; GEP, gene expression profiling; HRCA, high-risk cytogenetic abnormality; LDH, lactate dehydrogenase; MM, multiple myeloma.

Comprehensive patient characterization for precision medicine



New IMS-IMWG Recommendation on HR MM

1. del(17p) (with a cutoff of >20% clonal fraction) and/or TP53 mutation

2. t(4;14) or t(14;16) or t(14;20) along with +1 q and/or del(1p)

3. monoallelic del(1p32) along with +1 q, or bi-allelic del(1p32)

4. β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL)

Defining High Risk Disease: Non-Cytogenetic Biomarkers

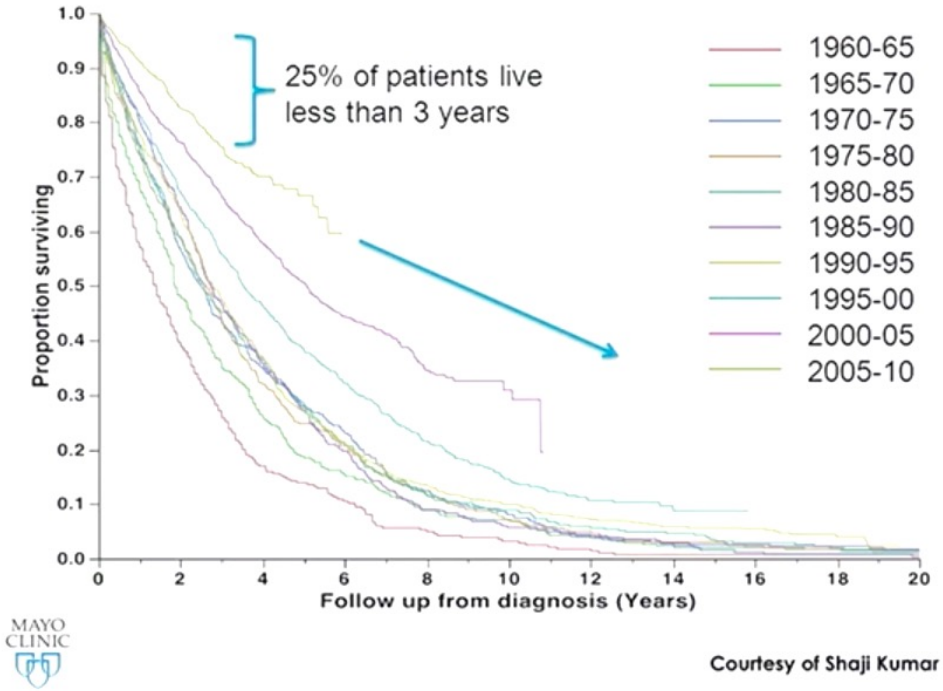
- ✓ IgD Subtype[1]
- ✓ Circulating tumor cells[2,3]
- ✓ Gene expression signatures (PR[4], EMC92[5])
- ✓ APOBEC Mutation Signature[6,7]
- ✓ Chromothripsis[8]

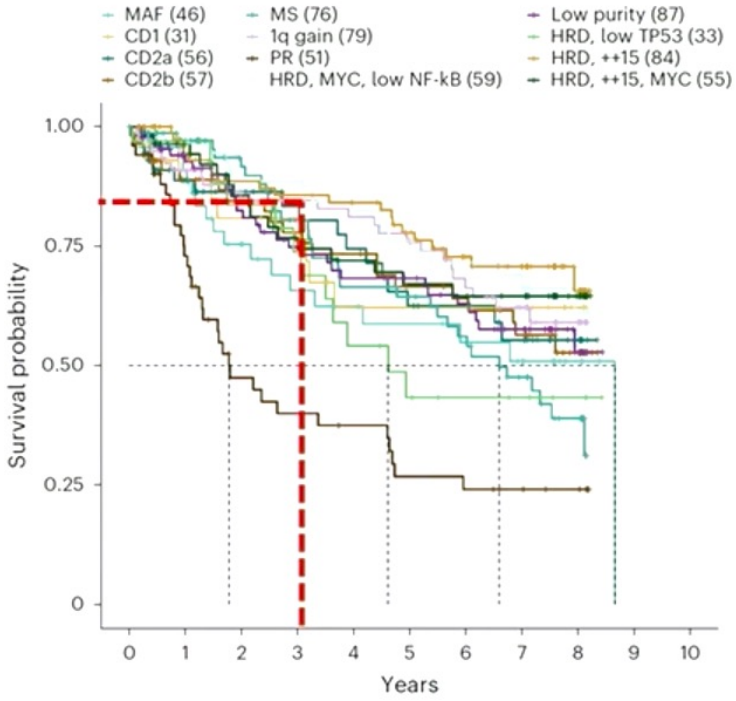
1. Liu J, et al. Leukemia 2021
2. Bertamini L, et al. JCO 2022
3. Garces JJ, et al. JCO 2022
4. Skerget S, et al. Nat Genet 2024
5. Kuipers R, et al, Leukemia 2013
6. Walker B, et al. Nat Comms 2015
7. Maura F, et al. Leukemia 2018
8. Maclachlan KH, et al. Nat Comms 2021

Defining High Risk Disease: Clinical Features

- ✓ Age and Frailty
- ✓ Extramedullary disease (not bone based)
- ✓ CNS disease

Operational Definition of HR-MM - OS of less than 3 years

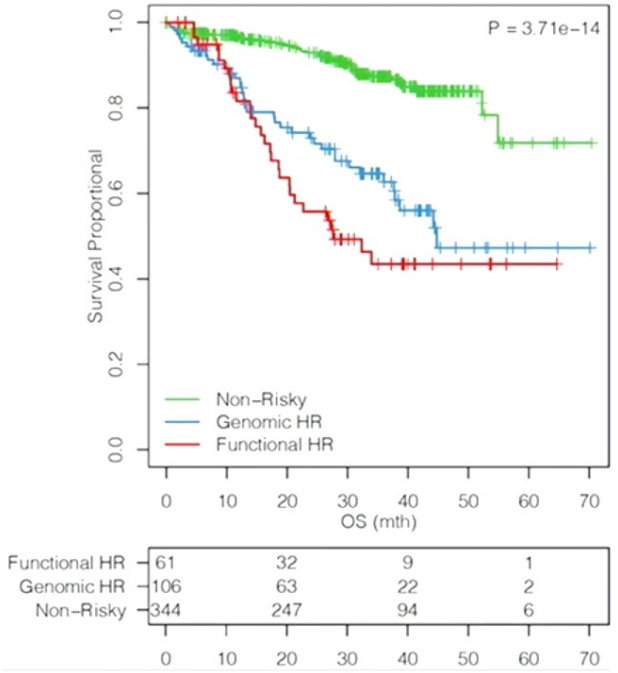




Skerget et al. Nat Genet 2024

Defining High Risk Disease: Functional High Risk

- ✓ Compass Dataset
- ✓ NDMM
- ✓ Suboptimal Response to Induction
- ✓ Progression within 12 Months of Induction



Soekojo Cet al. Blood Cancer J 2022

Definition of Functional High Risk

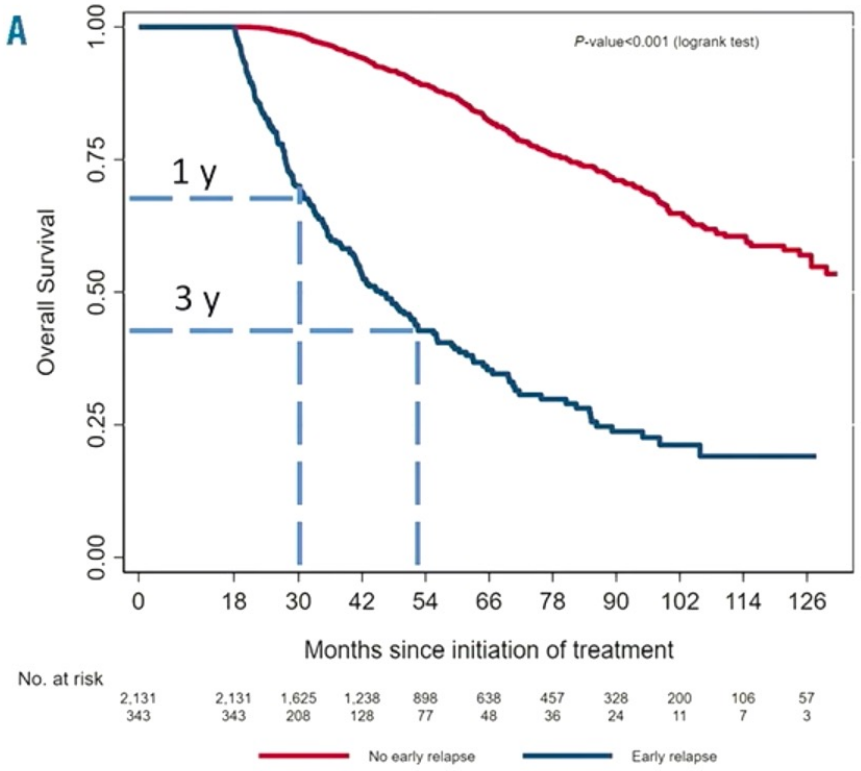
Early relapse from 1st line
Mostly after ASCT, within
1-2y from start Tx

+

No risk factors at diagnosis

(detected)

Early relapse from 1st line a clinical problem



-French experience, 2474 patients

-Primary refractory excluded

-Relapse within 18 months of start of Tx

-ca 16% patients with Early Relapse

-Consistent findings, e.g. MyXI and others

Once relapsed, difficult to rescue

→ Diagnosing High Risk early **to avoid patients becoming 'Functional High Risk'** should be primary aim

Corre et al, 2020
doi.org/10.3324/haematol.2019.236588

Bygrave et al, 2021
https://doi.org/10.1111/bih.16793

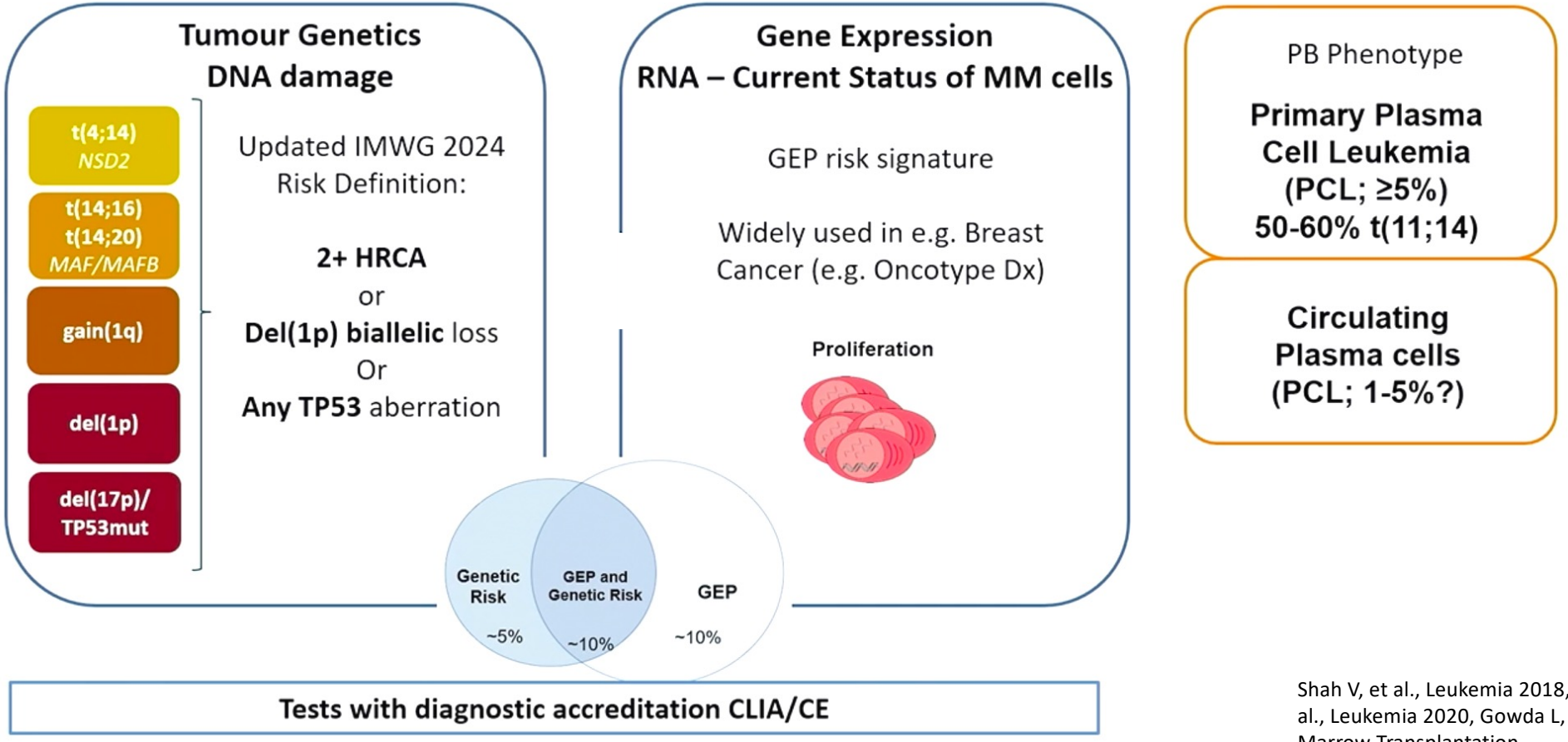
Esperienza della SC di Ematologia e CTMO – Ospedale Oncologico di Riferimento Regionale «A. Businco»

88 pazienti affetti da NDMM sottoposti a terapia con DaraVTD

- 13,6% (12 pz) dei pazienti «early relapse» – «progressive disease» – «low responders to induction»

- 7 pazienti hanno avuto una risposta < PR dopo induzione → **KRd + doppio autotrapianto + KRd + lenalidomide**
- 4 pazienti con malattia in progressione durante induzione (con malattia extramidollare) → **D-PACE + X**
- 1 paziente con malattia in progressione dopo un mese dal primo autotrapianto → **D-PACE + KRd + Cyclophosphamide HD + Teclistamab**
- Solo una paziente recidivata dopo 7 mesi di lenalidomide (+ 20 mesi da inizio di DaraVTD) → **IsaKd**

Combined and complete profiling matters to correctly diagnose high risk MM



Shah V, et al., Leukemia 2018, Shah V, et al., Leukemia 2020, Gowda L, et al., Bone Marrow Transplantation,

How much Functional High Risk (FHR) is left when profiling Genetics + GEP?

135 patients
Myeloma XI
ASCT
+ Len Maint

Complete Info On All markers

25 pts Relapse <24mo → 13 pts FHR → 7 pts FHR → **3 pts FHR**

12 pts IMWG24 High Risk

6 pts GEP High Risk

2 pts b2m>5.5
2 pts t(4;14)

Of which 2 with t(11;14)
Circulating PC not measured
Imaging not assessed

Martin Kaiser personal comunication

How much Functional High Risk (FHR) is left when profiling Genetics + GEP?

135 patients
Myeloma XI
ASCT
+ Len Maint

Complete
Info
On
All markers

Aim: test all IMWG24 high risk markers + if available, GEP to identify High Risk early
→Stratified treatment upfront

25 pts
Relapse
<24mo

13 pts
FHR

7 pts
FHR

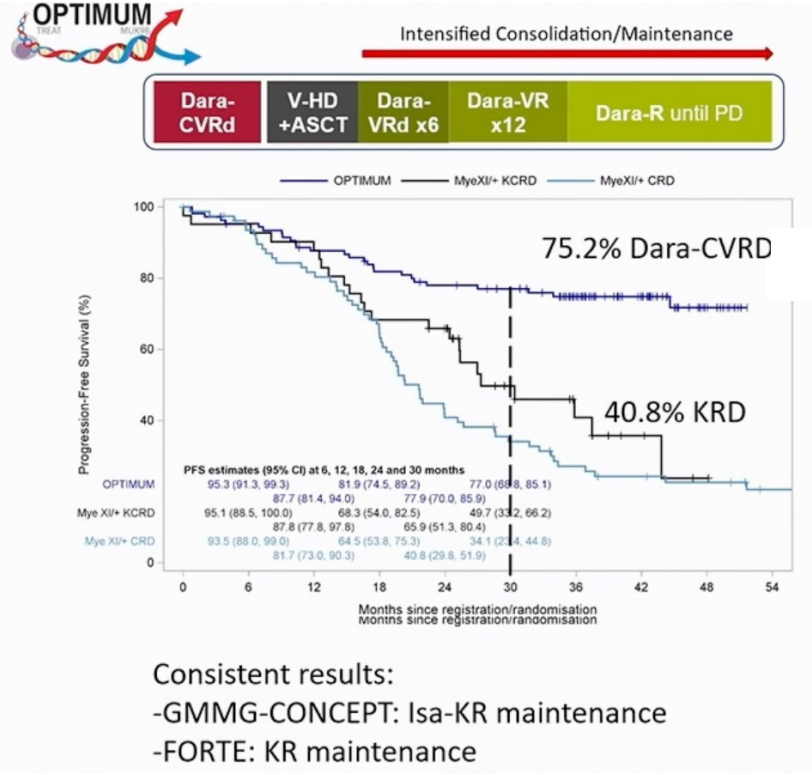
3 pts
FHR

12 pts
IMWG24
High Risk

6 pts
GEP
High Risk

2 pts
b2m>5.5
2 pts
t(4;14)

Stratified management for High-Risk MM can reduce Early Relapse

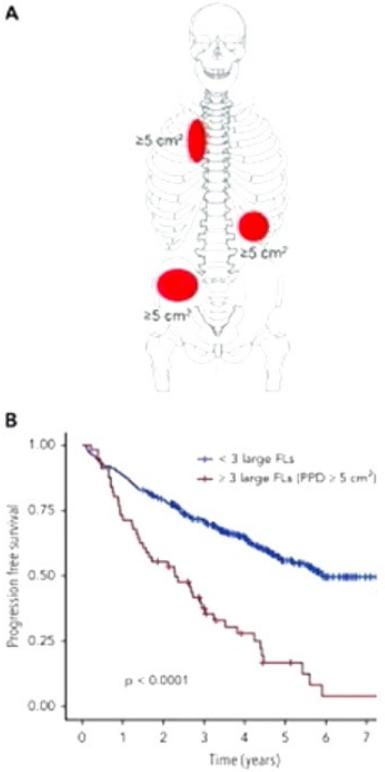


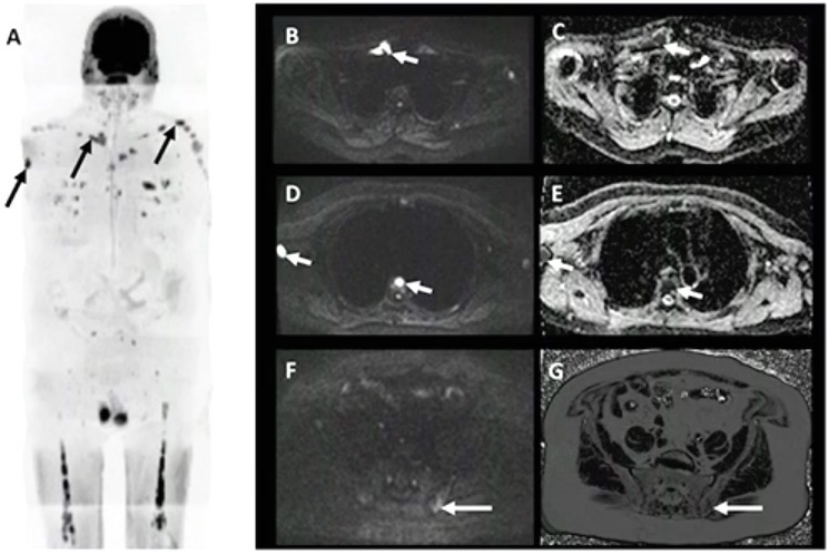
Stratified management for High-Risk MM can reduce Early Relapse:

- ✓ Discuss situation with the patient
- ✓ Keep treatment breaks to a minimum
- ✓ Continue treatment, even if MRD-negative (MASTER)
- ✓ If possible, maintain treatment intensity post-ASCT with combination maintenance

Leypoldt et al, https://doi.org/10.1200/jco.23.01696
Kaiser et al, https://doi.org/10.1200/jco.22.02567
Mina et al, 10.1016/51470-2045(22)00693-3

Next steps in diagnostics: spatial heterogeneity

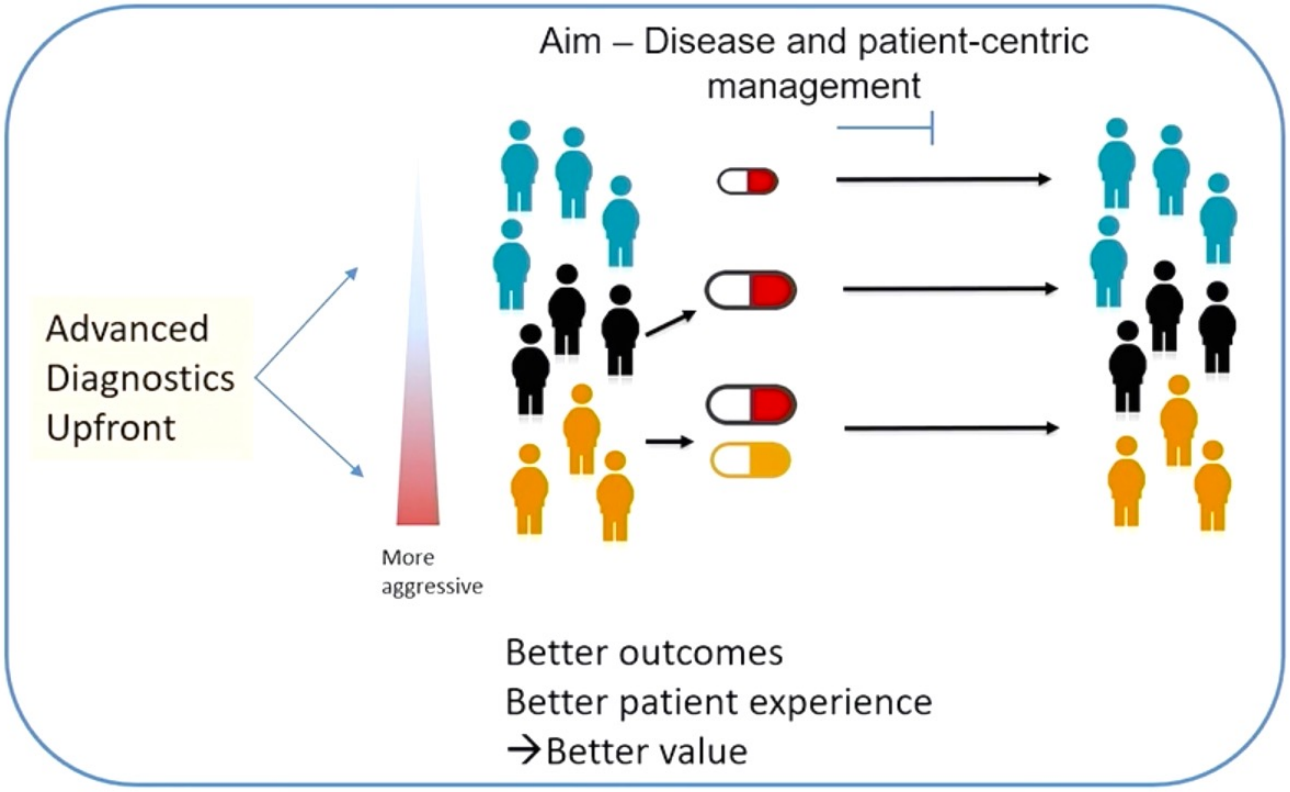




Whole body MRI with Machine Assisted Reporting – in development for many cancers
Likely to change the assessment of Risk in future

10.1182/blood-2018-04-842880
https://doi.org/10.1016/j.mri.2020.10.005

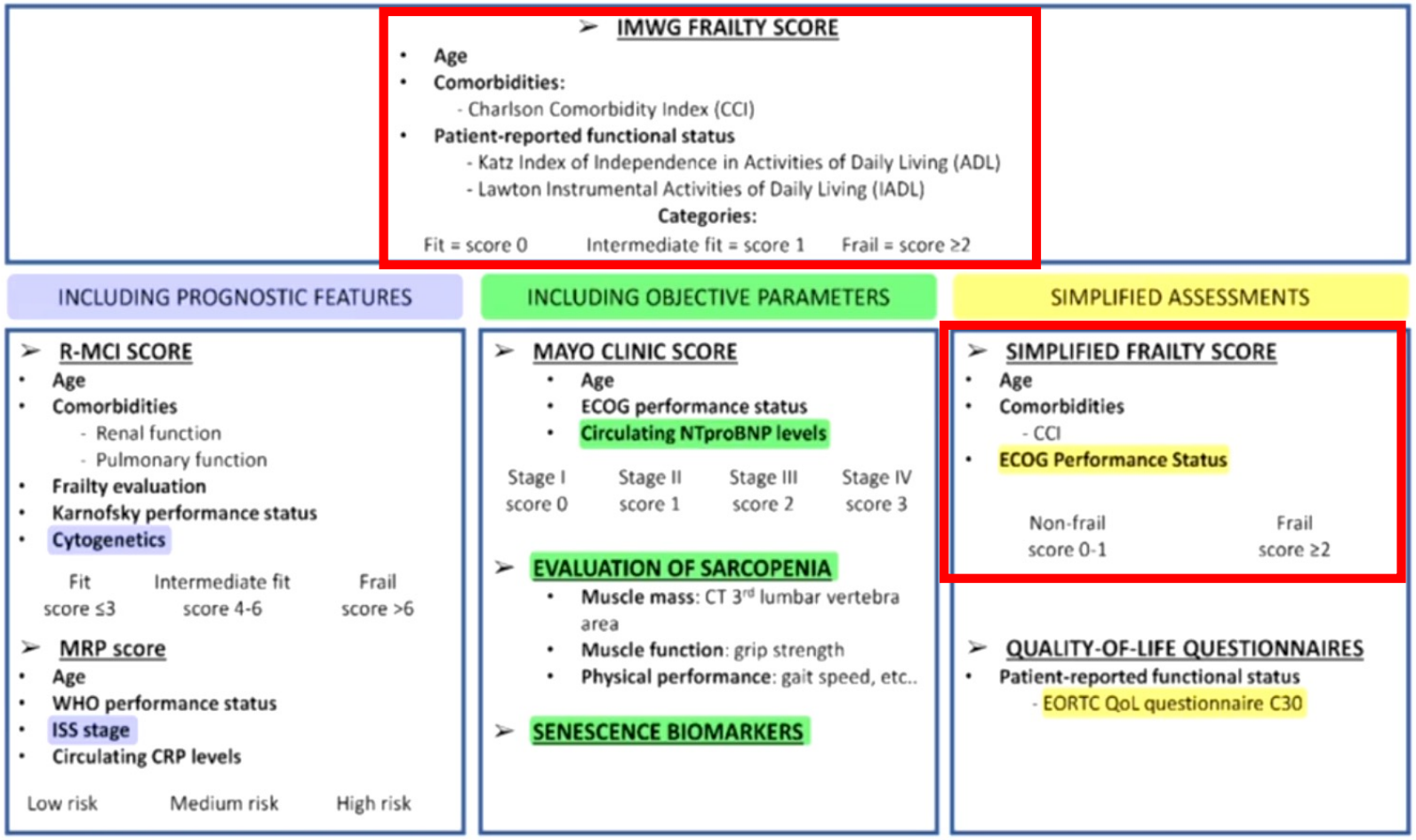
Better upfront diagnostics for improved care delivery across risk spectrum



Does require pursuing upfront diagnostics like in AML or ALL

Defining High Risk Disease: Clinical Features

- ✓ *Age and Frailty*
- ✓ Extramedullary disease (not bone based)
- ✓ CNS disease

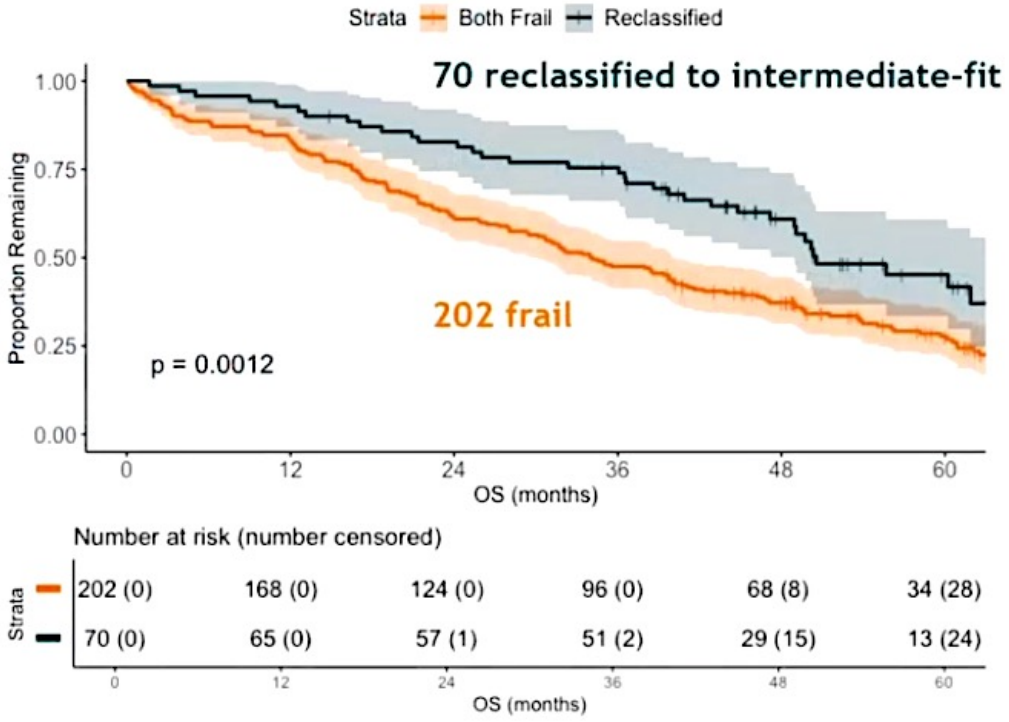

IMWG FRAILTY SCORE
Age
Comorbidities:
- Charlson Comorbidity Index (CCI)
Patient-reported functional status
- Katz Index of Independence in Activities of Daily Living (ADL)
- Lawton Instrumental Activities of Daily Living (IADL)
Categories:
Fit = score 0
Intermediate fit = score 1
Frail = score ≥2
INCLUDING PROGNOSTIC FEATURES
INCLUDING OBJECTIVE PARAMETERS
SIMPLIFIED ASSESSMENTS
R-MCI SCORE
Age
Comorbidities
- Renal function
- Pulmonary function
Frailty evaluation
Karnofsky performance status
Cytogenetics
Fit score ≤3
Intermediate fit score 4-6
Frail score >6
MRP score
Age
WHO performance status
ISS stage
Circulating CRP levels
Low risk
Medium risk
High risk
MAYO CLINIC SCORE
Age
ECOG performance status
Circulating NTproBNP levels
Stage I score 0
Stage II score 1
Stage III score 2
Stage IV score 3
EVALUATION OF SARCOPENIA
Muscle mass: CT 3rd lumbar vertebra area
Muscle function: grip strength
Physical performance: gait speed, etc..
SENESCENCE BIOMARKERS
SIMPLIFIED FRAILTY SCORE
Age
Comorbidities
- CCI
ECOG Performance Status
Non-frail score 0-1
Frail score ≥2
QUALITY-OF-LIFE QUESTIONNAIRES
Patient-reported functional status
- EORTC QoL questionnaire C30

2 PROSPECTIVE HOVON STUDIES - SIMPLIFIED FI INCORRECTLY CLASSIFIES INTERMEDIATE FIT PATIENTS AS FRAIL

272 frail patients according to the simplified frailty index

202 patients also frail according to the IMWG-FI

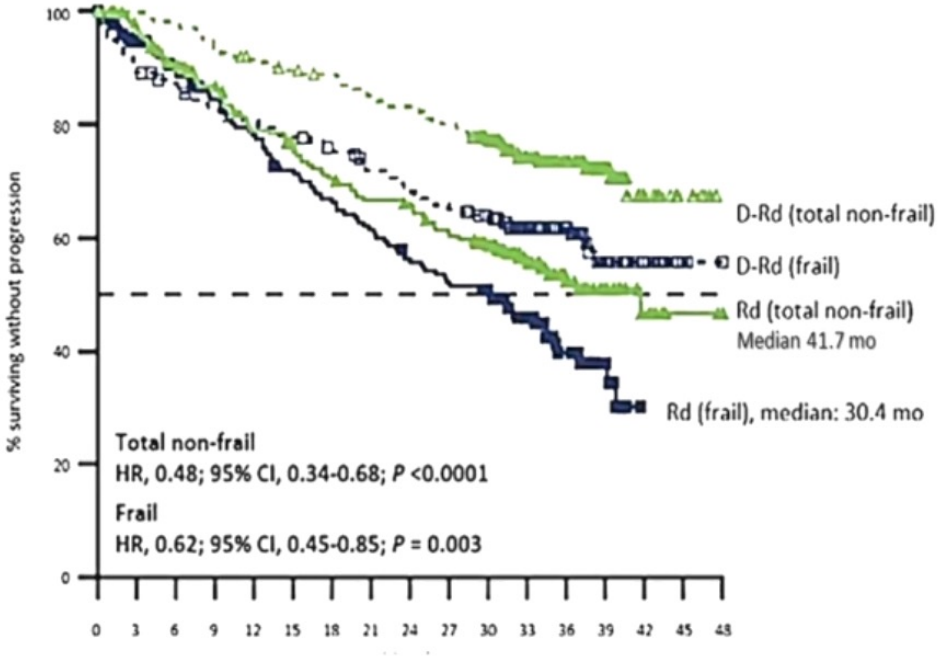
70 patients (25%) intermediate fit according to the IMWG-FI, showing better outcome



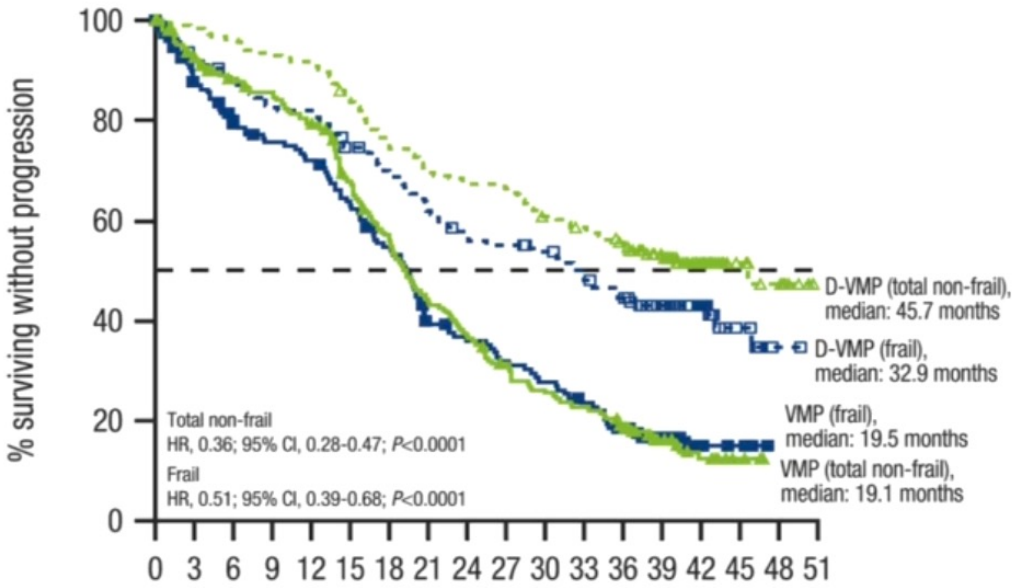
Groen et al, Hemasphere, 2024 Jul 4;8(7)

Frailty subgroup analysis of MAIA and ALCYONE

MAIA PFS



ALCYONE PFS



Facon, T. et al. Leukemia 2022, 36, 1066-1077. Mateos, M.V. et al. Clin. Lymphoma Myeloma Leuk. 2021, 21, 785-798.

Frailty subgroup analysis of MAIA and ALCYONE

	MAIA Trial		ALCYONE Trial	
Age, media				
<65, *n* (%				
65–<70 y				
70–<75 y				
≥75 yr, *n*				
≥80 yr, *n*				
ECOG-PS				
0, *n* (%)				
1, *n* (%)				
2, *n* (%)				
>2, *n* (%)				
Unknow				
Creatinine				
≥60, *n* (%)	133 (67.9)	73 (42.4)	121 (64.7)	79 (48.5)
30–<60, *n* (%)	63 (32.1)	92 (53.5)	65 (34.8)	82 (50.3)
<30, *n* (%)	0 (0.0)	7 (4.1)	1 (0.5)	2 (1.2)

The optimal treatment of frail patients is not easily derived from available clinical trials

The data from clinical trials cannot be simply extrapolated to real-world patients

The majority of real world patients are not eligible for clinical trials, since they have a poorer performance status and several comorbidities

Facon, T. et al. Leukemia 2022, 36, 1066-1077. Mateos, M.V. et al. Clin. Lymphoma Myeloma Leuk. 2021, 21, 785-798.

Treatment adjustment based on patient frailty/fitness

EHA-ESMO Guidelines

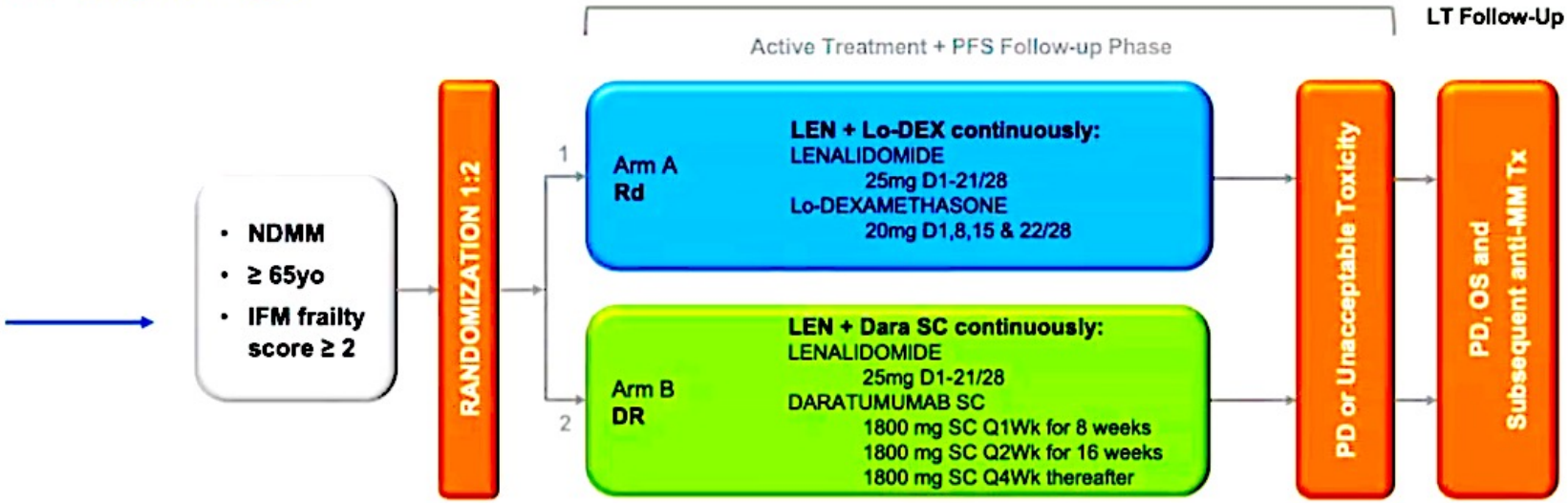
Frailty index risk factors				
IMWG frailty index[1]	0	1	1 + occurrence of grade 3-4 haematological AE	≥2
R-MCI[2]	1-3	4-6	7-9	
Dose level	0	1	-2	-2
Treatment doses	**Level 0**	**Level 1**	**Level 2**	
Prednisone	2 mg/kg days 1-4 of a 4-6-week cycle 60 mg/m^2 days 1-4 of a 6-week cycle	1 mg/kg days 1-4 of a 4-6-week cycle 30 mg/m^2 days 1-4 of a 6-week cycle	0.3-0.5 mg/kg days 1-4 of a 4-6-week cycle 10-15 mg/m^2 days 1-4 of a 6-week cycle	
Dexamethasone	40 mg day 1, 8, 15, 22 of a 28-day cycle	20 mg day 1, 8, 15, 22 of a 28-day cycle	10 mg day 1, 8, 15, 22 of a 28-day cycle	
Melphalan	0.25 mg/kg days 1-4 of a 4-6 week cycle 9 mg/ m^2 days 1-4 of a 6-week cycle	0.18 mg/kg days 1-4 of a 4-6 week cycle 7.5 mg/m^2 days 1-4 of a 6-week cycle	0.13 mg/kg days 1-4 of a 4-6-week cycle 5 mg/ m^2 days 1-4 of a 6-week cycle	
Thalidomide	100 (-200) mg/day	50 (-100) mg/day	50 mg qod (- 50 mg/day)	
Lenalidomide	25 mg days 1-21 of a 28-day cycle	15 mg days 1-21 of a 28-day cycle	10 mg days 1-21 of a 28-day cycle	
Pomalidomide	4 mg days 1-21 of a 28-day cycle	3 mg days 1-21 of a 28-day cycle	2 mg days 1-21 of a 28-day cycle	
Bortezomib	1.3 mg/m^2 twice weekly	1.3 mg/m^2 once weekly	1.0 mg/m^2 once weekly	

	Day 1, 4, 8, 11 every 3 weeks	Day 1, 8, 15, 22 every 5 weeks	Day 1, 8, 15, 22 every 5 weeks
Carfilzomib[a]	20 mg/m^2 day 1, 2, 8, 9, 15, 16 cycle 1, 27 mg/m^2 cycle 2 every 3 weeks	20 mg/m^2 cycle 1 → 27 mg/m^2 cycle 2, day 1, 8, 15, every 3 weeks	20 mg/m^2 day 1, 8, 15, every 4 (5) weeks
Ixazomib	4 mg day 1, 8, 15, every 4 weeks	3 mg day 1, 8, 15, every 4 weeks	2.3 mg day 1, 8, 15, every 4 weeks
Daratumumab[a]	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1þ15, from week 25: every 4 weeks	16 mg/kg bw,cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks
Elotuzumab[b]	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw, day 1, 8, 15, 22 cycle 1þ2, from cycle 3: day 1þ15
Panobinostat	20 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	15 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	10 mg day 1, 3, 5, 8, 10, 12 every 5 weeks

Expert-opinion dose modification guidelines are available to adapt treatment

Dimopouolos MA et al. Annals of Oncology 2021

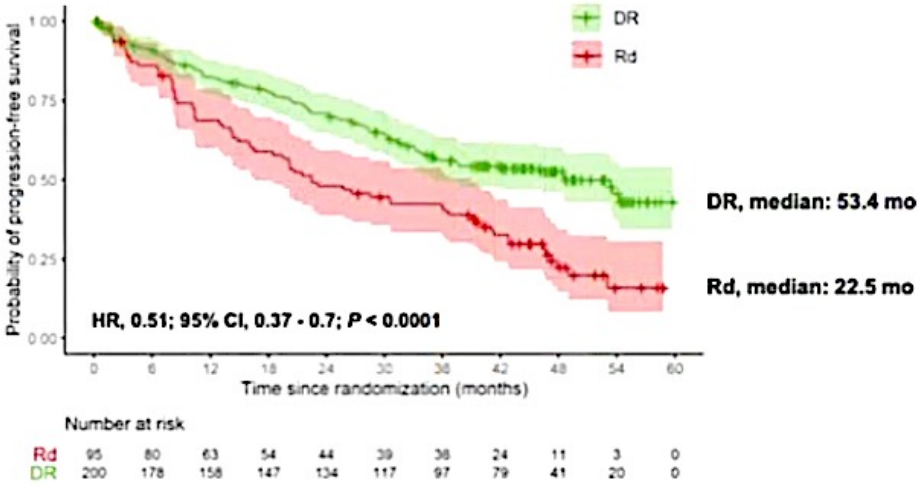
A DEXAMETHASONE-SPARING REGIMEN INCLUDING DARATUMUMAB IN FRAIL NDMM PATIENTS
IFM 2017-03

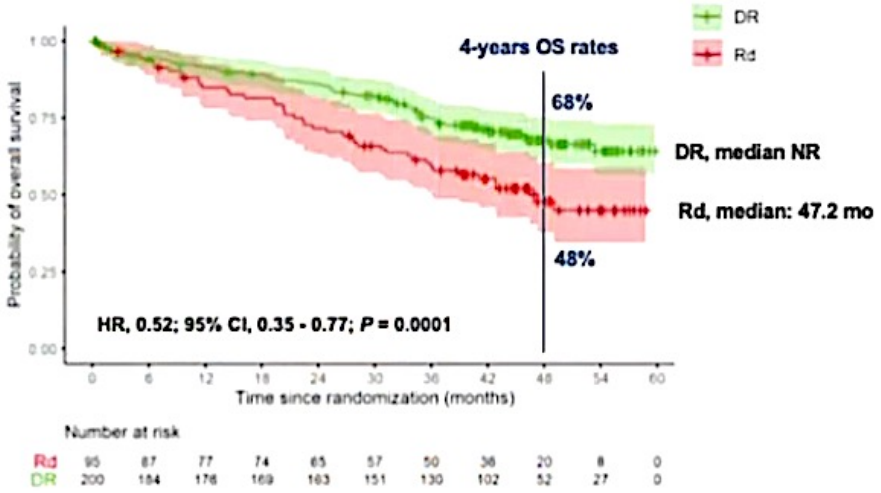


Randomization stratified by ISS (I vs II vs III) and age (<80 vs ≥80) - ~60% ≥80
In Arm B low-dose dex (20mg/week) during Cycle 1 and 2 (with SC dara)

Manier A et al. ASH 2022

A DEXAMETHASONE-SPARING REGIMEN INCLUDING DARATUMUMAB IN FRAIL NDMM PATIENTS RESULTED IN A PROMISING PFS AND OS
IFM 2017-03





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Frail....

- ✓ Novel therapy regimens including CD38 mAb improved the outcome in frail patients, but have not totally overcome the negative impact of frailty
- ✓ May be explained by lower tolerability as indicated by higher severe toxicity leading to more discontinuation of therapy
- ✓ Limited evidence how to adapt treatment in frail patients
- ✓ Post-hoc subanalysis based on the simplified frailty index
- ✓ Studies specifically designed for frail patients - using the IMWG frailty score - are scarce
- ✓ Only one RCT in frail patients - also using the simplified frailty index

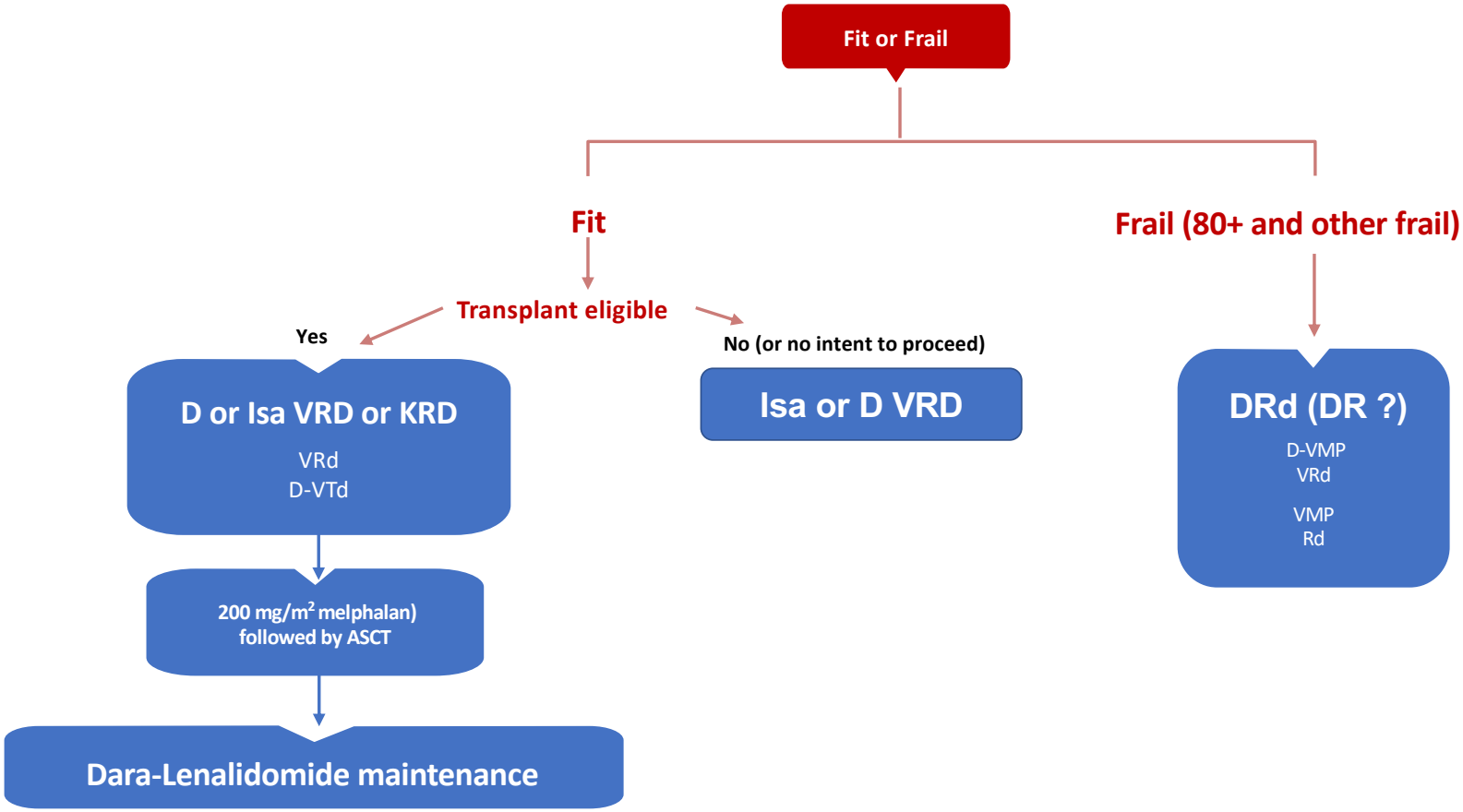
How to treat frail patients

LIMITED EVIDENCE, OFTEN EXPERT OPINIONS

- ✓ Adapt the dose in order to improve tolerability
- ✓ Daratumumab - feasible - no dose adaptations
- ✓ Lenalidomide
  - Lower dose at the start
  - **After 9 cycles 10 mg** - also in the CD38 mAb - quad era?
- ✓ Dexamethasone
  - Start with 20 mg/week
  - **After 9 cycles** discontinue if in combination with lenalidomide
  - After 2 cycles reduce to 10 mg? **Or even discontinue?**

Be aware that low grade side effects (especially neuropathy) can have high impact in frail and lead discontinuation - slow start, lower dose, once-weekly dosing

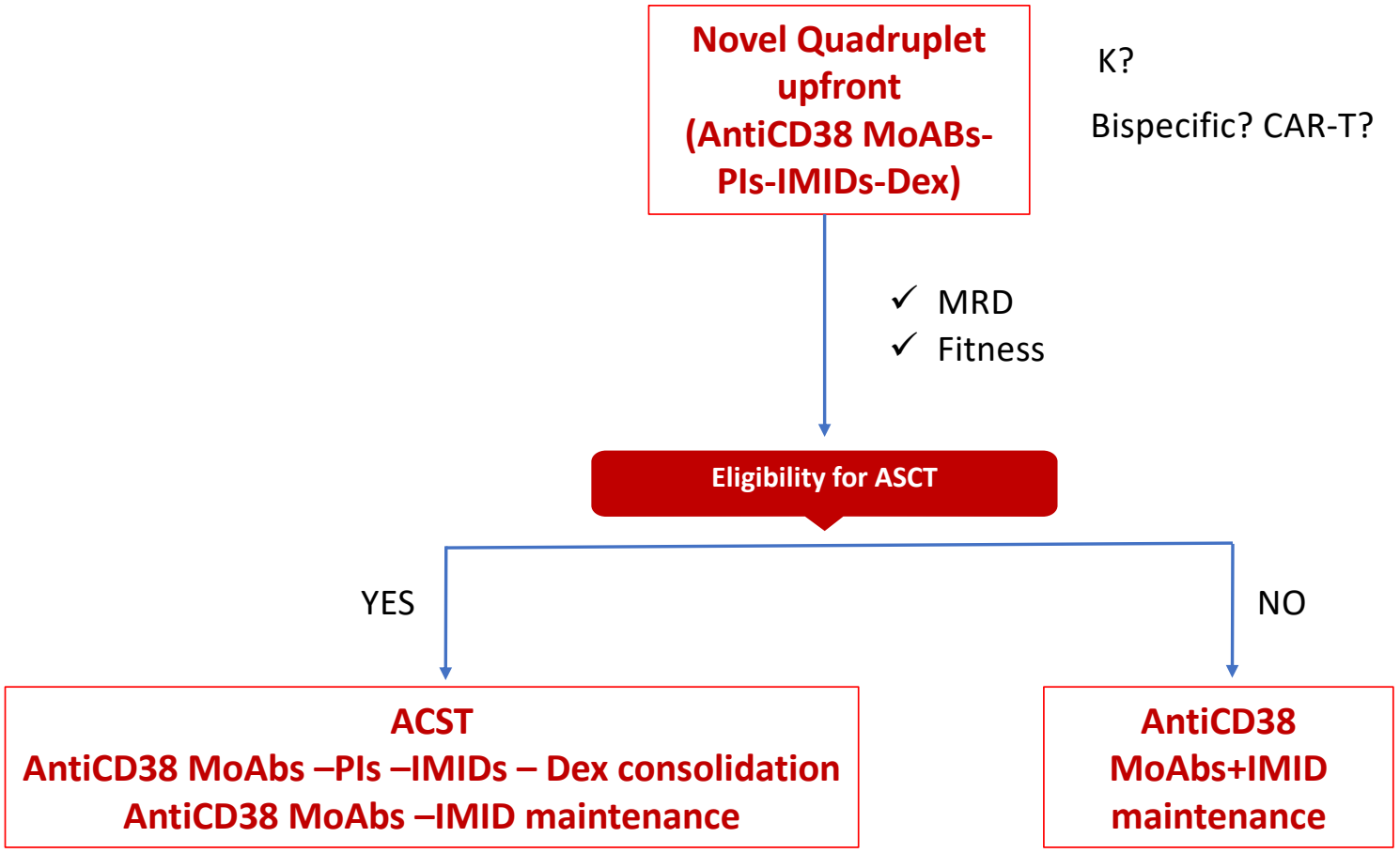
Newly diagnosed **Multiple Myeloma – 2024 +**



- Risk (high vs.std) may impact treatment decision
- CART vs. ASCT eligibility
- MRD?

ASCT, autologous stem cell transplantation; DRd, daratumumab + lenalidomide + dexamethasone; D-VMP, daratumumab + bortezomib + melphalan + prednisone; D-VRd, daratumumab + bortezomib + lenalidomide + dexamethasone; D-VTd, daratumumab + bortezomib + thalidomide + dexamethasone; Rd, lenalidomide + dexamethasone; VMP, bortezomib + melphalan + prednisone; VRd, bortezomib + lenalidomide + dexamethasone; VTd, bortezomib + thalidomide + dexamethasone; DVRD, Daratumumab-VRD; IsaVRD, Isatuximab-VRD; KRD, Carfilzomib+ lenalidomide+dexamethasone

Frontline beyond 2025



Gruppo gammopatie

Grazie per l'attenzione!