HIGHLIGHTS IN EMATOLOGIA

TREVISO
7-8 NOVEMBRE 2025

Ruolo attuale (e futuro) dell'autotrapianto nel Mieloma MUltiplo

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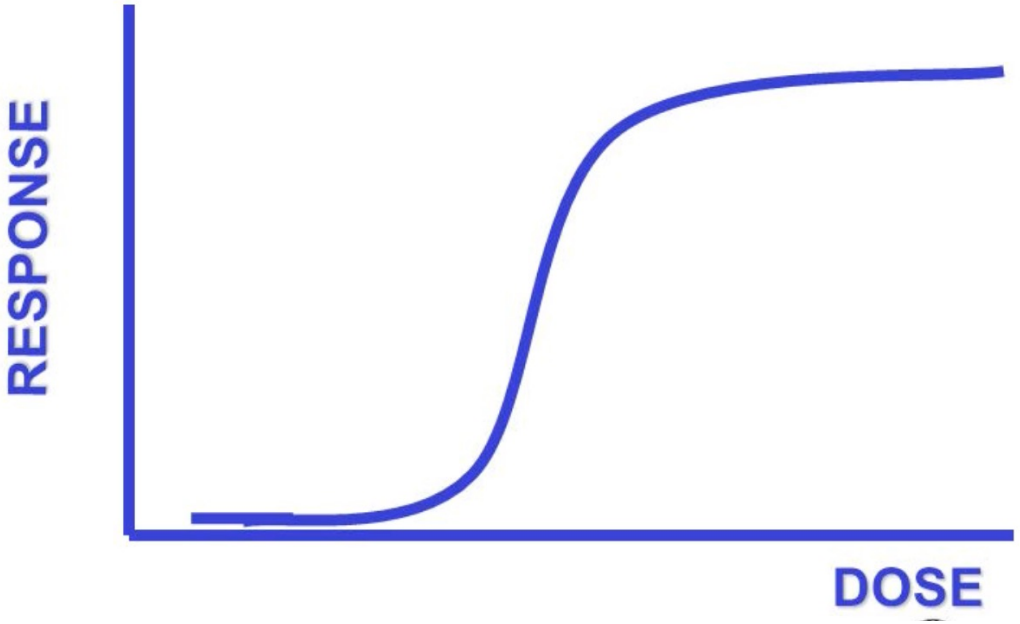
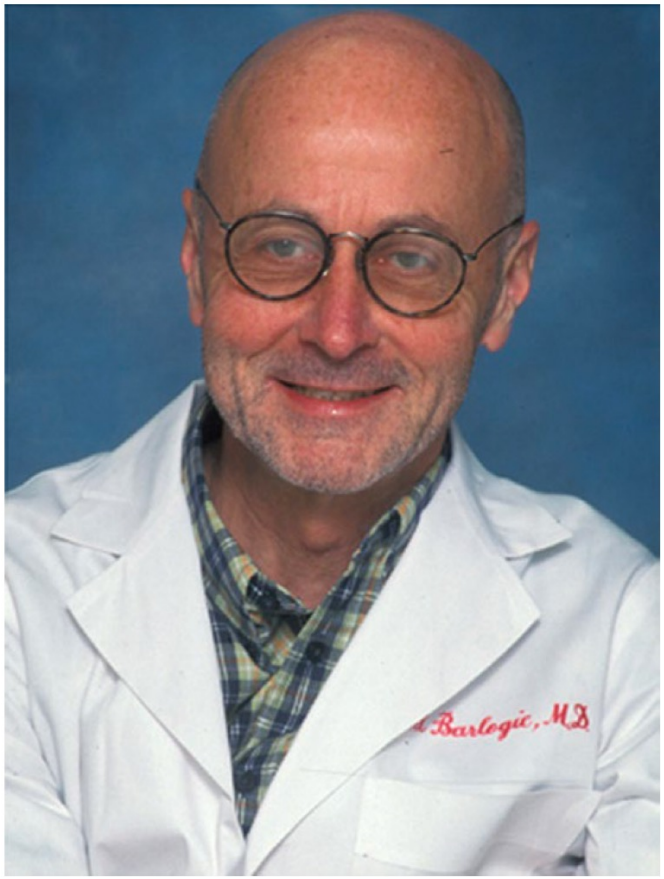
My Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK					x	x	
Janssen						x	
Menarini Stemline						x	
Amgen					x	x	
Sanofi					x	x	
Oncopeptides						x	
Pfizer					x	x	

MULTIPLE MYELOMA

Melphalan dose-response curve





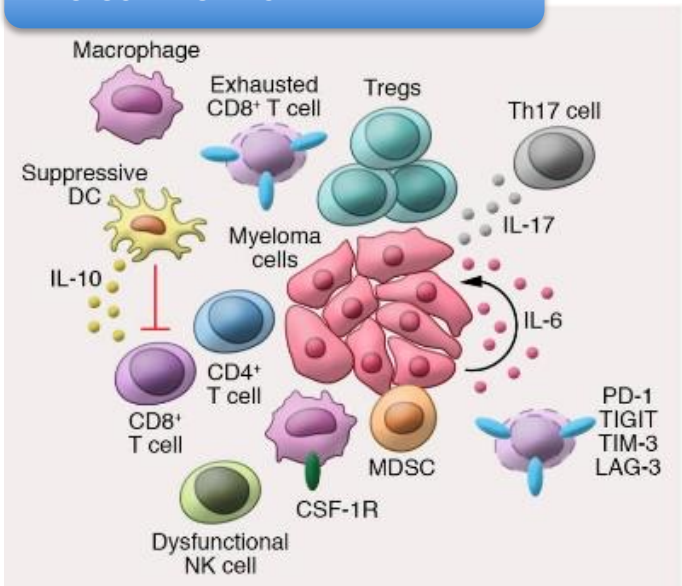
Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67:1298-1301.

Immune effects of high-dose melphalan + ASCT

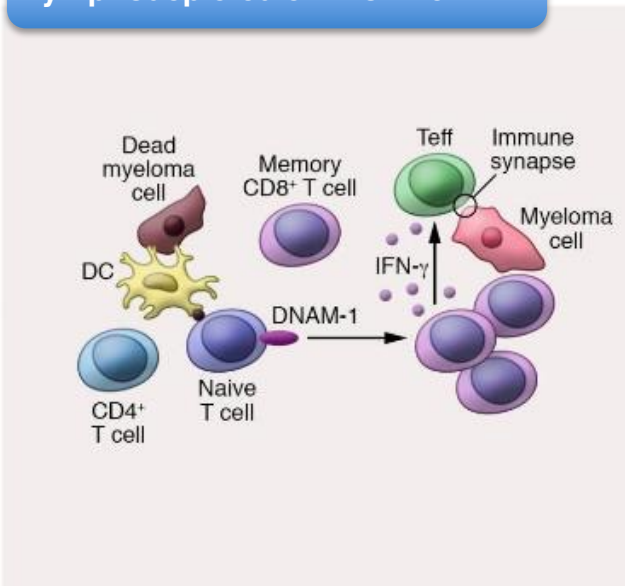
HDMEL200+ASCT[1,2]

- **Reduces immune suppression**
- **Disrupts tumor microenvironment / suppressive myeloid cells**
- **Increases T cell proliferation**
- **Increases antigen presentation**

Active MM – suppressive microenvironment[1,2]



Post-ASCT – inflamed lymphodepleted environment[1,2]

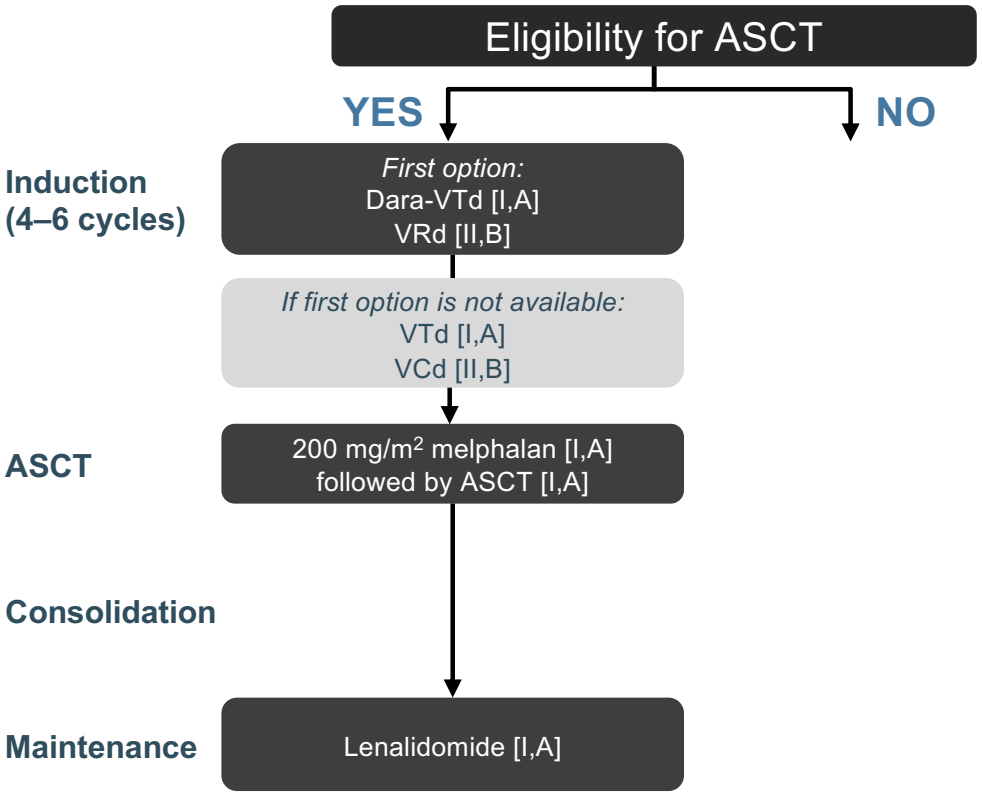


Combined immunologic and cytoreductive therapy[2] → deep and durable responses,[3] improved antitumor immune microenvironment, tumor-specific immunity following cellular reconstitution

1. Minnie SA, Hill GR. J Clin Invest 2020;130(4):1565–75. 2. Minnie SA, Hill GR. Front Immunol 2021;12:651288.
3. Attal M et al. N Engl J Med 2017;376(14):1311–20. 4. Swamydas M, et al. J Hematol Oncol 2022;15:17.

Dove siamo

EHA-ESMO Guidelines 2021

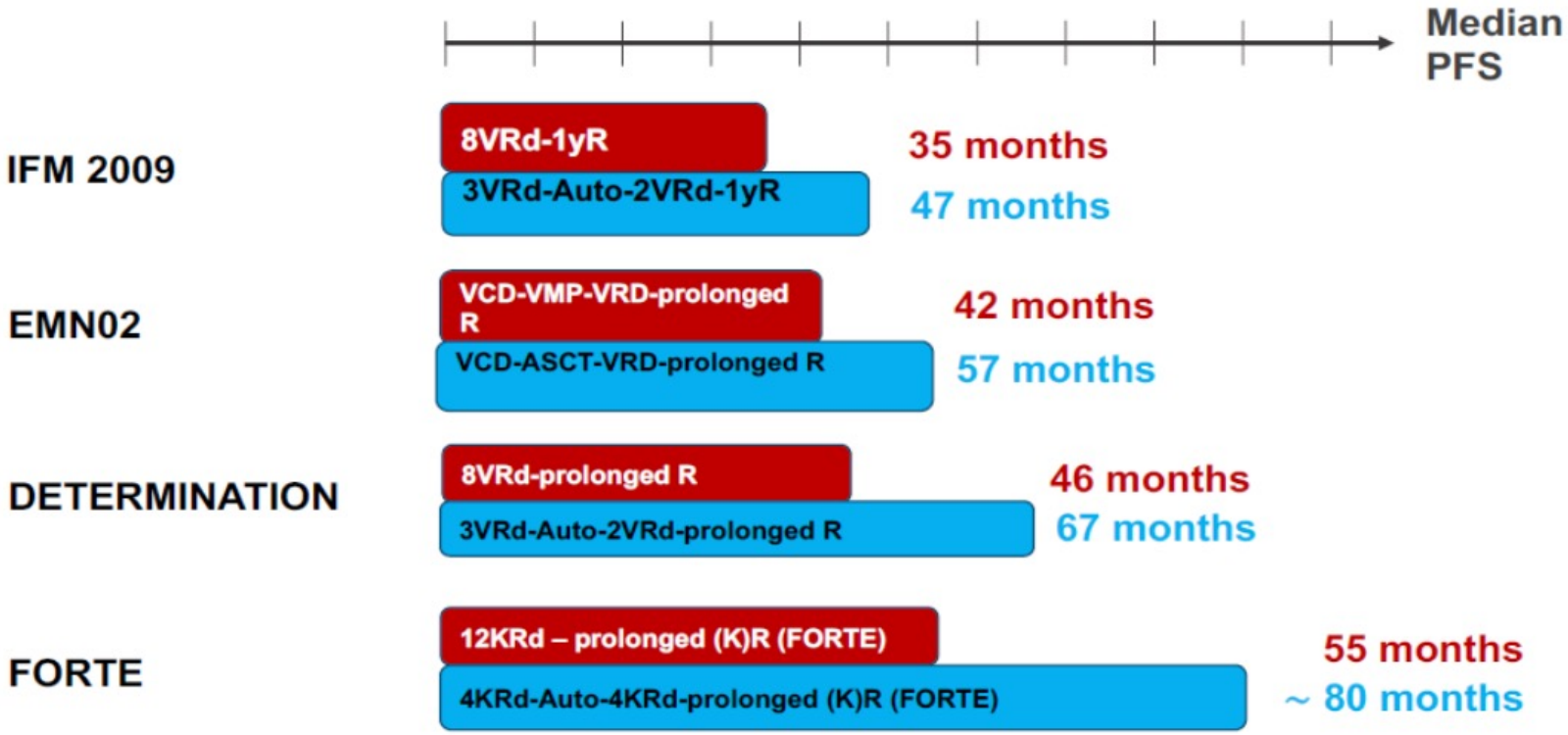


Dimopoulos MA, et al. Ann Oncol 2021;32:309–322;

EHA-EMN Guidelines 2025

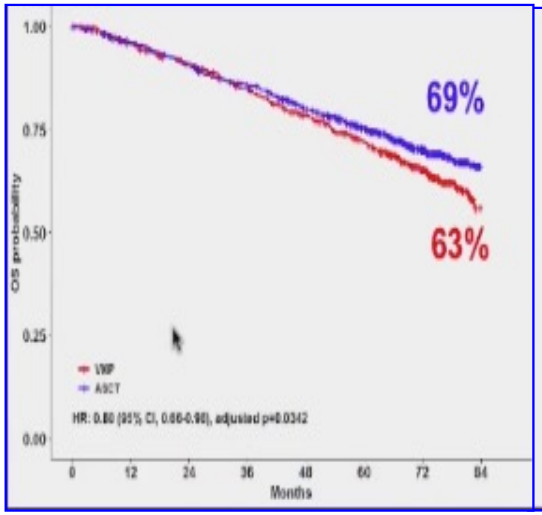
Dimopoulos MA et al. Nature Reviews Clinical

PFS with triplets with/without ABMT

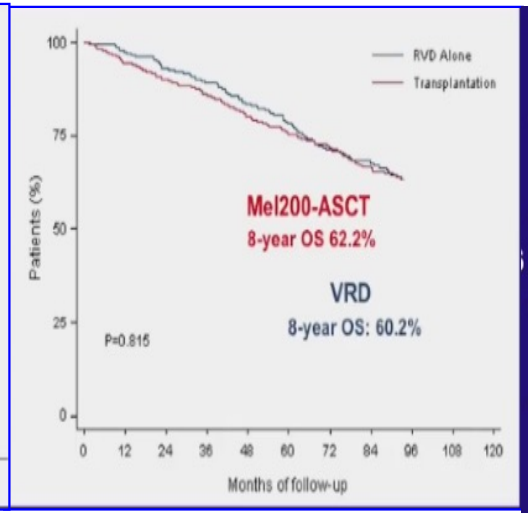


ASCT vs novel triplet based therapy : OS analysis

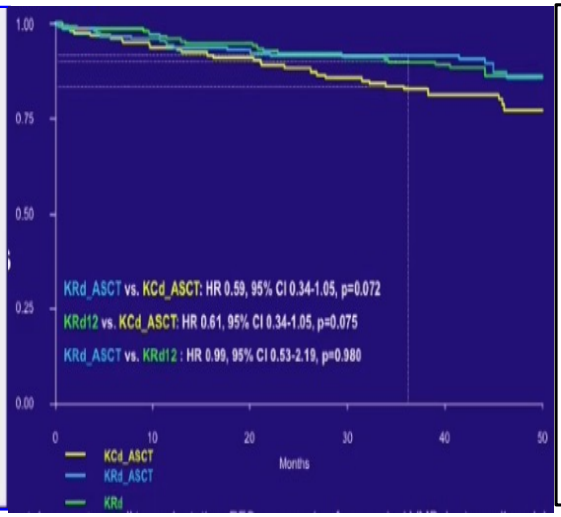
EMN-02: ASCT vs VMP
(median follow-up 75 months)



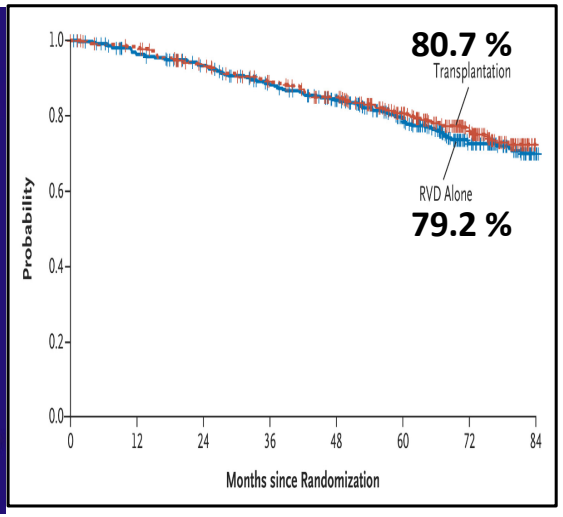
IFM09/DFCI: ASCT vs VRD
(median follow-up 89.8 months)



Forte: ASCT vs KRD
(median follow-up 45 months)

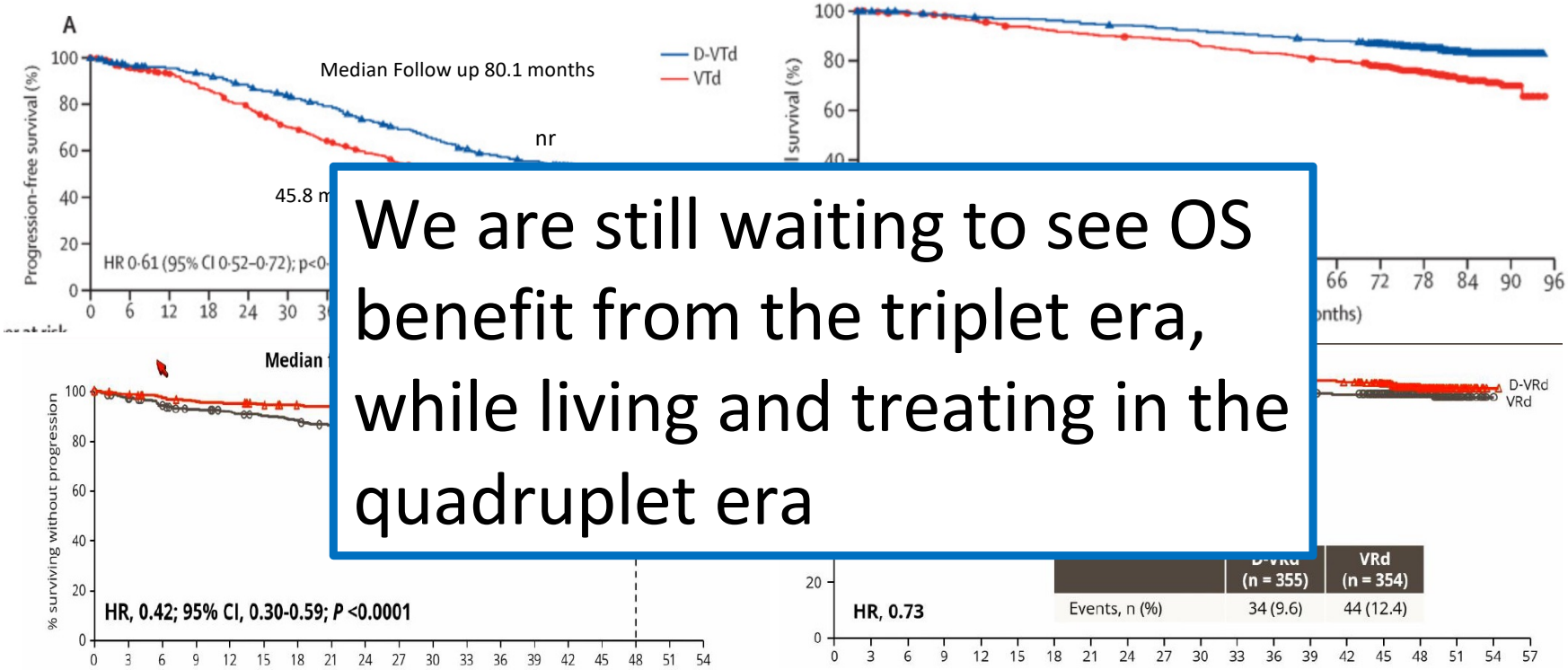


Determination: ASCT vs VRD
(median follow-up 76 months)



Parrot A et al ASH 2020; Cavo M et al ASH 2020; Gay F et al Lancet Oncol 2020; Richardson P et al NEJM 2022

ASCT with novel quadruplet-based therapy : OS analysis



We are still waiting to see OS benefit from the triplet era, while living and treating in the quadruplet era

Cassiopeia (DaraVTD vs VTD)

Perseus (DaraVRD vs VRD)

Moreau P et al Lancet Oncology 2024; Sonneveld p et al NEJM 2023

Immune effects of high-dose melphalan + ASCT

HDMEL200+ASCT[1,2]

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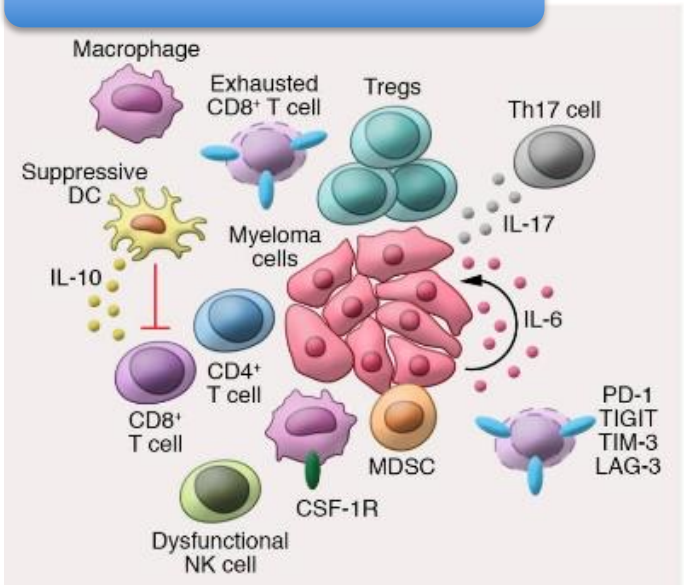
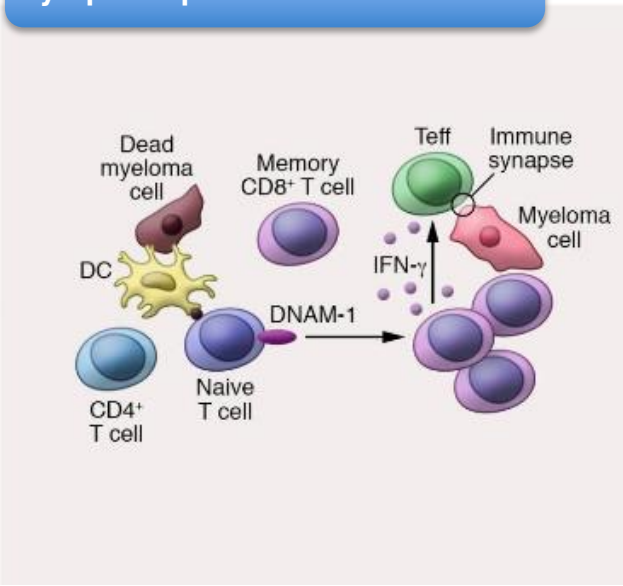


Post-ASCT – inflamed lymphodepleted environment[1,2]



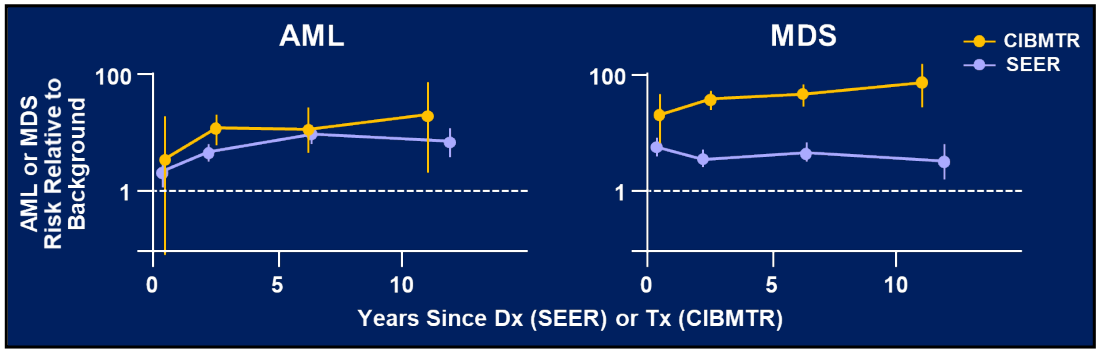
Combined immunologic and cytoreductive therapy[2] → deep and durable responses,[3] improved antitumor immune microenvironment, tumor-specific immunity following cellular reconstitution

But effects are highly variable and non-uniform,[4] with increased rates of infections post-ASCT,[3] prolonged cytopenias, and second cancers

1. Minnie SA, Hill GR. J Clin Invest 2020;130(4):1565–75. 2. Minnie SA, Hill GR. Front Immunol 2021;12:651288.
3. Attal M et al. N Engl J Med 2017;376(14):1311–20. 4. Swamydas M, et al. J Hematol Oncol 2022;15:17.

Risk of AML/MDS and mutational burden in MM cells at relapse after high-dose melphalan + ASCT

Risk of AML/MDS increased after high-dose melphalan + ASCT[1]



SEER data:

- Risks for AML/MDS in MM patients 5–10 times the background rate

CIBMTR data (n=4,566):

- Relative risks 10–50 for AML and ~100 for MDS in the HDM/ASCT cohort
- Adverse impact on PFS and OS of SPMs post-ASCT[2]

Mutational burden significantly increased after high-dose melphalan + ASCT (IFM 2009)[3,4]

Known mutagenic effect of high-dose melphalan[5]

Paired purified MM cells at diagnosis and at relapse from 68 patients using deep (75×) whole-genome sequencing to identify genomic changes induced by HDM and observed at relapse[3]

Impact on prognosis

	RVd	RVd→HDM+ASCT	*P*-value
Patients, n	45	23	—
Median follow-up, mos	29	31	—
Mutations at diagnosis, n	7137 [IQR=3741]	7230 [IQR=3702]	0.67
Mutations at relapse, n	9242	13,383	0.005
Indels* at relapse, n	360	467	0.02

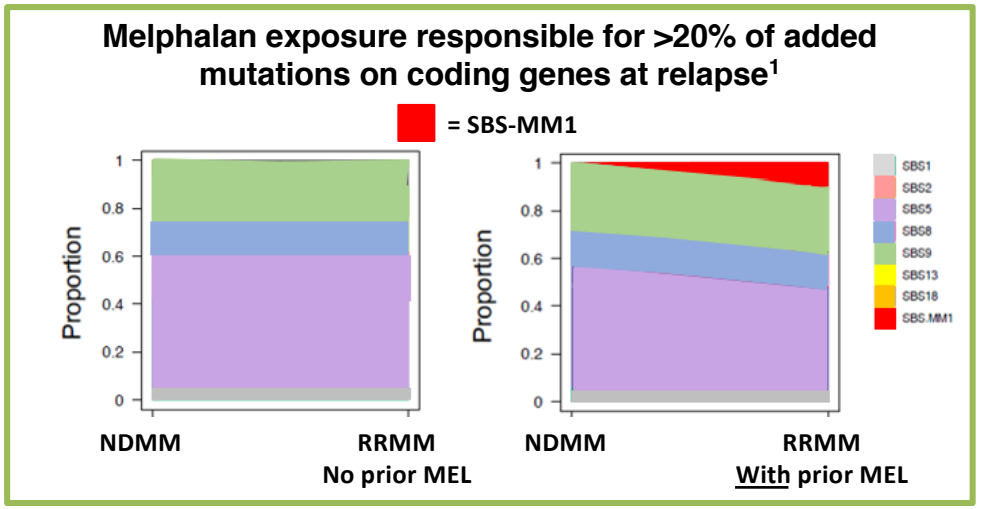
*The insertion or deletion of one or several nucleotides within a sequence

HDM causes a 4.1-fold higher mutation accumulation rate per month than RVd only (158.3 vs 38.3 mutations/month; *P*=0.003)

1. Radivoyevitch T, et al. Leuk Res. 2018;74:130. 2. Ragon BK, et al. Blood Adv 2023; e-pub ahead of print. 3. Samur MK, et al. Blood 2020;136(suppl):abstract 61. 4. Samur MK, et al. Blood 2023;141(14):1724–36. 5. Maura F, et al. Leukemia 2021;35:2145–50.

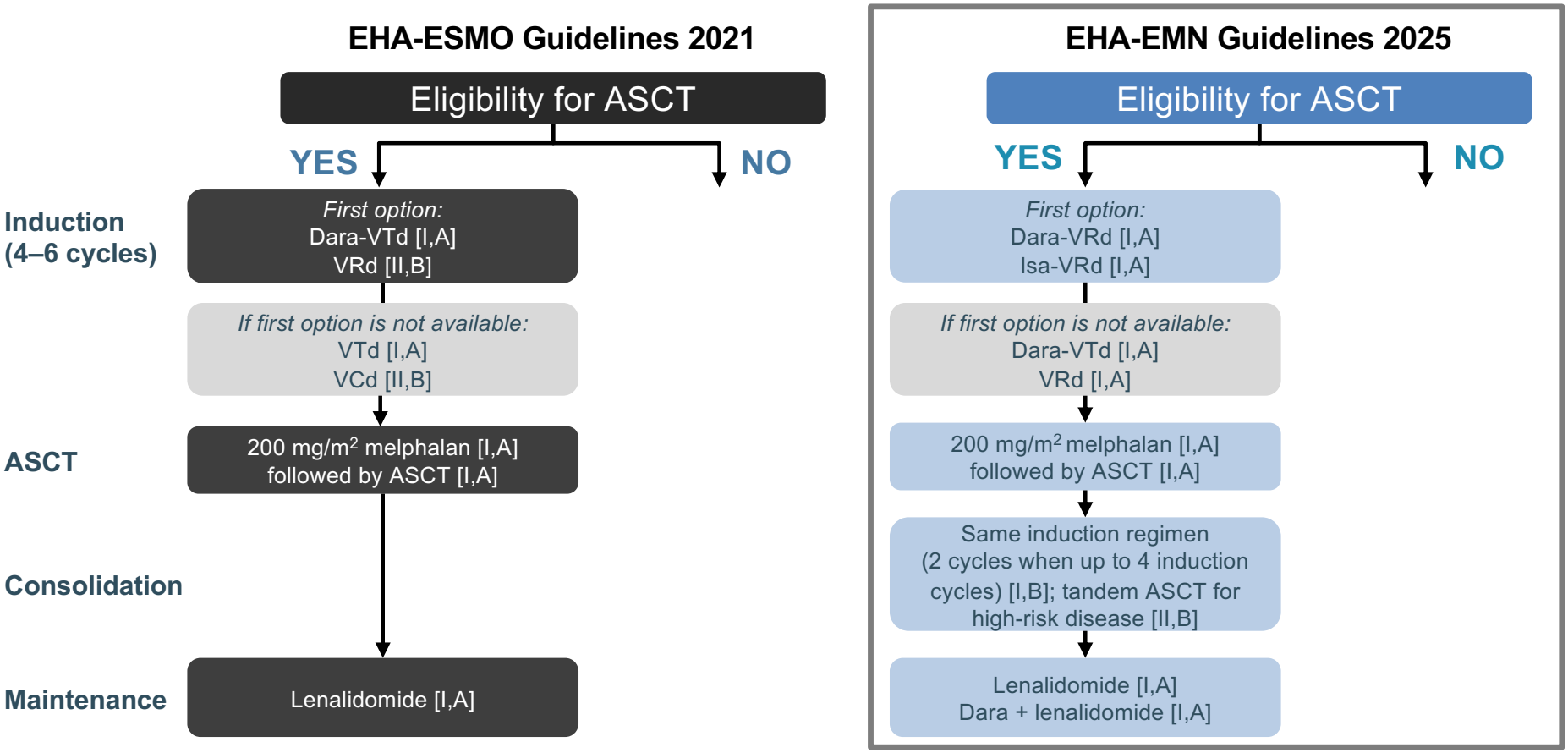
Melphalan mutational signatures in MM[1] –short-term and long-term implications

- **2014/2015: APOBEC genomic signature identified in MM**
- **2016: APOBEC confirmed; new signature (SBS-MM1) observed**
- **2018/2019: SBS-MM1 enriched in RRMM vs NDMM patients**
- **2020: SBS-MM1 shown to be caused by melphalan exposure[2-4]**
- **ASH 2020: confirmation of link between melphalan chemotherapy and SBS-MM1**



1. Maura F, et al. Leukemia 2021;35:2145–50. **2. Rustad E, et al. Nat Commun 2020;11(1):1917.** 3. **Zicchedu B, et al. Blood Adv 2020;4(5):830–44.**
4. **Landau H, et al. Nat Commun 2020;11(1):3617. 5. Thibaud S, et al. Blood 2022;140(Suppl 1):614–6, oral presentation, ASH 2022.**

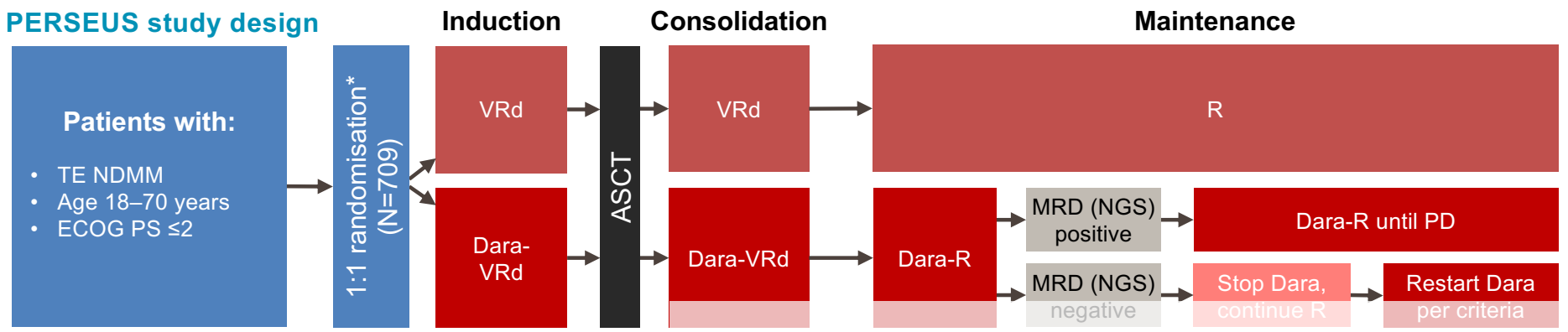
Dove andiamo nel prossimo futuro



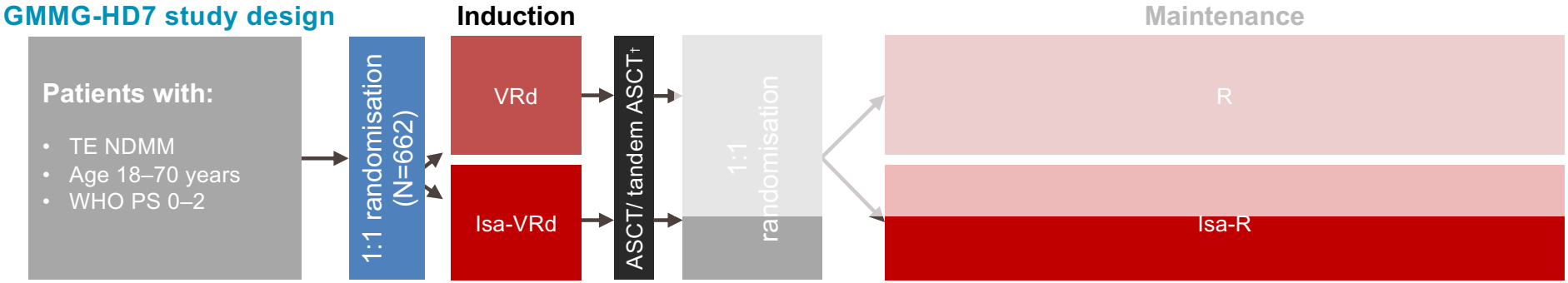
Dimopoulos MA, et al. Ann Oncol 2021;32:309–322;
Dimopoulos MA et al. Nature Reviews Clinical Oncology 2025 Sep;22(9):680-700

PERSEUS and GMMG-HD7:

anti-CD38-based induction and maintenance in TE NDMM



Primary endpoint: PFS



Primary endpoint: Post-induction MRD negativity (NGF, 10^{-5})

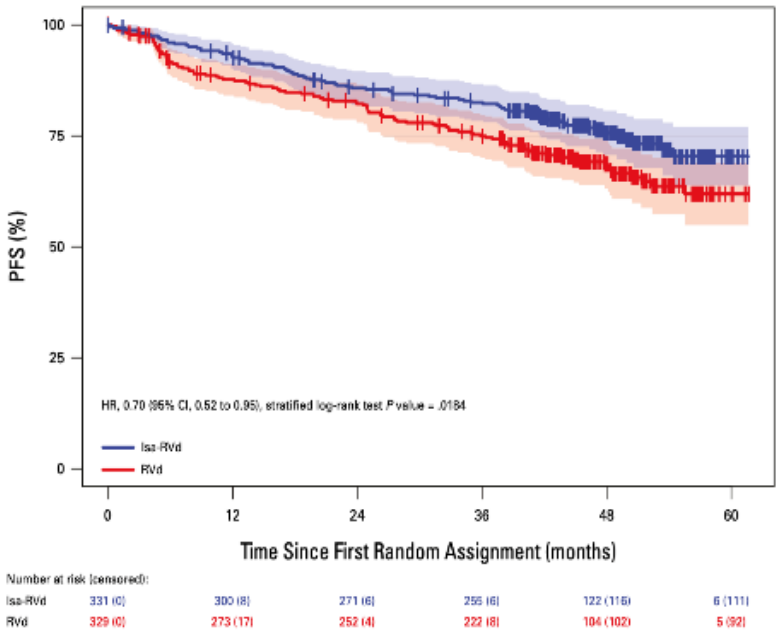
Sonneveld P, et al. EHA 2024 (Abstract No. S201 – oral presentation); Sonneveld P, et al. N Engl J Med 2024;390:301–313; Goldschmidt H, et al. Lancet Haematol 2022;9:e810–e821;
Mai EK, et al. ASH 2024 (Abstract No. 364 – oral presentation).

GMMG-HD7:

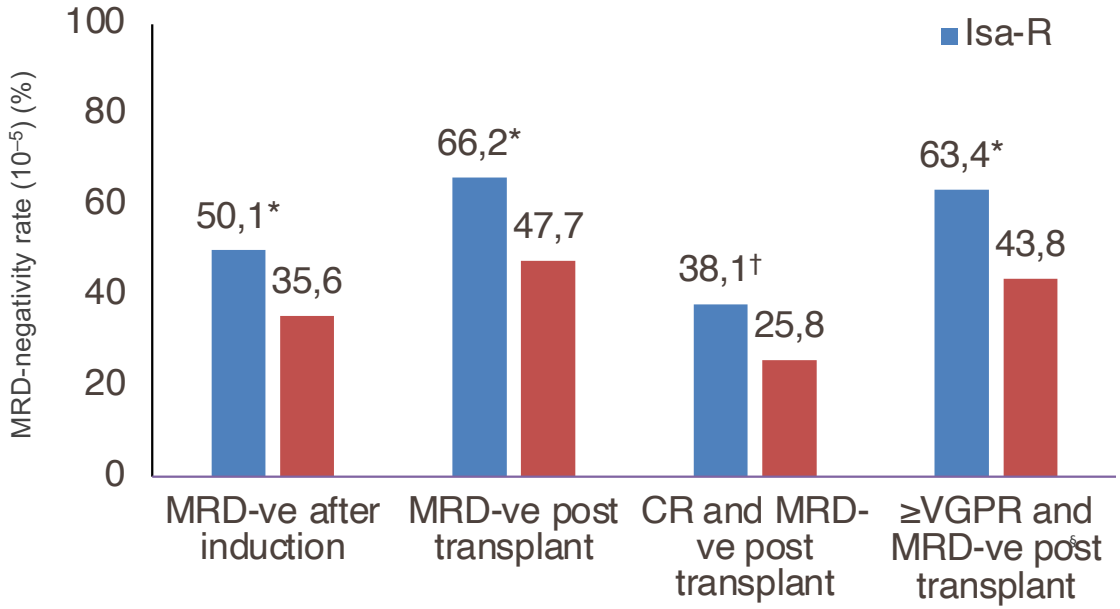
Isa-VRd significantly improved PFS and MRD-negativity vs VRd

Median follow-up: 48 months

PFS



MRD-negativity rates (NGF, 10^{-5})

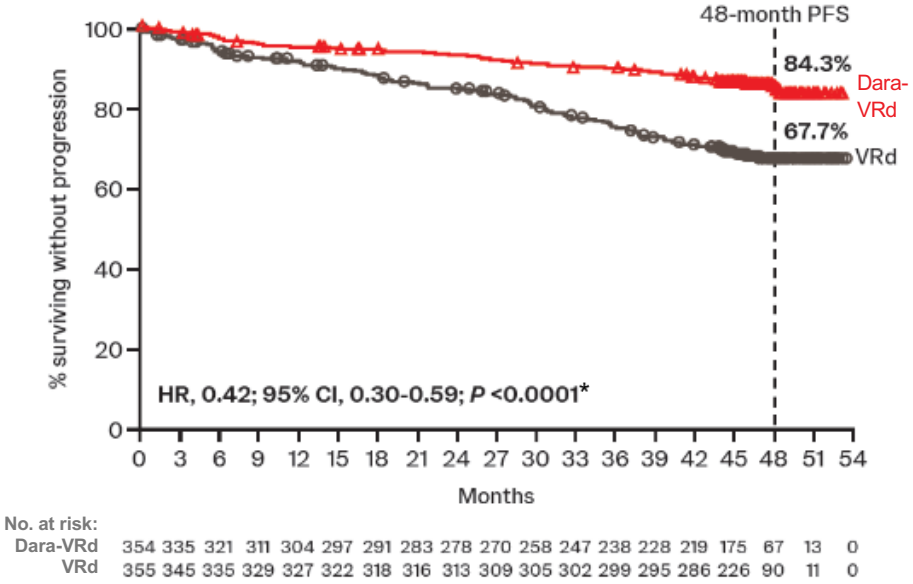


The safety profile of isatuximab with VRd was consistent and manageable

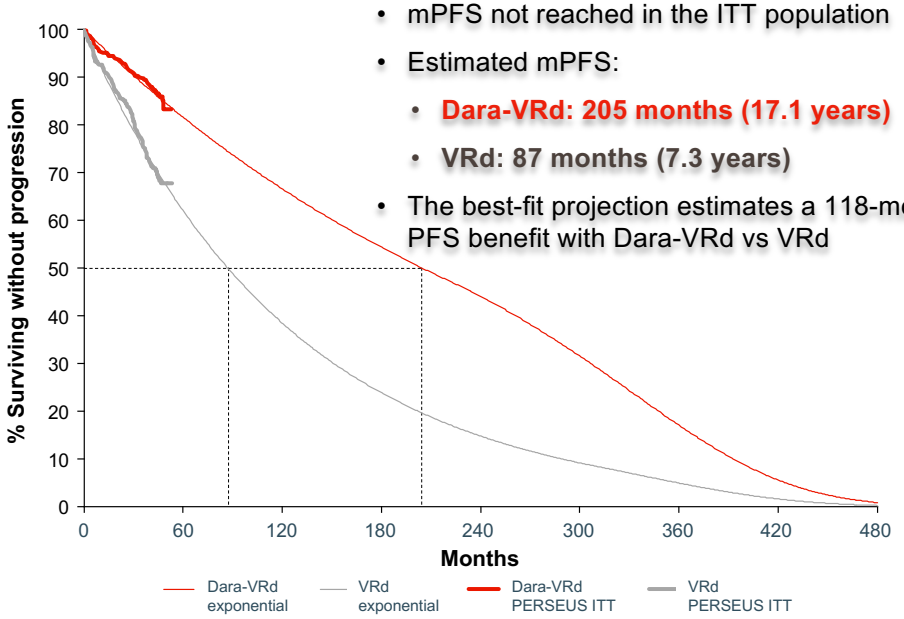
Mai EK et al. J Clin Oncol 2025;43:1279–1288;
Mai EK, et al. ASH 2024 (Abstract No. 364 – oral presentation).

PERSEUS: 17-year PFS projection with Dara-VRd based on best-fit modelling

PFS in the ITT population
(median follow-up: 47.5 months)



Projected PFS (observed and best fit)



- mPFS not reached in the ITT population
- Estimated mPFS:
  - **Dara-VRd: 205 months (17.1 years)**
  - **VRd: 87 months (7.3 years)**
- The best-fit projection estimates a 118-month PFS benefit with Dara-VRd vs VRd

The safety profile of Dara-VRd was consistent with the known safety profiles of daratumumab and VRd

Sonneveld P, et al. EMN 2025 (Abstract No. B04 – oral presentation);
Sonneveld P, et al. N Engl J Med 2024;390:301–313;
Sonneveld P, et al. IMS 2024 (Abstract No. P-368 – poster);
Sonneveld P, et al. EHA 2024 (Abstract No. S201 – oral presentation).

C’è spazio per doppio autotrapianto ?

LONG-TERM SURVIVORS AFTER TANDEM ASCT (EMN02 trial)

480 pts < 65 y

TD vs VTD, tandem ASCT, TD vs VTD consolidation, no maintenance

Extended follow-up of median 10 y

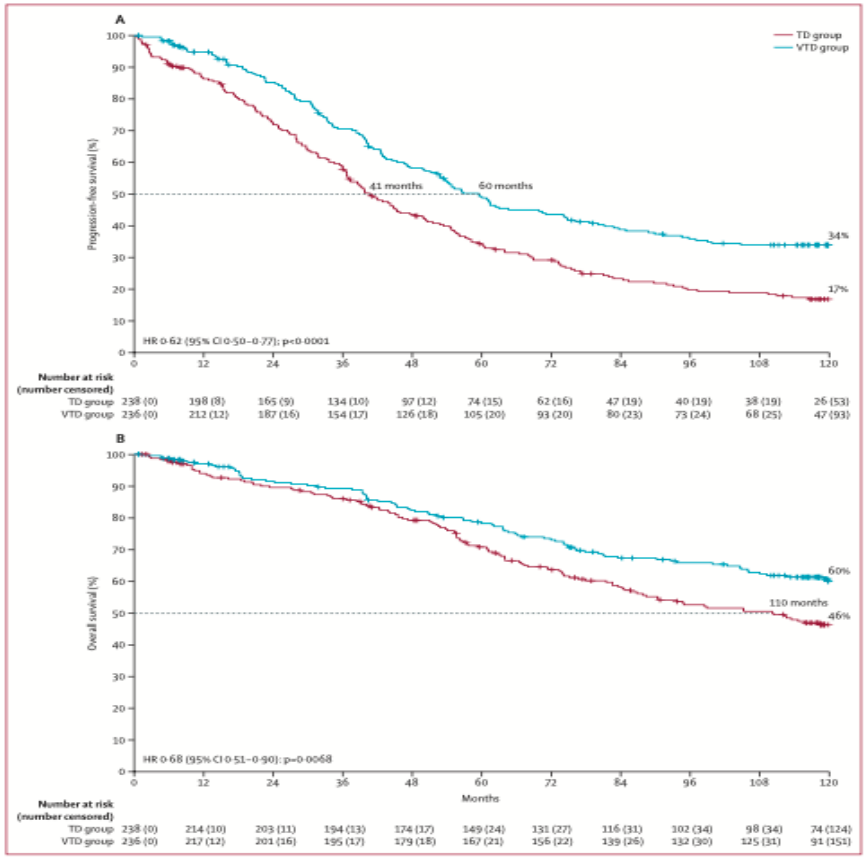
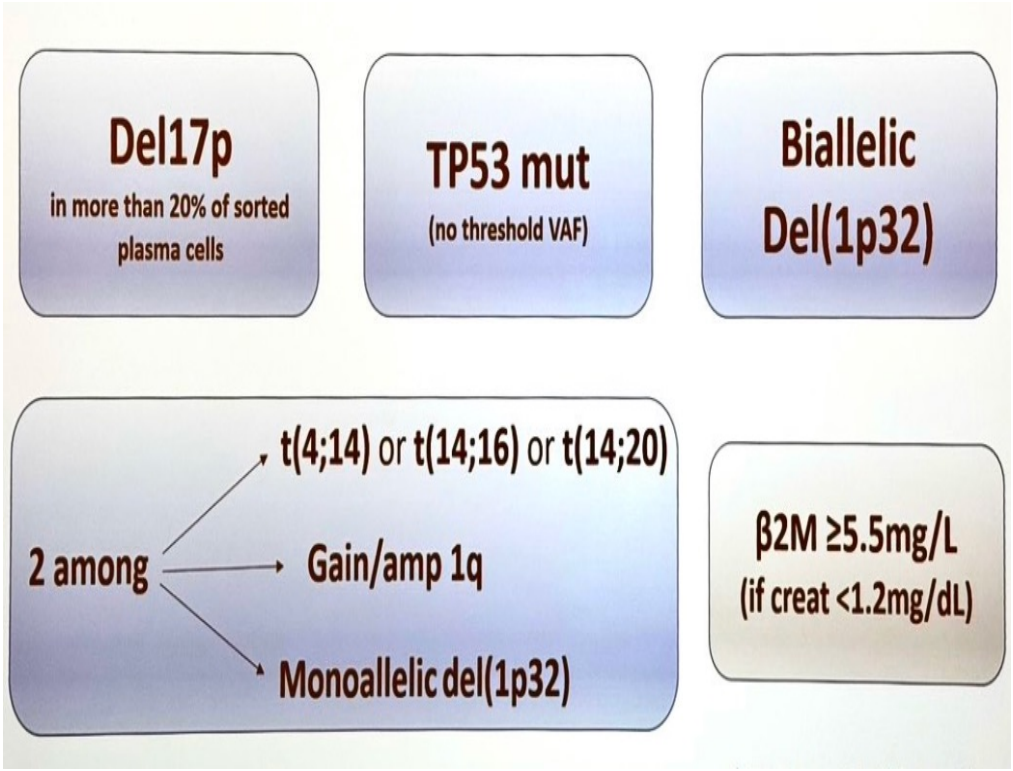
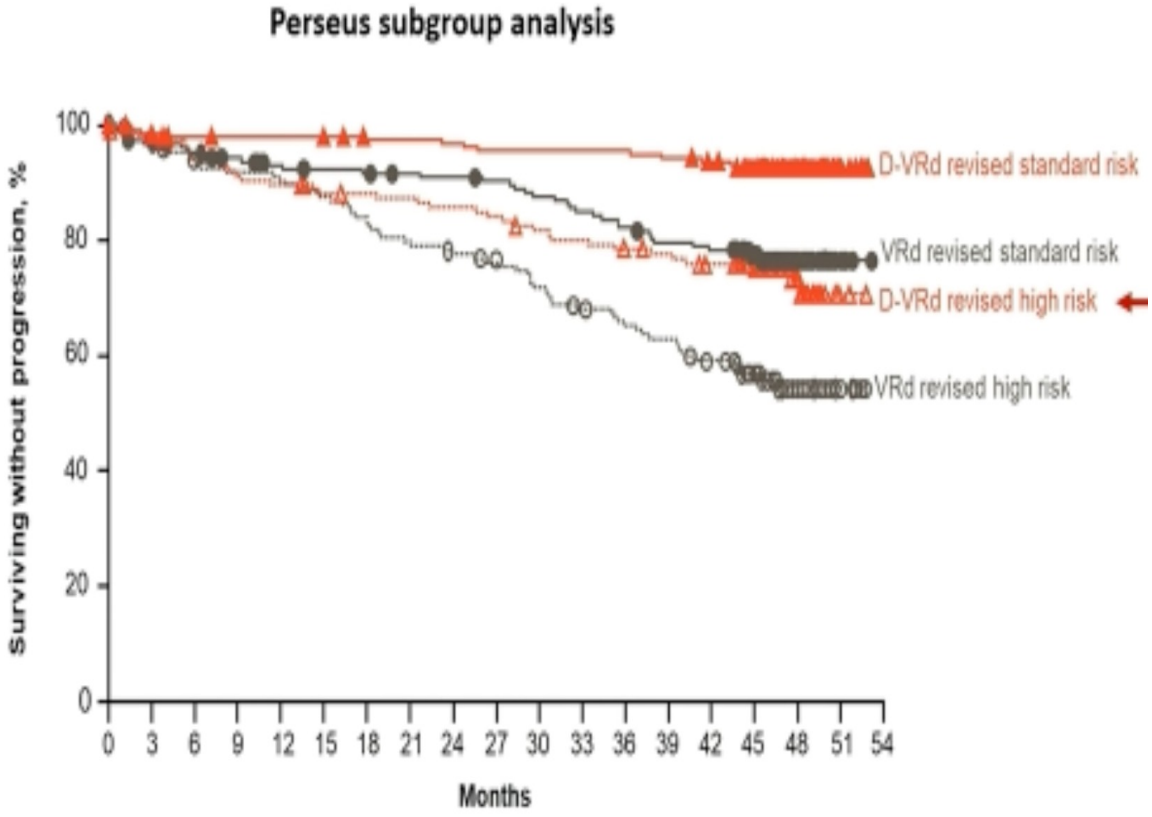


Figure 2: Progression-free survival (A) and overall survival (B) by treatment group
HR=hazard ratio. TD=thalidomide and dexamethasone. VTD=bortezomib, thalidomide, and dexamethasone.

Tacchetti P et al Lancet Hematology 2020

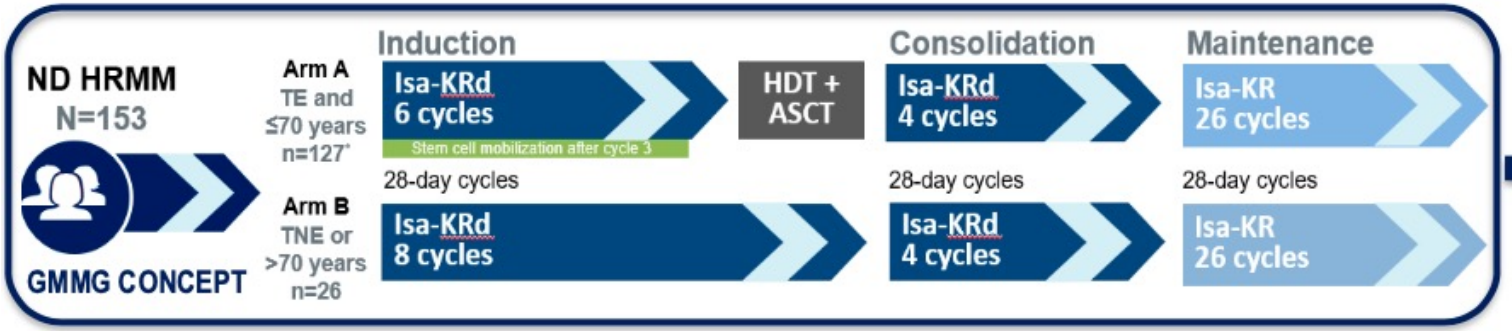
Impact of New HR Criteria in Perseus trial



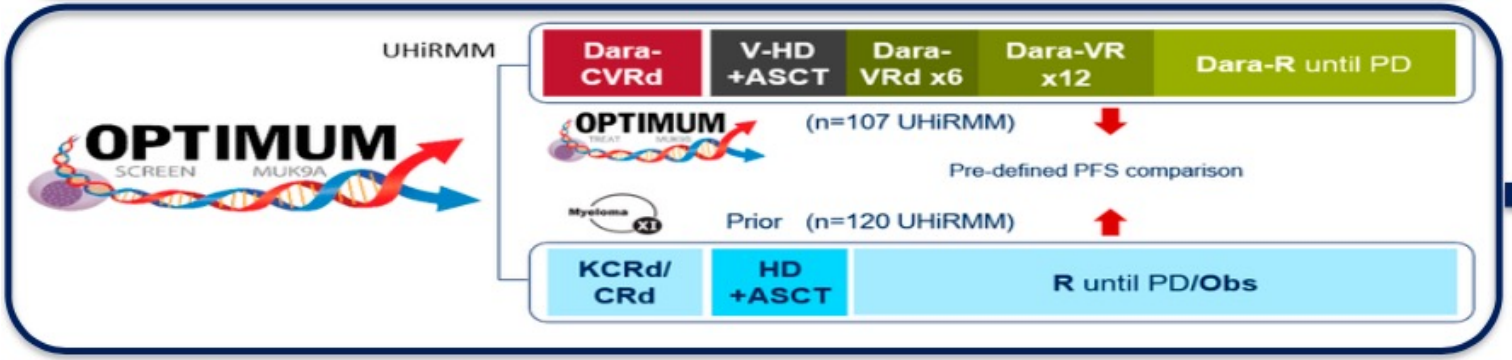


Avet Loiseau JCO 2025; Dimopoulos M IMW 2024

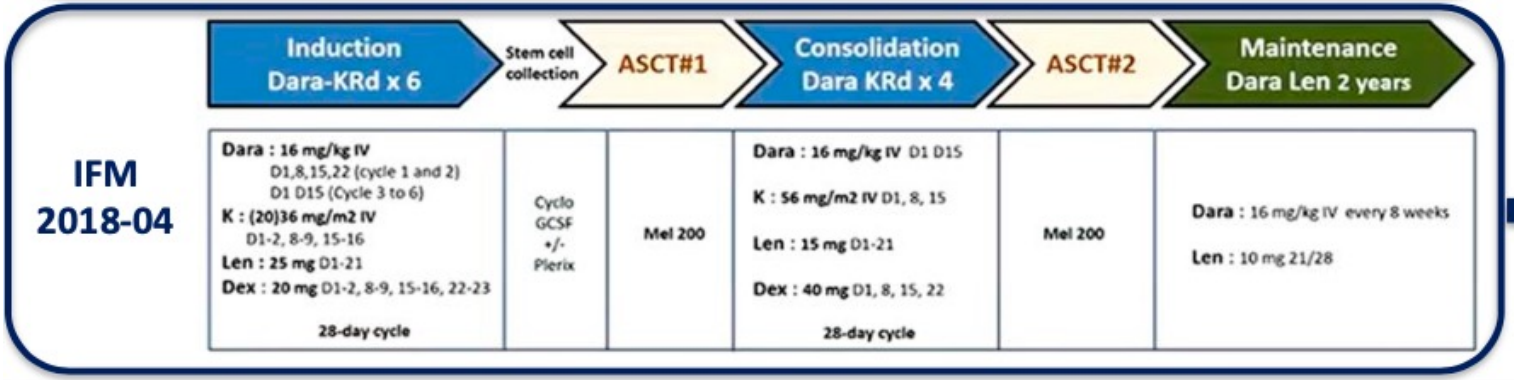
Dedicated Trials on High-Risk Patients With Transplant-Eligible NDMM



HRMM criteria:
- ISS stage II or III **PLUS**
- ≥1 of HRCA:
  - del(17p),
  - t(4;14), t(14;16)
  - amp(1q21)



HRMM criteria:
- ≥2 HRCA
  - t(4;14) or (14;14) or (14;20)
  - del(17p) or del(1p)
  - gain(1q)
- GEP: HR SKY92
- PCL: >20% cPB

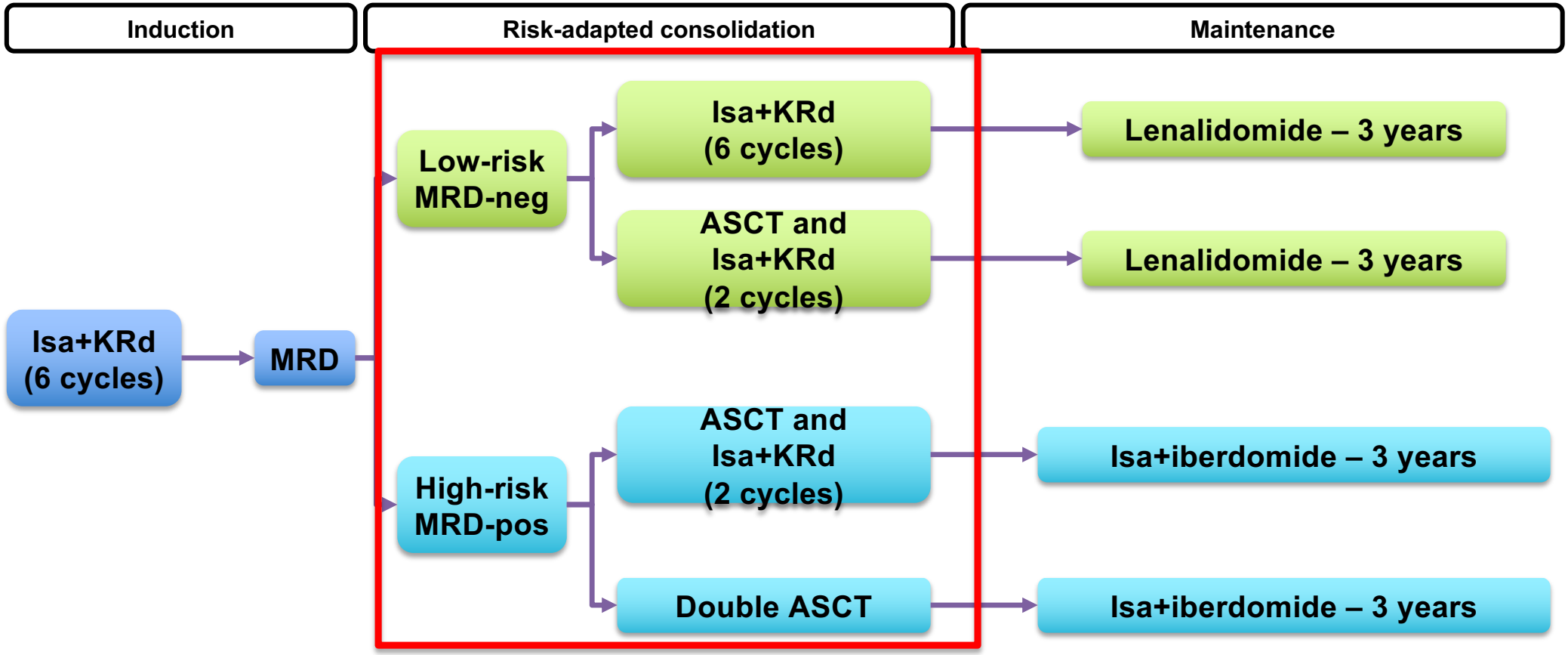


HRMM criteria:
- ≥1 of:
  - del(17p)
  - t(4;14) or t(14;16)

	GMMG CONCEPT	OPTIMUM	IFM 2018-04
Study phase	II	II (with historical comparison)	II
Primary end point	MRD neg	PFS 18 mo	feasibility
Author	Leypoldt et al , Leukemia 2024	Kaiser MF et al, JCO 2023	Touzeau C et al, Blood 2024
N° pts	TE: 127; NTE:26	TE:107	TE:50
Median follow-up	44 mo	41 mo	33 mo
MDR negativity at end of consolidation	TE:67.7%* NTE:54.2%*	63.6%** (after ASCT)	94%**
PFS	TE: 68.9% (36 mo) NTE: 58.4% (36 mo)	77% (30 mo)	80% (30 mo)
Discontinuation	6 (5%) AE	22	20 total 4 AE

* NGF **NGS

MRD-adapted therapeutic approaches – MIDAS (IFM 2020-02)



Perrot A, et al. COMy 2021. https://clinicaltrials.gov/ct2/show/NCT04934475

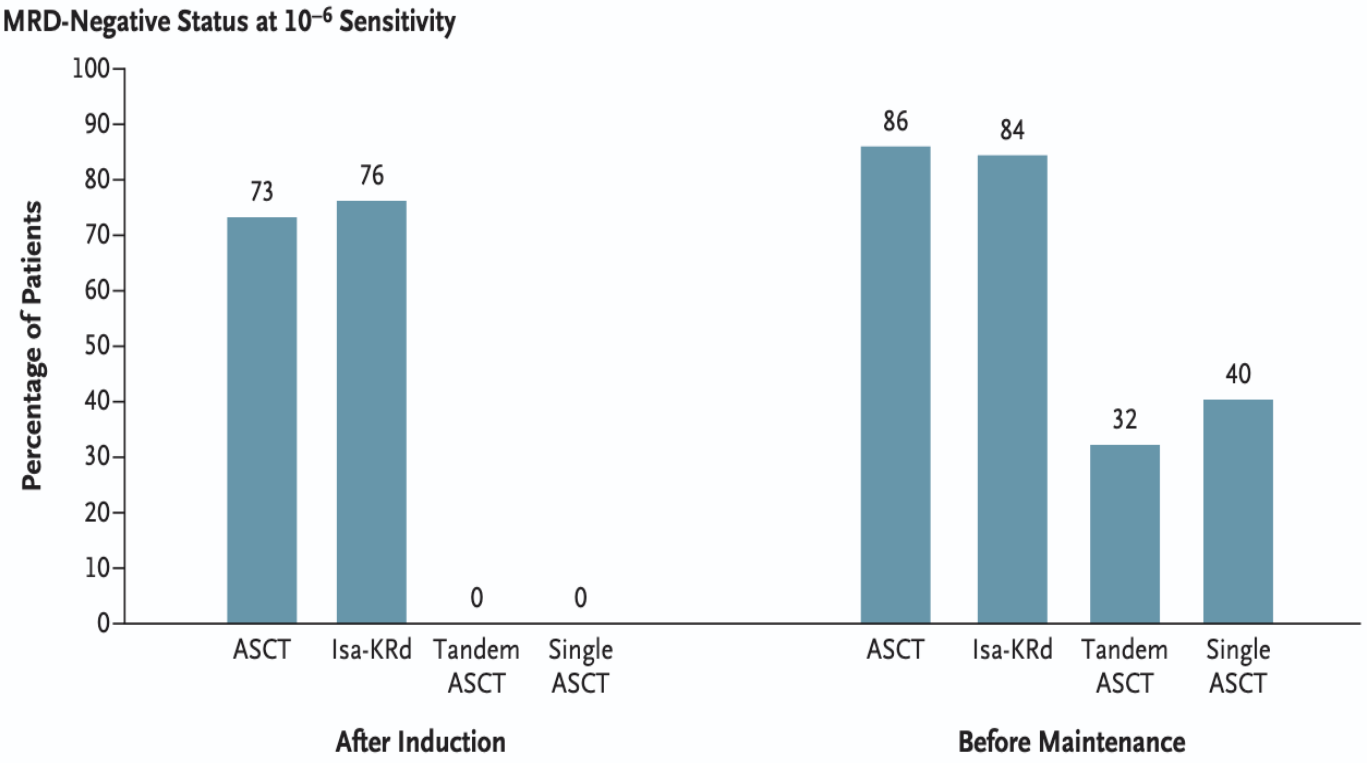
Subgroup analyses of MRD-negativity

Interesting variability across some cytogenetic groups

MRD-negativity rate after induction (sensitivity level 10^{-5}):

- **t(4;14): 81%**
- **t(11;14): 40%**
- **t(14;16): only 7 patients**
- **del(17p): 48%**

Post-consolidation results and kinetics are pending

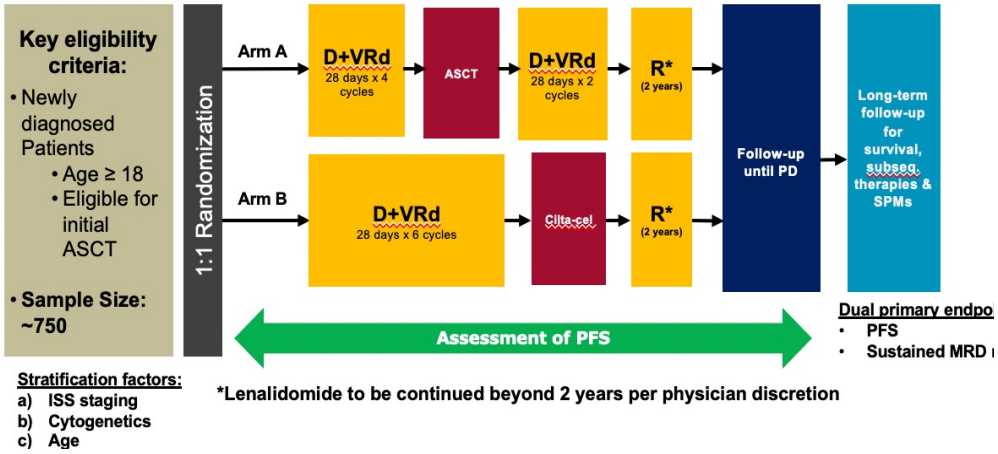


International Myeloma Society

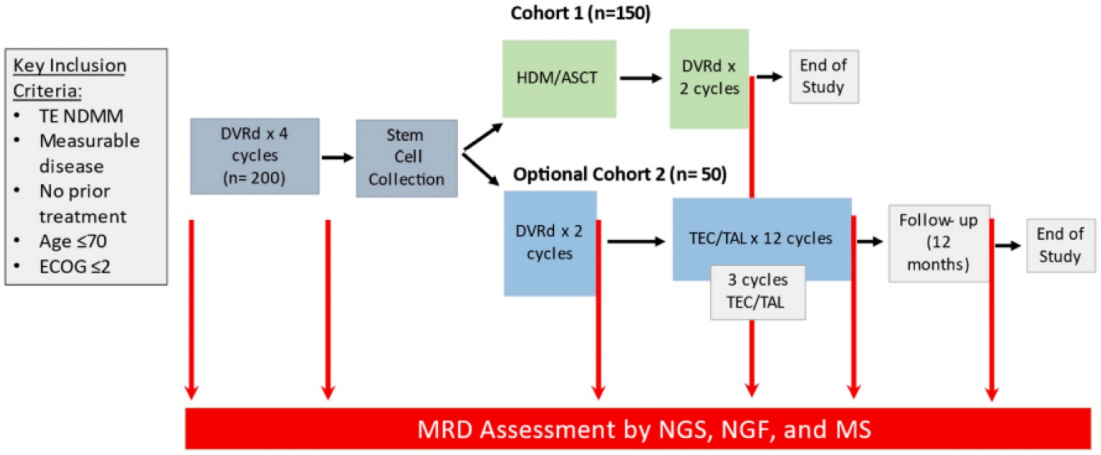
Perrot A et al Oral IMS 2024; Perrot NEJM 2025

T-cell redirecting therapies to replace HDM/ASCT?

The randomized, phase III EMN28/CARTITUDE-6 study: Cilta-cel vs ASCT



The phase II EMN33/TAURUS study



Conclusions

- *HDM-ASCT has been an invaluable and life-saving therapy for patients with MM for decades and it continues to be so (and we are grateful for that).*

- *HDM-ASCT comes with a relatively low but non-zero risk of early TRM in even the healthiest of patients, as well as a likely non-plateauing risk of secondary leukemia.*

- *Highly efficacious immunotherapies may ultimately prove more beneficial for high-risk patients than HDM-ASCT.*

Grazie per l’attenzione