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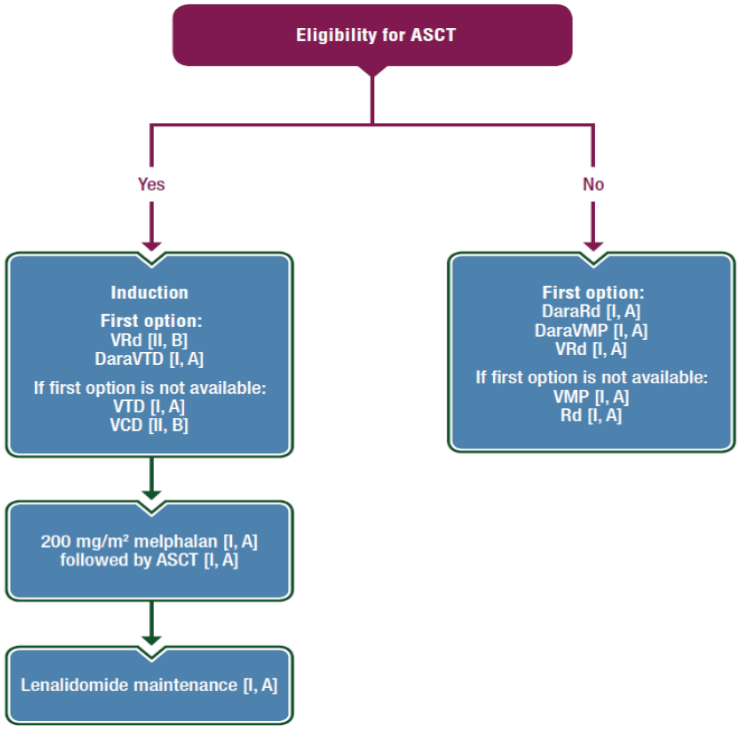
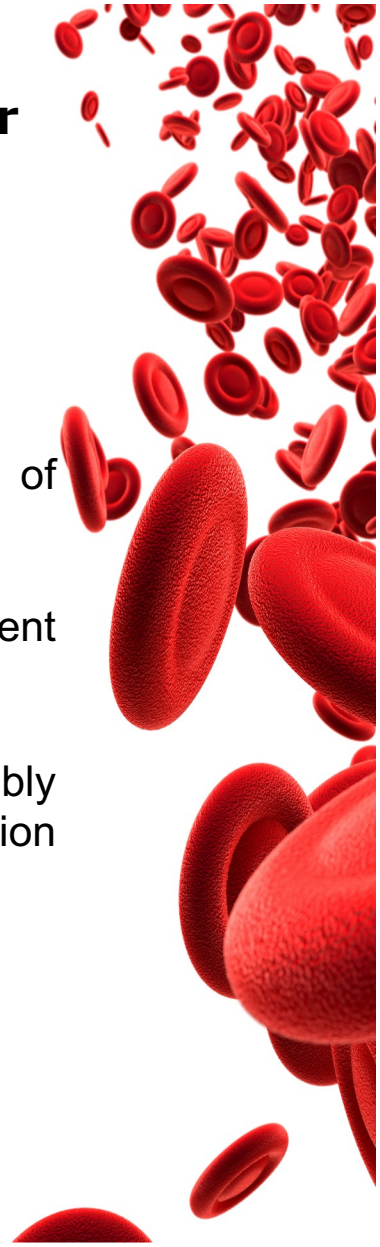
Il trapianto autologo nella terapia di prima linea nel mieloma: alla luce delle nuove terapie disponibili, in che modo e su quali basi possiamo ottimizzare la selezione del paziente candidabile?

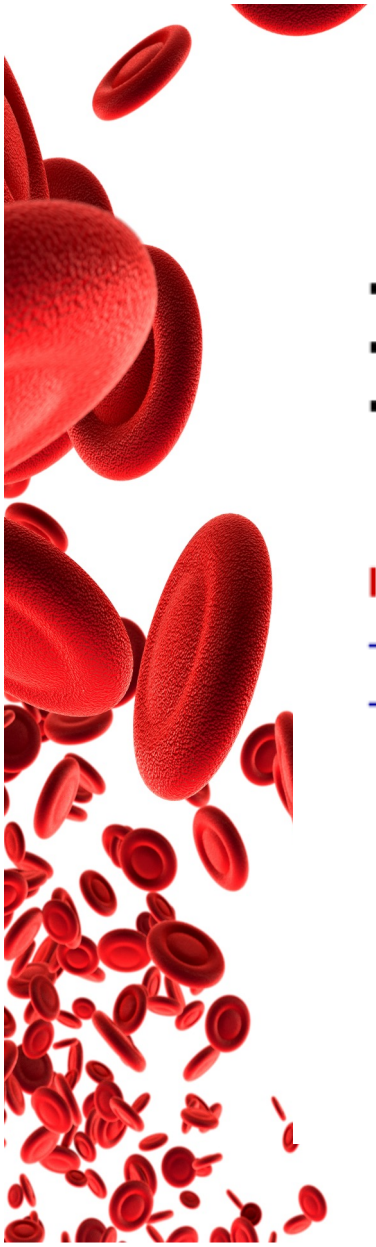
Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: transplant-eligible (TE) patients



Key endpoints

- ✓ Maximize the rate and depth of response
- ✓ Sustain MRD negativity and prevent or delay clinical relapse
- ✓ Increase PFS and OS, possibly offering a chance of cure to a fraction of patients





Treatment paradigm for fit transplant-eligible patients

- quickly reverse disease-related complications
- maximize the speed and depth of tumour burden reduction
- prolong disease control → **EXTEND OVERALL SURIVAL**

Importance of biological background:

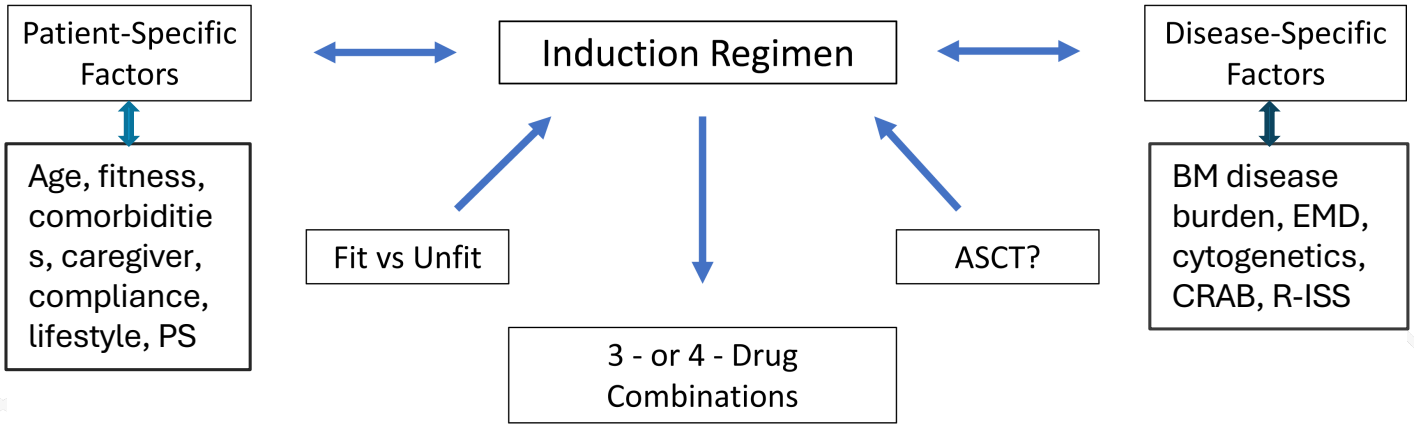
- Genomic complexity of multiple myeloma
- Clonal evolution / development of drug-resistance
  - Multiple clones with variable drug sensitivity
  - Minor drug-resistant clones potentially lethal

Combination regimens + continuous suppressive therapy

- Faster and deeper response
- Different mechanisms target multiple clones simultaneously
- Prevention of drug-resistant subclones emergence / eradication of all clones

Debulk and maintain disease at a level below detection (MRD)

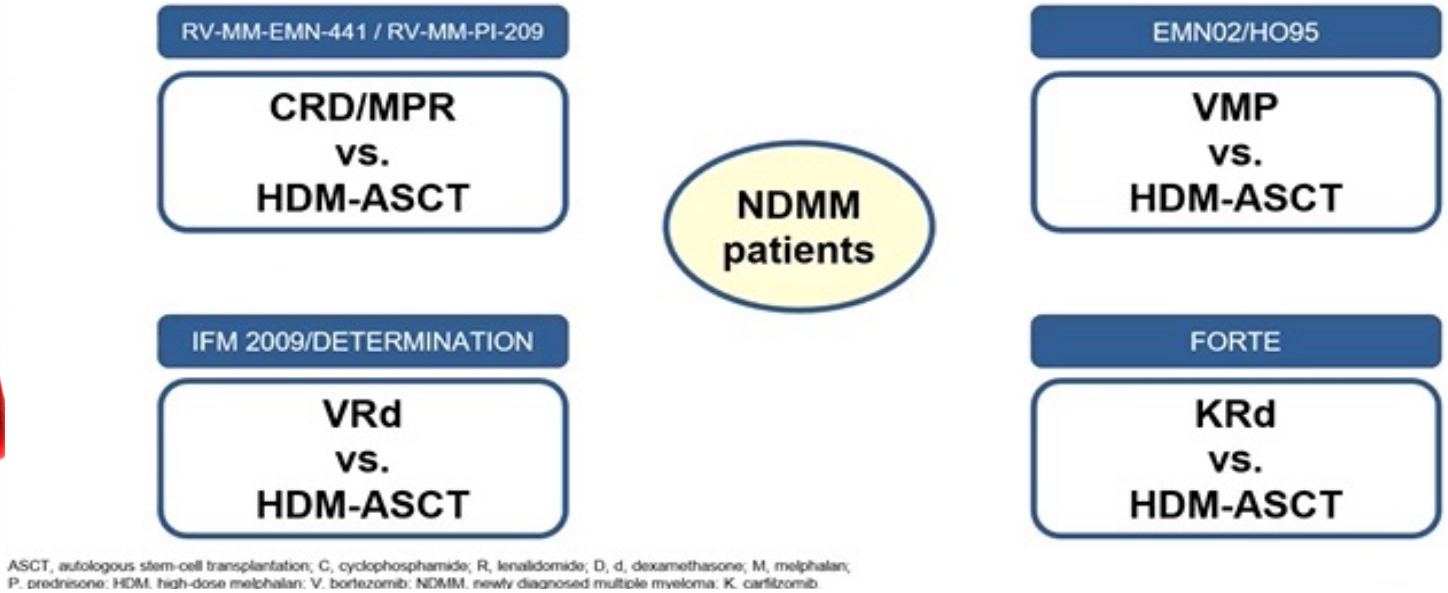
Newly Diagnosed Multiple Myeloma: Making Sense of the Menu



Deep & Durable Responses

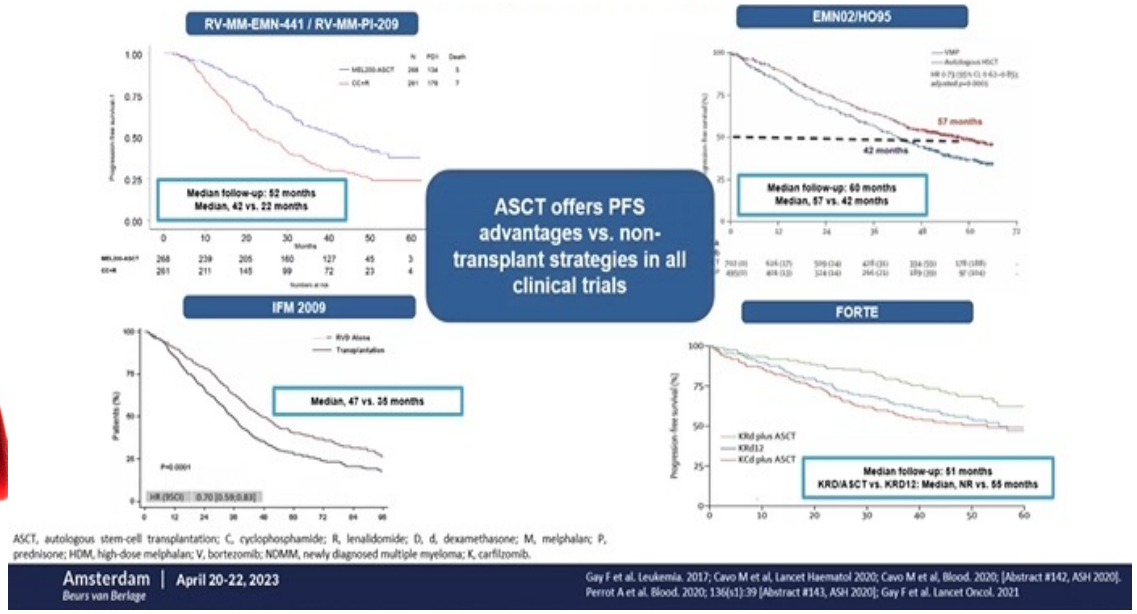
Modified Caitlin L. Costello, Newly diagnosed multiple myeloma: making sense of the menu, Hematology Am Soc Hematol Educ Program, 2022,

Ruolo autotrapianto upfront (I)



ASCT, autologous stem-cell transplantation; C, cyclophosphamide; R, lenalidomide; D, d, dexamethasone; M, melphalan; P, prednisone; HDM, high-dose melphalan; V, bortezomib; NDMM, newly diagnosed multiple myeloma; K, carfilzomib

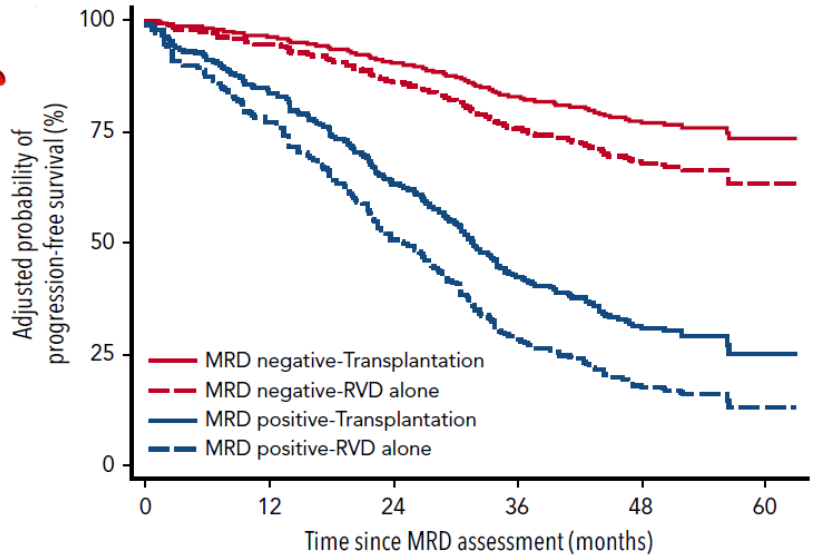
Ruolo autotrapianto upfront (II)



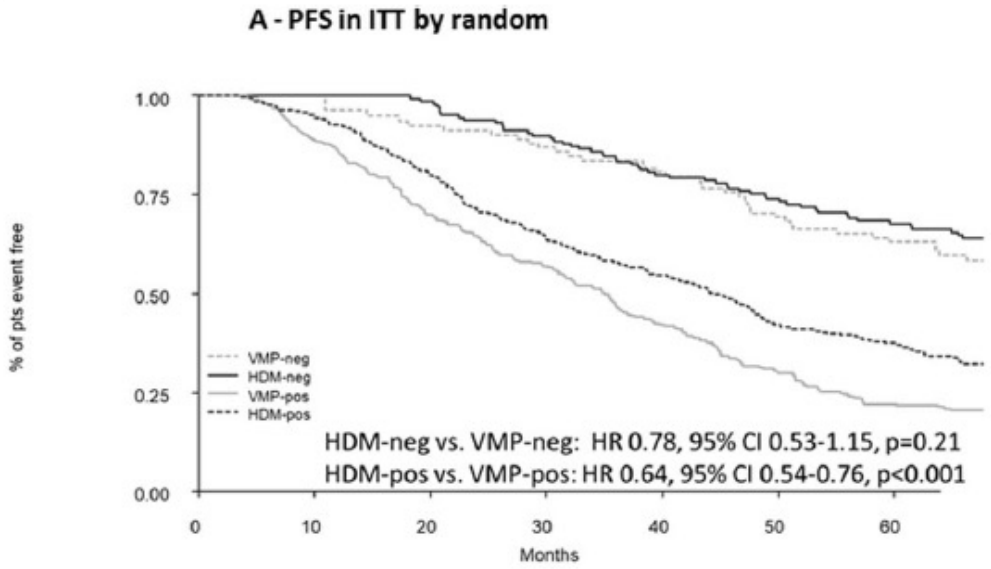
	Induction regimen in AHCT group	PFS (months) (Upfront AHCT vs control)
IFM-2009	VRd	Median: 50 vs 36
EMN-02/H095	VCd	Median: 56.7 vs 41.9
FORTE	KRd*	3-year PFS: 56% vs 33%
DETERMINATION	VRd	Median: 67.5 vs 46.2

MRD more than the treatment arm is the key prognostic factor

IFM 2009 trial[1]
MRD NGS 10^{-6}



EMN-02 trial[2]
MRD Flow 10^{-5}



The benefit of ASCT is questionable in patients achieving MRD negativity

ASCT, autologous stem cell transplant; CI, confidence interval; EMN, European Migration Network; HDM, high-dose melphalan; HR, hazard ratio; IFM, international myeloma foundation; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; neg, negative; NGS, next-generation sequencing; PFS, progression-free survival; pos, positive; RVD, lenalidomide-bortezomib-dexamethasone; TE, transplant-eligible; VMP, bortezomib-melphalan-prednisone

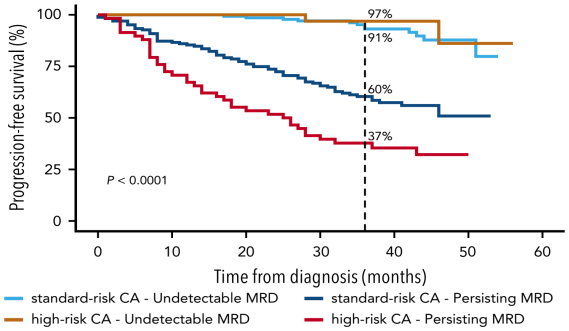
1. Perrot et al. Blood 2018; ;132(23):2456–2464
2. Oliva et al. Blood Canc J 2021;11(6):106

Reaching MRD negativity can modulate the poor prognosis of high-risk chromosomal abnormalities
Only way to obtain durable disease control

GEM2012MENOS65 trial (10^{-6})

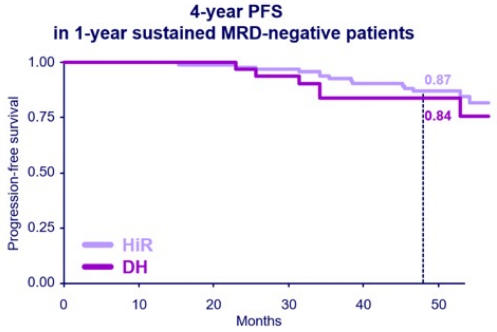
FORTE trial (10^{-5})

3-year PFS
In MRD negative patients

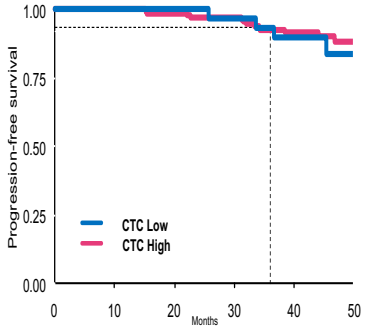


CA, cytogenetic abnormalities; MM, multiple myeloma; MRD, minimal residual disease.; HiR, high risk; DH, double hit

4-year PFS
in 1-year sustained MRD-negative patients



3-year PFS
in 1-year sust-MRD negative patients



Goicoechea I et al. Blood 2021;137(1):49-60; Mina R et al EHA 2021;abstract S182; Bertamini L. et al, JCO 2022.

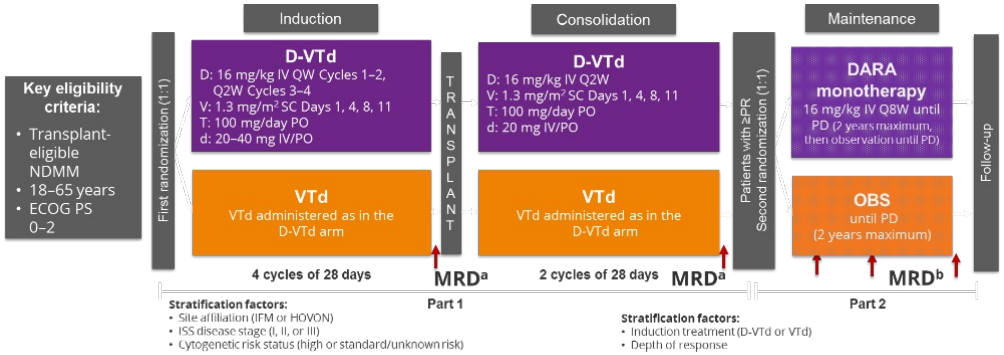
MRD is now considered the main factor able to mitigate the adverse prognosis related to baseline features

Ruolo autotrapianto upfront nell'era delle "quadruplette"

	Use of AHCT	Induction regimen	**PFS**	**OS**	**MRD-Negative Rate** (%, time-point, sensitivity)
CASSIOPEA	All arms received upfront AHCT	Dara-VTd	93% 2-year PFS	Not reported	64% at 100 days post-AHCT (10^{-5})
GRIFFIN	All arms received upfront AHCT	Dara-VRd	95.8% 2-year PFS	92.7% 4-year OS:	Post-induction: 22%/1% Post-consolidation: 50%/11% Post-1-year-maintenance: 59%/21% End of study: 64%/36% (10^{-5}/10^{-6})
PERSEUS	All arms received upfront AHCT	Dara-VRd	84.3% 4-year PFS	Not reported	75%/65% any timepoint during study (10^{-5}/10^{-6}) 64.8% sustained negativity for ≥12months (10^{-5})
MASTER	All arms received AHCT	Dara-KRd	87% 2-year PFS	94% 2-year OS	81%/71% at post-consolidation (10^{-5}/10^{-6})
MANHATTAN	No AHCT	Dara-KRd	98% 1-year PFS	100% 1-year OS	71% post-cycle 8 (10^{-5})

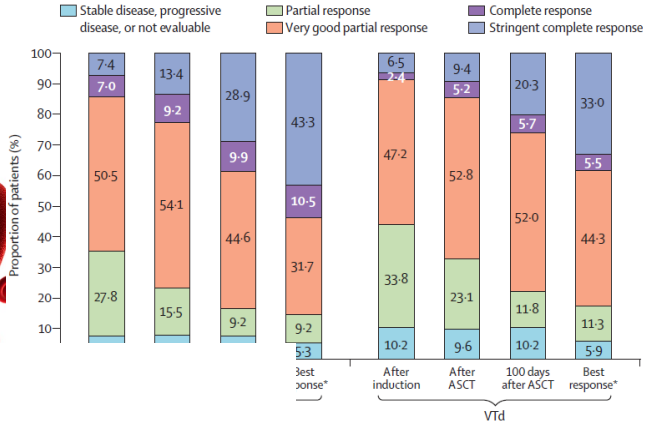
Benefit of anti-CD38 containing quad-therapy on newly diagnosed myeloma

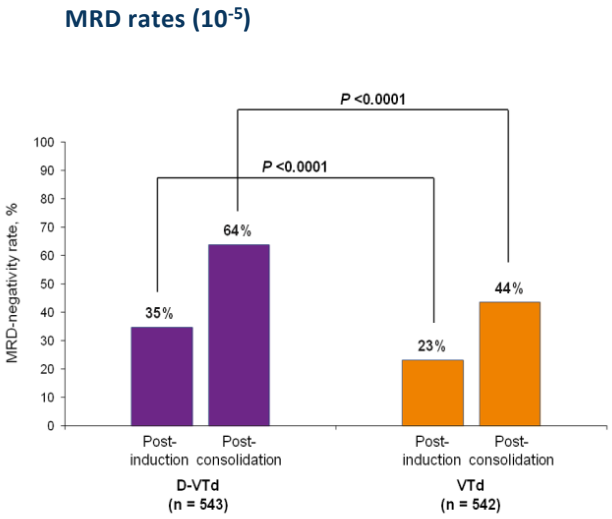
Presente: DARA-VTd in TE-NDMM: CASSIOPEIA phase 3 trial

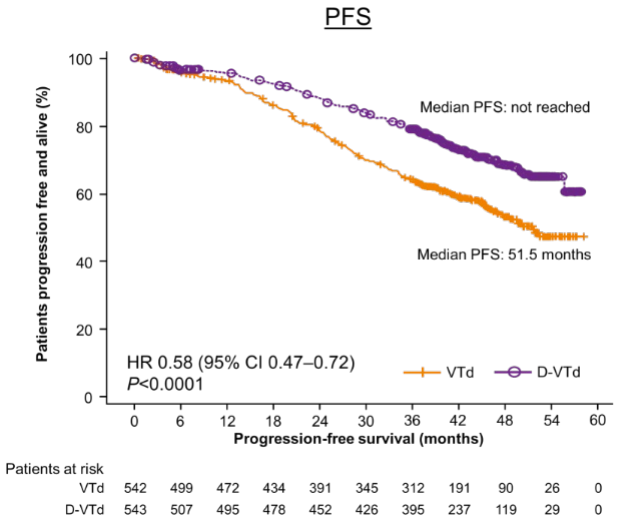


- CASSIOPEIA is a randomized, open-label, active-controlled, parallel-group, phase 3 study in patients with TE NDMM
- In Part 1, **D-VTd induction/consolidation improved depth of response, including increased rates of sCR, ≥CR, and MRD negativity, and prolonged PFS**

Median follow-up: 44.5 months







Moreau P et al, Lancet 2019; 394: 29-38; Moreau P et al, ASCO 2021

Prossimo futuro: DARA-VRd in TE-NDMM: PERSEUS phase 3 trial

EMN17-PERSEUS: Study Design

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo

Stratified by ISS stage and cytogenetic risk

Transplant-eligible adults aged 18-70 yr with NDMM; ECOG PS ≤2* (N = 709)

Induction: Cycles 1-4 (28-day cycles)

- **D-VRd**: D: 1800 mg SC QW/Q2W*; V: 1.3 mg/m² SC D1, 4, 8, 11; R: 25 mg PO D1-21; d: 40 mg PO/IV D1-4, 9-12 (n = 355)
- **VRd**: V: 1.3 mg/m² SC D1, 4, 8, 11; R: 25 mg PO D1-21; d: 40 mg PO/IV D1-4, 9-12 (n = 354)

ASCT

Consolidation: Cycles 5-6 (28-day cycles)

- **D-VRd**: D: 1800 mg SC Q2W; VRd: as in induction
- **VRd**: VRd: as in induction

Maintenance: Cycles 7+ (28-day cycles)

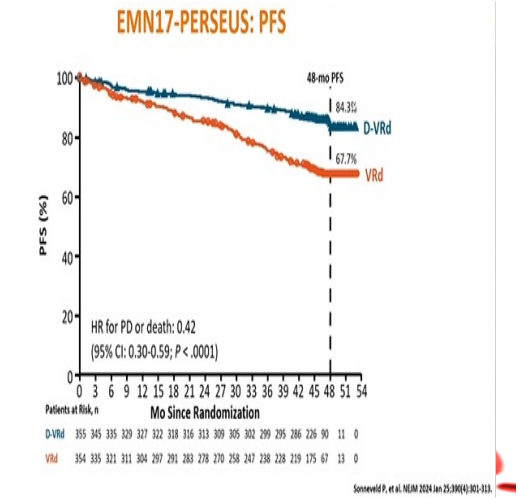
- **D-R**: D: 1800 mg SC Q4W; R: 10 mg PO D1-28
  - MRD+ → **D-R** until PD
  - MRD− → **R†** Discontinue D
- **R** 10 mg PO D1-28 until PD

*QW during cycles 1-2, Q2W during cycles 3-4. †D discontinued after ≥24 mo in patients with ≥CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.

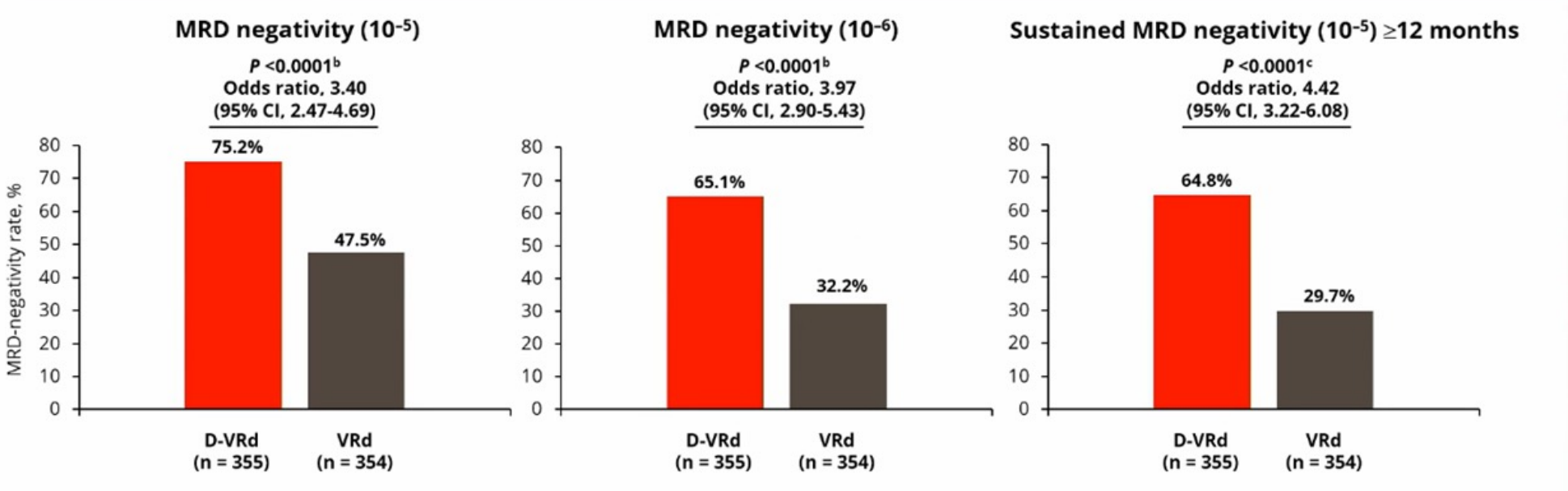
- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

Sonneveld P, et al. NEJM 2024 Jan 25;390(4):301-313.

- Improvment in ≥CR rate in DARA-VRd vs VRD observed across all group
- 64% of patients in DARA-VRd + D-R discontinued D after reaching susteined MRD negativity per protocol
- OS data immature



PERSEUS: Overall and Sustained MRD-negativity Rates[a]



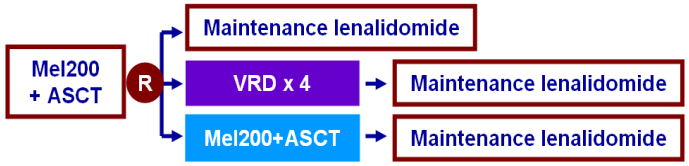
- **Deep and durable MRD negativity was achieved with D-VRd**
- **64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol[d]**

[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). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-squared test. [c]*P* value was calculated with the use of Fisher's exact test. [d]After ≥24 months of maintenance therapy, DARA was discontinued in patients who achieved ≥CR and sustained MRD negativity (10^{-5}) for ≥12 months.

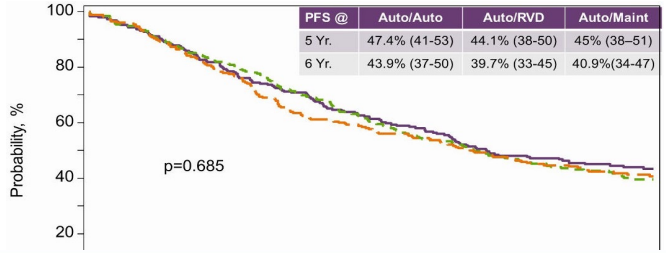
Presented by P Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA

Sonneveld P, et al. ASH 2023., NEJM 2024

Second ASCT (tandem) as consolidation therapy: more is always better?

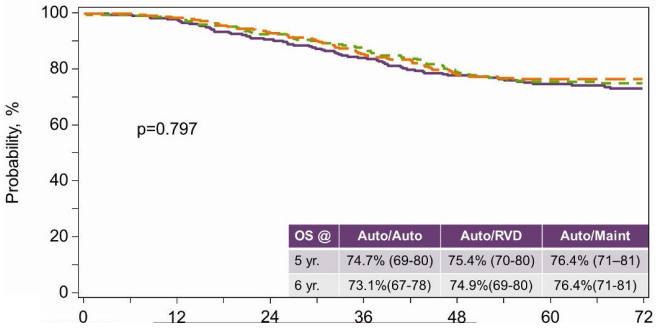


PFS



NO DIFFERENCE BETWEEN STUDY ARMS

OS

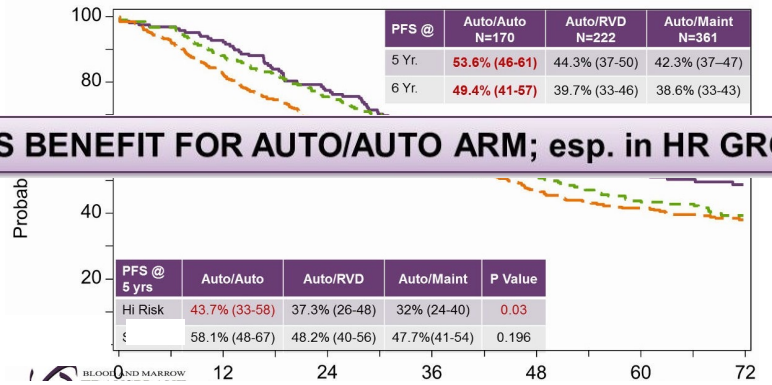


BMT CTN 0702 ph.2 trial (STaMINA)

	EMN02	STAMINA
Newly diagnosed (%)	100	85
Induction regimen (%)	VCD (100)	VCD (14) / VRD (55)
Length of induction therapy (months)	2-3	2-14
Failure to receive double ASCT (%)	19.8	32
Consolidation therapy (%)	Yes (50)	NO (100)
Maintenance therapy	Len (10 mg)	Len (10-15) mg
PFS at 36-38 mos (%) - All patients - High-risk patients*	 73.6 64.9	 56.5 42.2

2019

STaMINA: PFS by Treatment Received

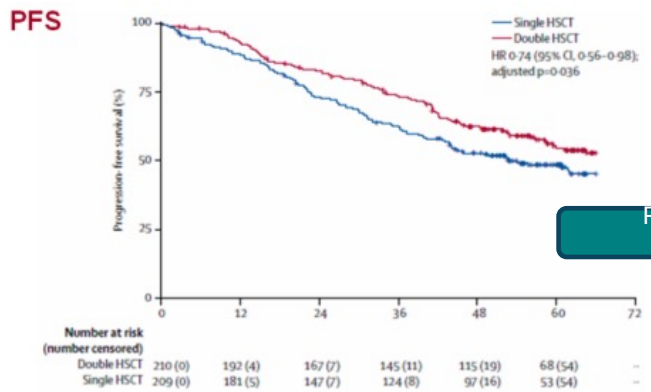


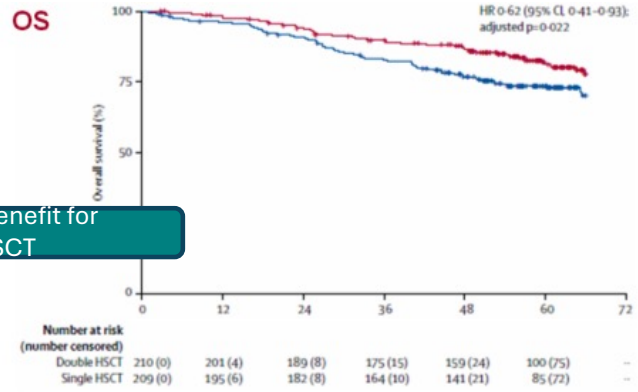
PFS BENEFIT FOR AUTO/AUTO ARM; esp. in HR GROUP

Stadtmauer EA, JCO 2019;37:589-597 - Hari P, ASCO 2020 oral presentation

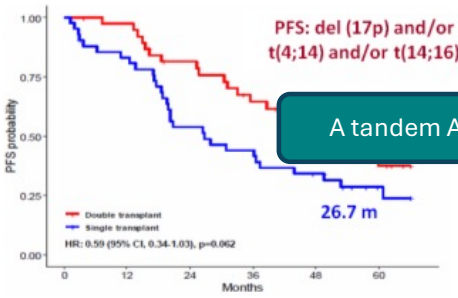
Second ASCT (tandem) as consolidation therapy: more is always better?

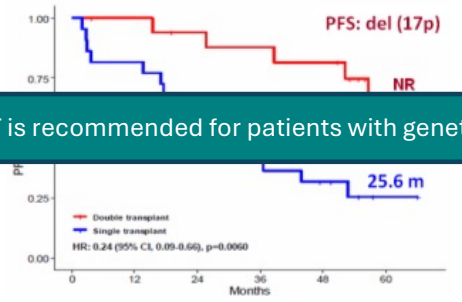
EMN02/HO95 phase 3 study

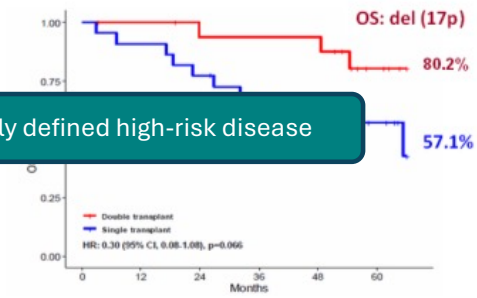




PFS and OS benefit for ASCT/ASCT





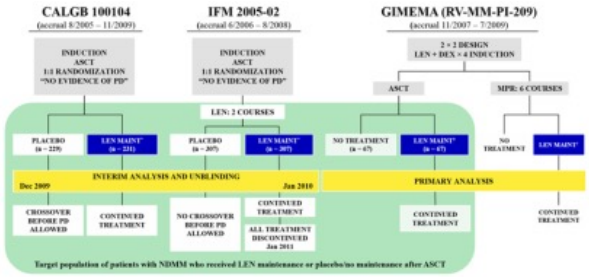


A tandem ASCT is recommended for patients with genetically defined high-risk disease

MAINTENANCE: Lenalidomide post ASCT

Maintenance with lenalidomide is considered the standard of care for all MM patients post-ASCT (EMA-approved until PD)

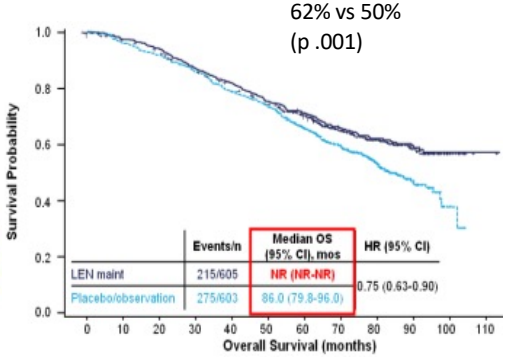
Meta-analysis

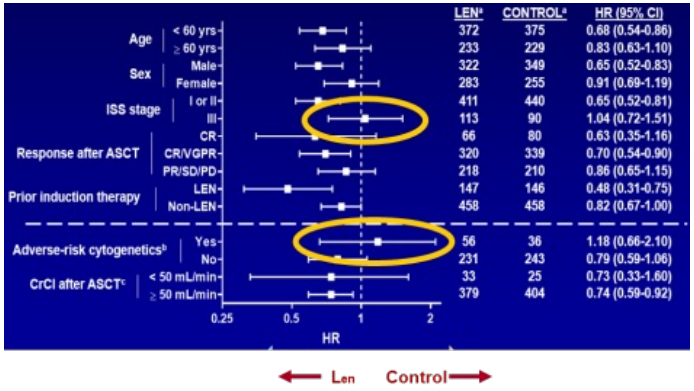


McCarthy, et al. JCO 2017;35:3279-89

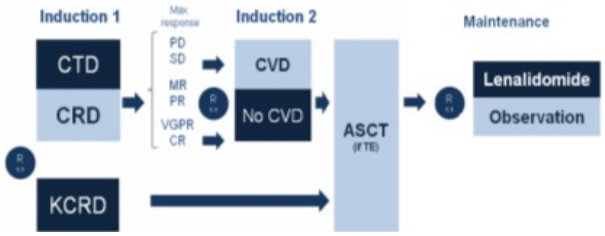
OS

7-year OS rate
62% vs 50%
(p .001)



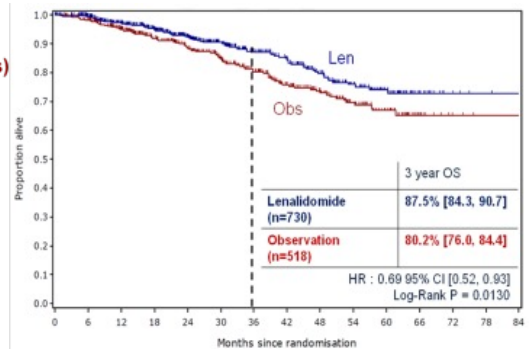


Myeloma XI trial



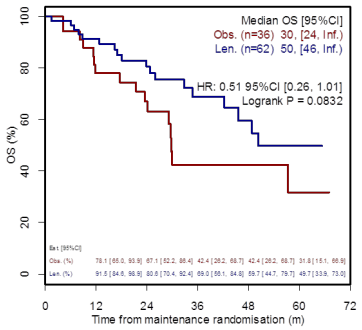
Jackson et al. Lancet Oncol 2019;20:57-73

OS
(TE pts)

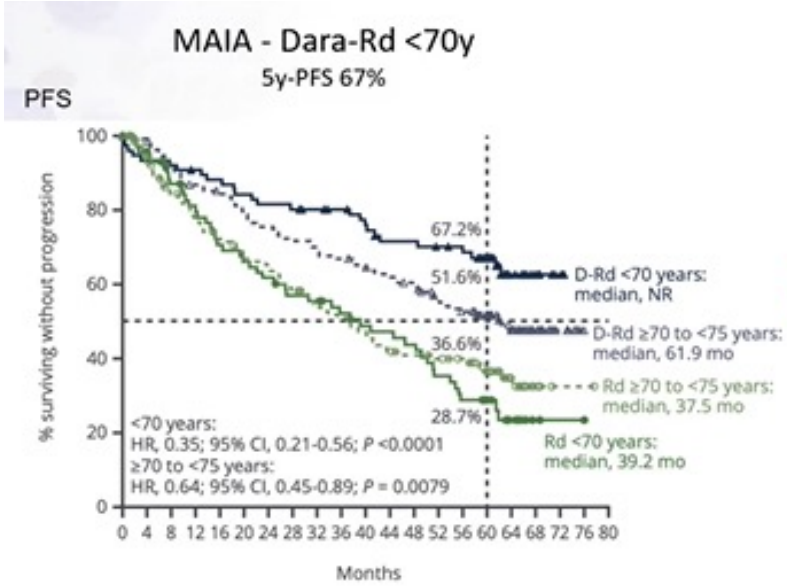


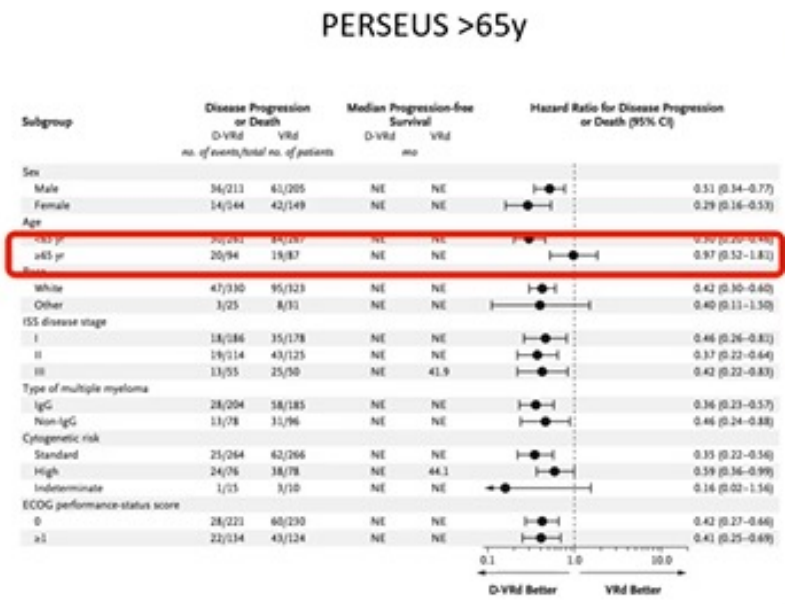
t(4;14) and/or del(17p) present

OS



Choices between – 65-70y: DRd /anti-CD38 VRd +/- transplant

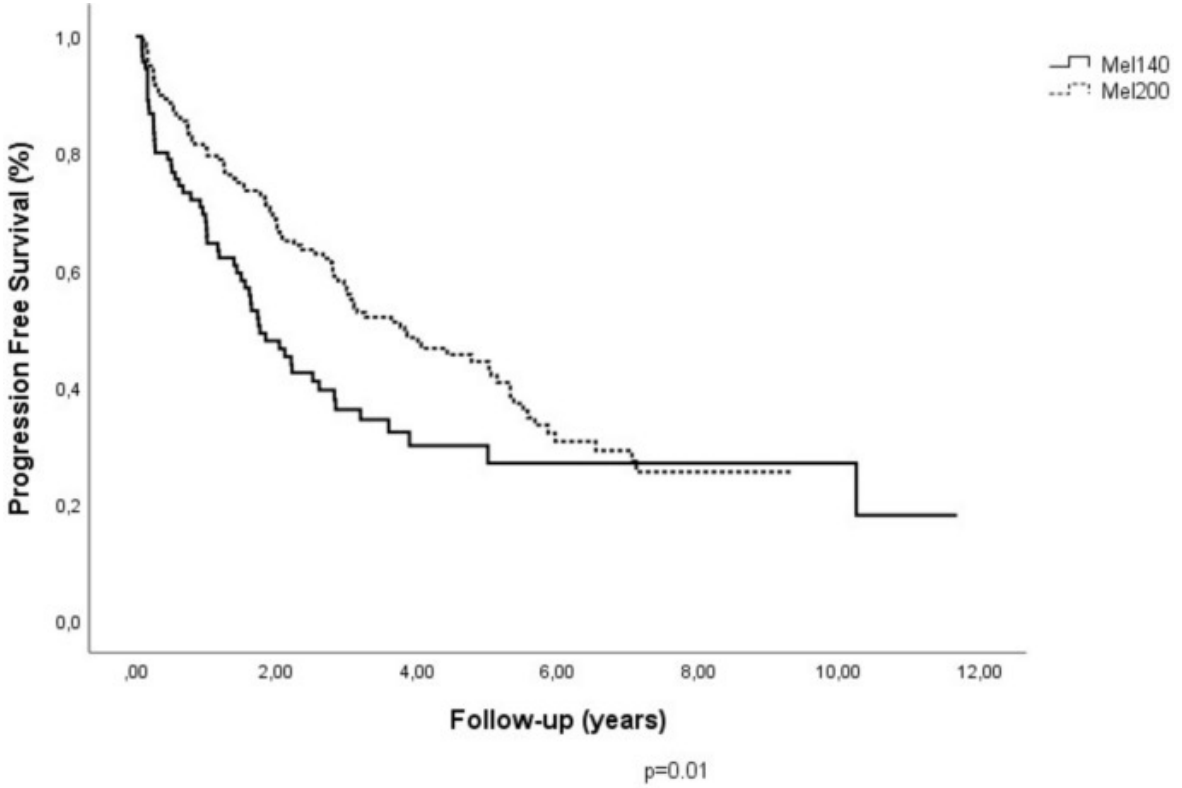




INDICAZIONE AL TRAPIANTO E SAFETY

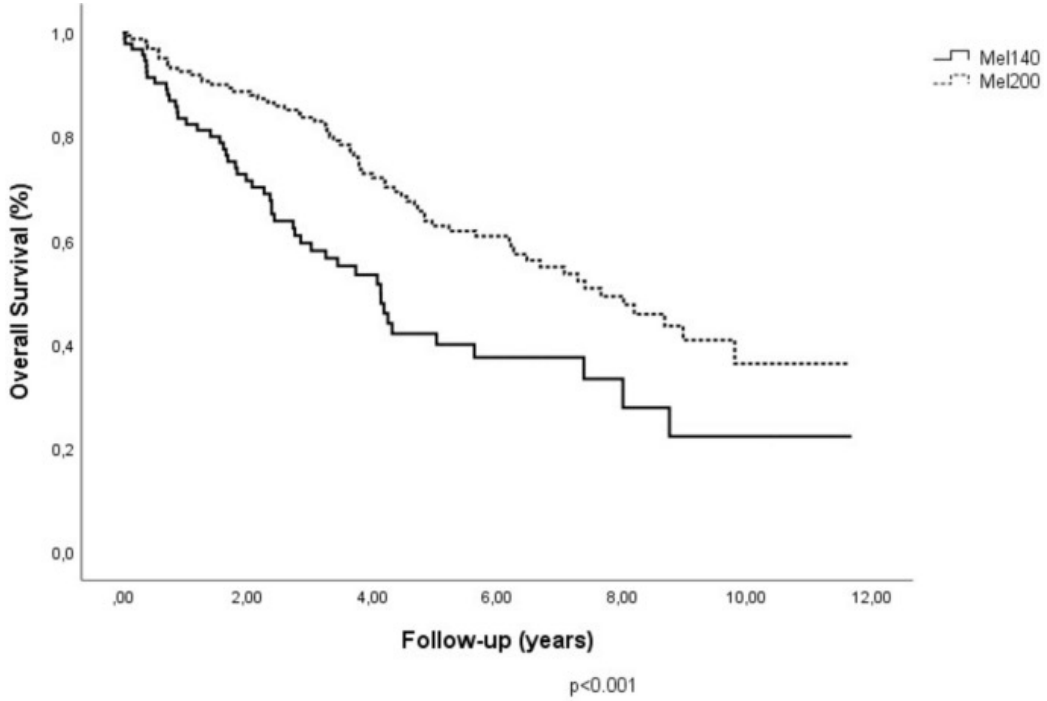
T Facon et al, ASH 2022
P Sonneveld et al, N Engl J Med 2023

Conditioning Mel200 vs Mel140 (II)



The probability of PFS was significantly higher in Mel200 group compared to Mel140 (25.4% vs 17.9%; $p = 0.01$)

Conditioning Mel200 vs Mel140



The probability of OS was significantly higher in Mel200 group compared to Mel140 (36.2% vs 22.1%; $p < 0.001$)

Dark side ASCT: treatment-related AEs (G≥3)

	RV-MM-PI-209		RV-MM-EMN-441		EMN02		IFM-2009		DETERMINATION	
	MPR (N=132)	HDM-ASCT (N=141)	CRD (N=129)	HDM-ASCT (N=127)	VMP (n=495)	ASCT (N=702)	Rvd-alone (N=350)	Rvd+ASCT (N=350)	RVd-alone (N=357)	RVd+ASCT (N=365)
ACUTE TOXICITY → Anemia	51%	94%	2%	13%	<1%	16%	9%	92%	18%	30%
ACUTE TOXICITY → Neutropenia	8%	93%	26%	80%	29%	78%	47%	92%	43%	86%
ACUTE TOXICITY → Thrombocytopenia	1%	22%	5%	70%	16%	83%	14%	20%	20%	82%
Mucositis	NA	NA	NA	NA	0%	16%	0	17%	0	5%
LATE TOXICITY → Infections	1%	16%	6%	19%	5%	25%	9%	20%	9%	18%
LATE TOXICITY → SPMs	0	4%	1%	1%	6%	6%	6%	7%	10%	10%

- More hematologic AEs and infections due to HDM-ASCT
- No differences regarding SPMs incidence

AE: adverse events; SPMs: second primary malignancies

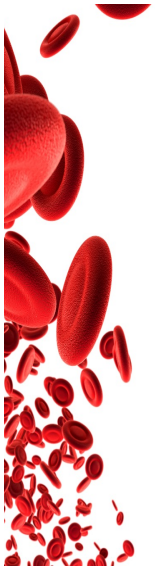
Gay F et al. Leukemia. 2017; Cavo M et al, Lancet Haematol 2020; Cavo M et al, Blood. 2020; [Abstract #142, ASH 2020]. Perrot A et al. Blood. 2020; 136(s1):39 [Abstract #143, ASH 2020]; Gay F et al. Lancet Oncol. 2021; Richardson PG et al. N Engl J Med. 2022

Current "statements" in the treatment of newly diagnosed TE MM

- **Quadruplets + upfront ASCT** represent the current **standard of care**: **Dara-VTd** the current, **Dara-VRd** hopefully soon
- **The number of induction cycles varies from 4 to 6**, upon response/toxicity/logistics; subsequently **consolidation** is proposed or not
- **Stem-cell collection** is **lowered** by the use of up-front daratumumab but in a **"not-clinically relevant way"**
- **Double ASCT** is what we can currently use to improve the outcomes of **HR patients**
- **Lenalidomide until progression** is the current unique SOC for maintenance
- ASCT is proposed "systematically" **up to 70 yo? Mel 200/Mel140?**
- The goal of treatment in NDTEMM is **MRD achievement and sustained MRD negativity;** currently this goal is achieved in 50-70% of the patients, sustained up to 70%!
- **Sustained MRD negativity** is even more important in **HR MM**

Considerazioni generali

- Tenere conto dei **fattori legati al paziente, alla malattia e al trattamento**
- Tenere conto della **tossicità acuta o ritardata del trapianto**
- Per la **fascia di età tra 65 e 70 aa** va dimostrata la **necessità e la sicurezza del trapianto vs non trapianto** (anche alla luce dei risultati dei regimi di condizionamento a intensità ridotta)
- **Valutazione trapiantologica** nei pazienti con indicazione borderline per fattori legati al paziente (es. età, comorbdità, caregiver) o alla malattia (es. IR)



Futuro

Il campo dell'immunoterapia nel MM è in rapida evoluzione

L'l'immunoterapia con CAR-T e BsAb rivoluzionerà presto il panorama terapeutico del MM

Considerando sia le tossicità acute dell'HDM (come la tossicità ematologica e gastrointestinale, le infezioni) sia le tossicità a lungo termine (SPM)

Considerando anche il significativo aumento delle risposte profonde (MRD) con la terapia di induzione quadrupletta e gli ottimi risultati del trattamento con cellule CAR-T e BsAbs

E' probabile che nel prossimo futuro l'HDM-ASCT sarà differito o riservato a casi selezionati, portando a una terapia adattata al rischio e alla risposta, migliorando la qualità della vita e la sopravvivenza del paziente

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Grazie per l'attenzione!