Il mieloma multiplo nel paziente trapiantabile: il trapianto rimane un cardine del trattamento?

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Disclosures

Speakers bureau e advisory board: Amgen

Review > Eur J Haematol Suppl. 1989:51:152-6. doi: 10.1111/j.1600-0609.1989.tb01509.x.

High-dose chemotherapy and autologous bone marrow transplantation for myeloma

T J McElwain, P J Selby, M E Gore, C Viner, M Meldrum, B C Millar, J S Malpas

High-Dose Melphalan With Autologous Bone Marrow Transplantation for Multiple Myeloma

By Bart Barlogie, Roy Hall, Axel Zander, Karel Dicke, and Raymond Alexanian

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO > Guidelines > Guidelines by topic > Haematological Malignancies

Clinical Practice Guidelines – Multiple Myeloma

→ **For younger patients <70 years without comorbidities, induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) is the recommended treatment**

Dimopoulos MA et al. Ann Oncol 2021

Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

→ **Upfront transplant should be offered to all transplant-eligible patients.**

J Clin Oncol 2019; 37:1228-1263

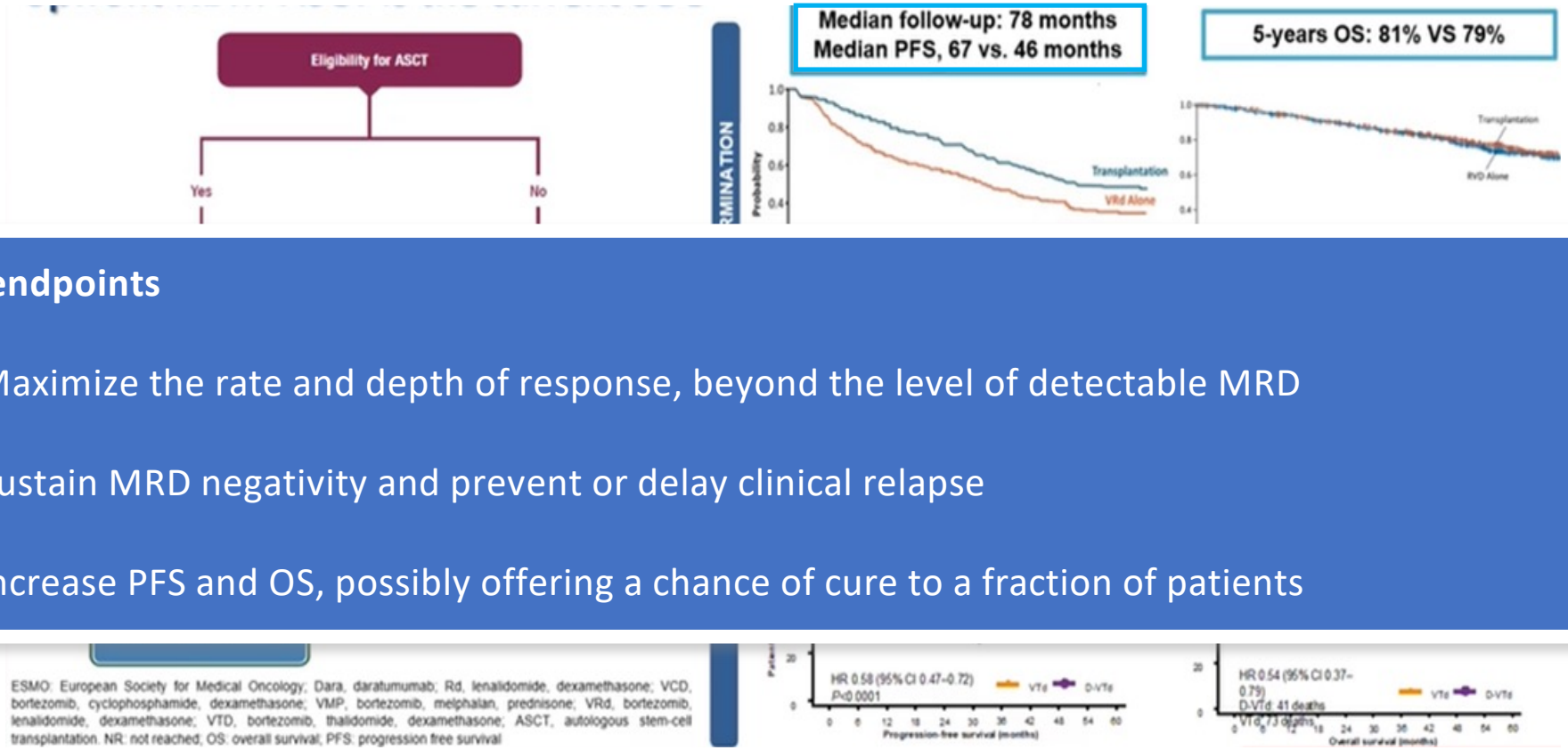
NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020 Multiple Myeloma

→ **Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant. All candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. Chronologic age alone or a specific age cut off is not optimal to determine transplant eligibility**

Moreau P, Ann Oncol, 2017;28(suppl_4):iv52-iv61 - NCCN Guidelines Version2,2020 Multiple Myeloma - Mikhael J, J Olin Oncol 2019. 37(14):1228-1263

Upfront ASCT and new drugs



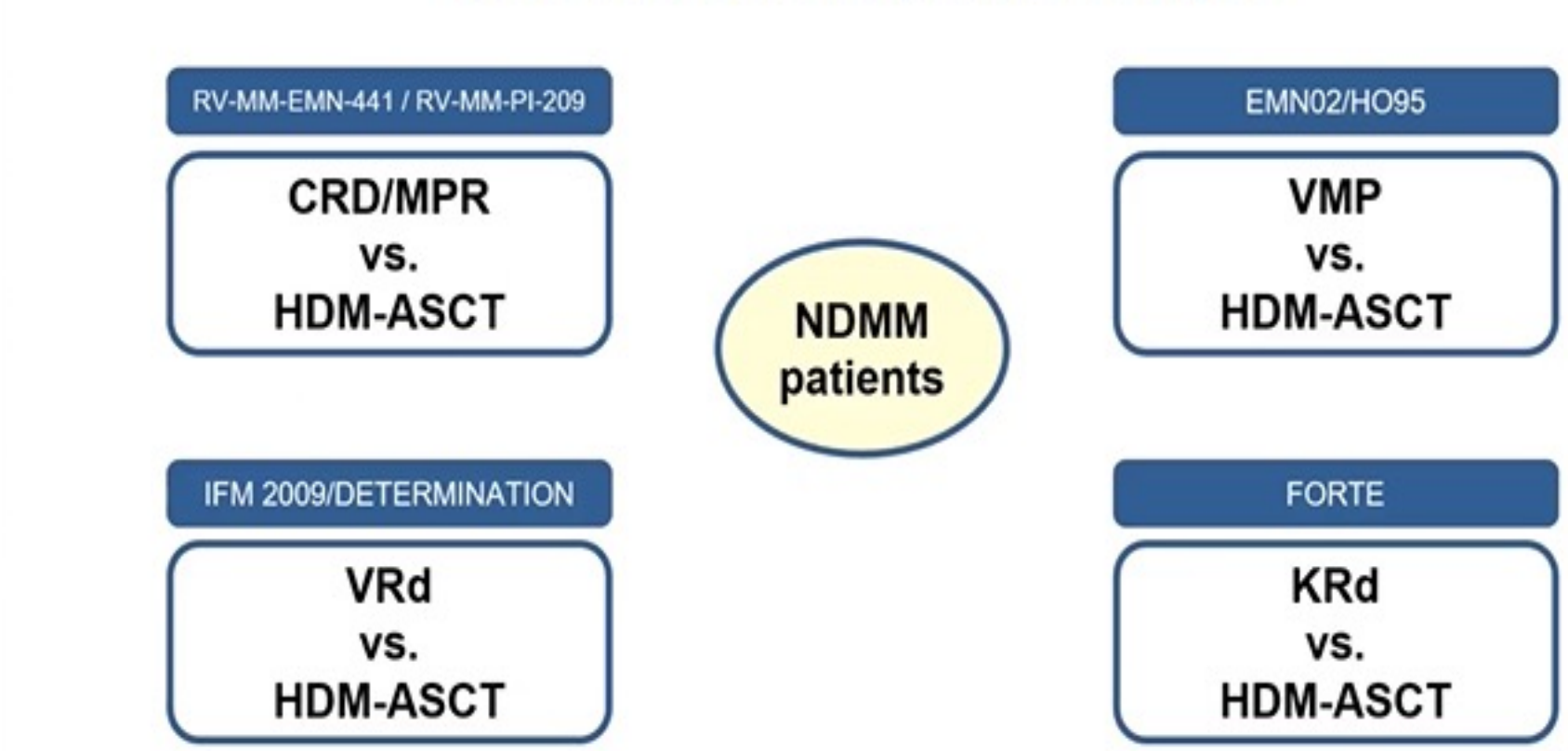
ESMO: European Society for Medical Oncology; Dara, daratumumab; Rd, lenalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisone; VRd, bortezomib, lenalidomide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; ASCT, autologous stem-cell transplantation. NR: not reached; OS: overall survival; PFS: progression free survival

Key endpoints

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

Dimopoulos MA et al. Ann Oncol. 2021 Mar.
Moreau et al. Lancet 2019; Richardson PG et al. N Engl J Med. 2022

ASCT vs. non-transplant strategies

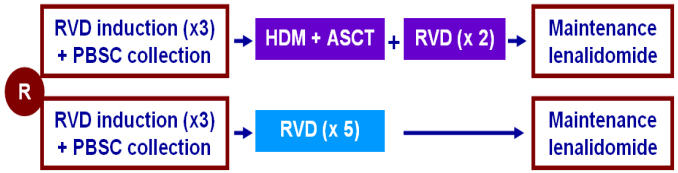


ASCT, autologous stem-cell transplantation; C, cyclophosphamide; R, lenalidomide; D, d, dexamethasone; M, melphalan; P, prednisone; HDM, high-dose melphalan; V, bortezomib; NDMM, newly diagnosed multiple myeloma; K, carfilzomib

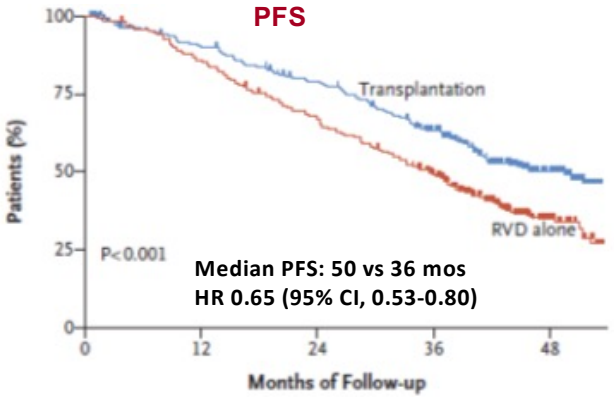
INTENSIFICATION phase: ASCT (btz-based triplets induction)

Upfront high-dose melphalan with ASCT is still the standard of care for fit patients with NDMM, even in the novel agent era

IFM 2009 phase 3 study



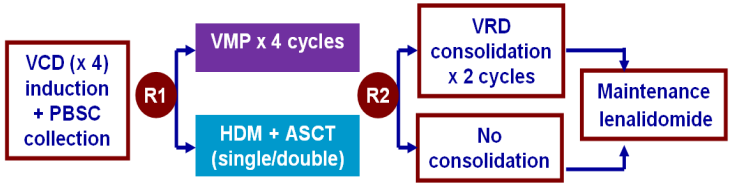
Attal M, et al. NEJM 2017; 376: 1311-1320



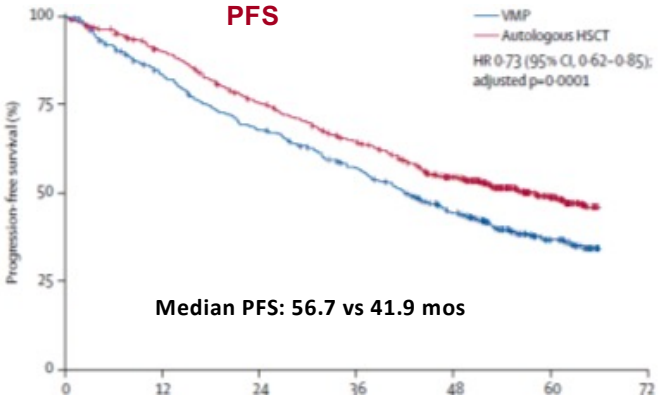
Response

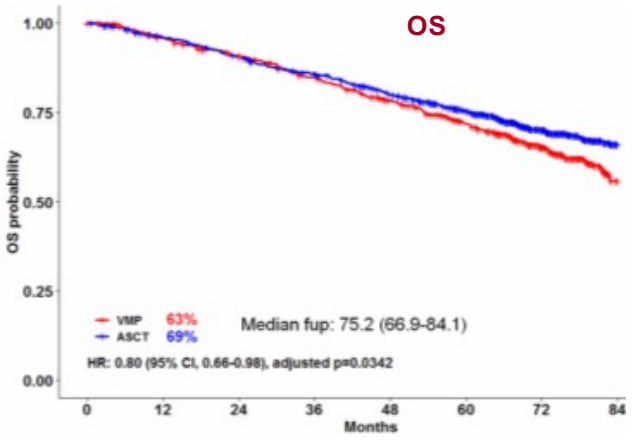
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

EMN02/HO95 phase 3 study



Cavo et al. Lancet Haematol 2020;7: e456-68
Cavo et al. ASH meeting 2020

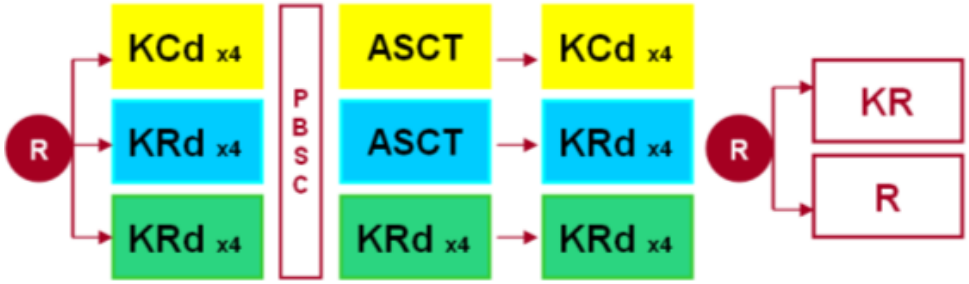




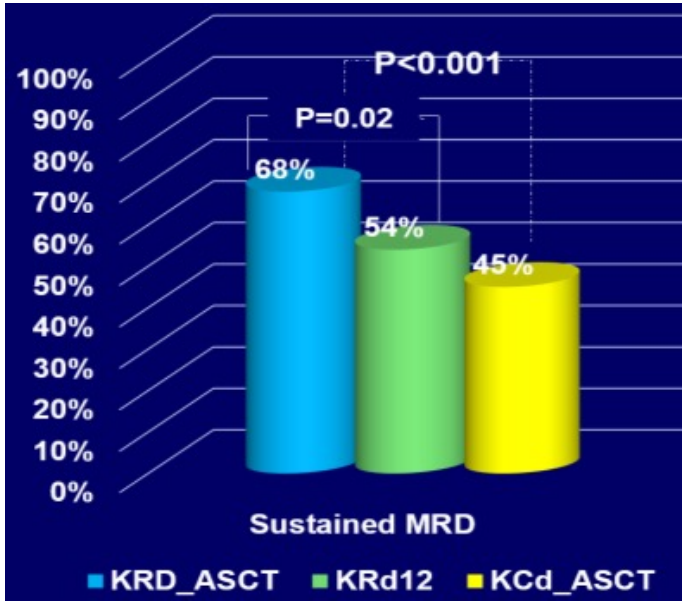
INTENSIFICATION phase: ASCT (2nd generation PI-based triplets induction)

FORTE phase 2 study

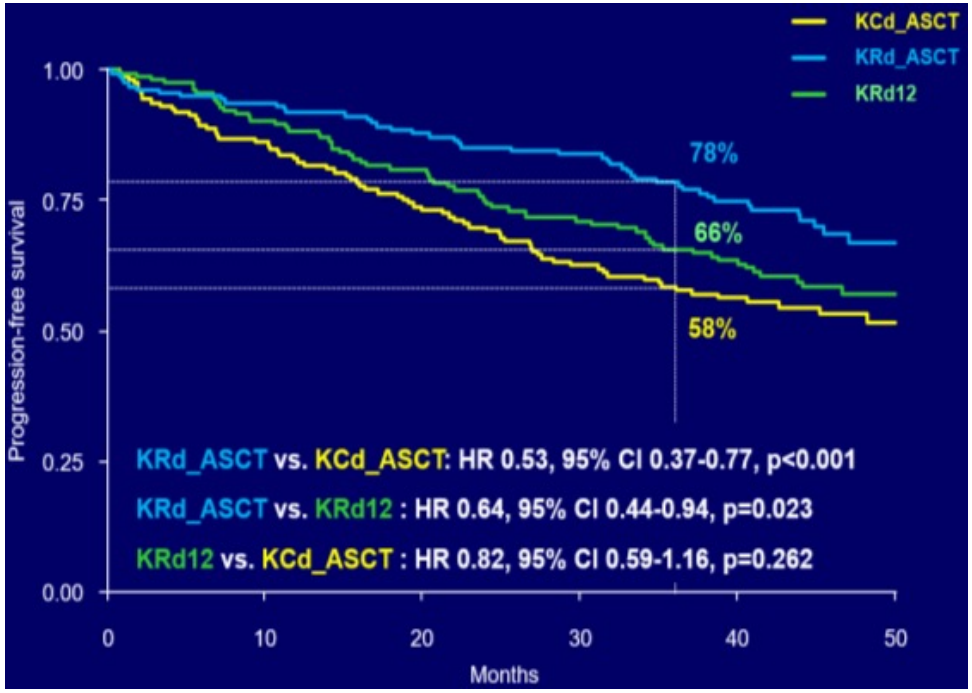
Median FUP 45 mos



MRD rates MFC 10^{-5}



Progression Free Survival



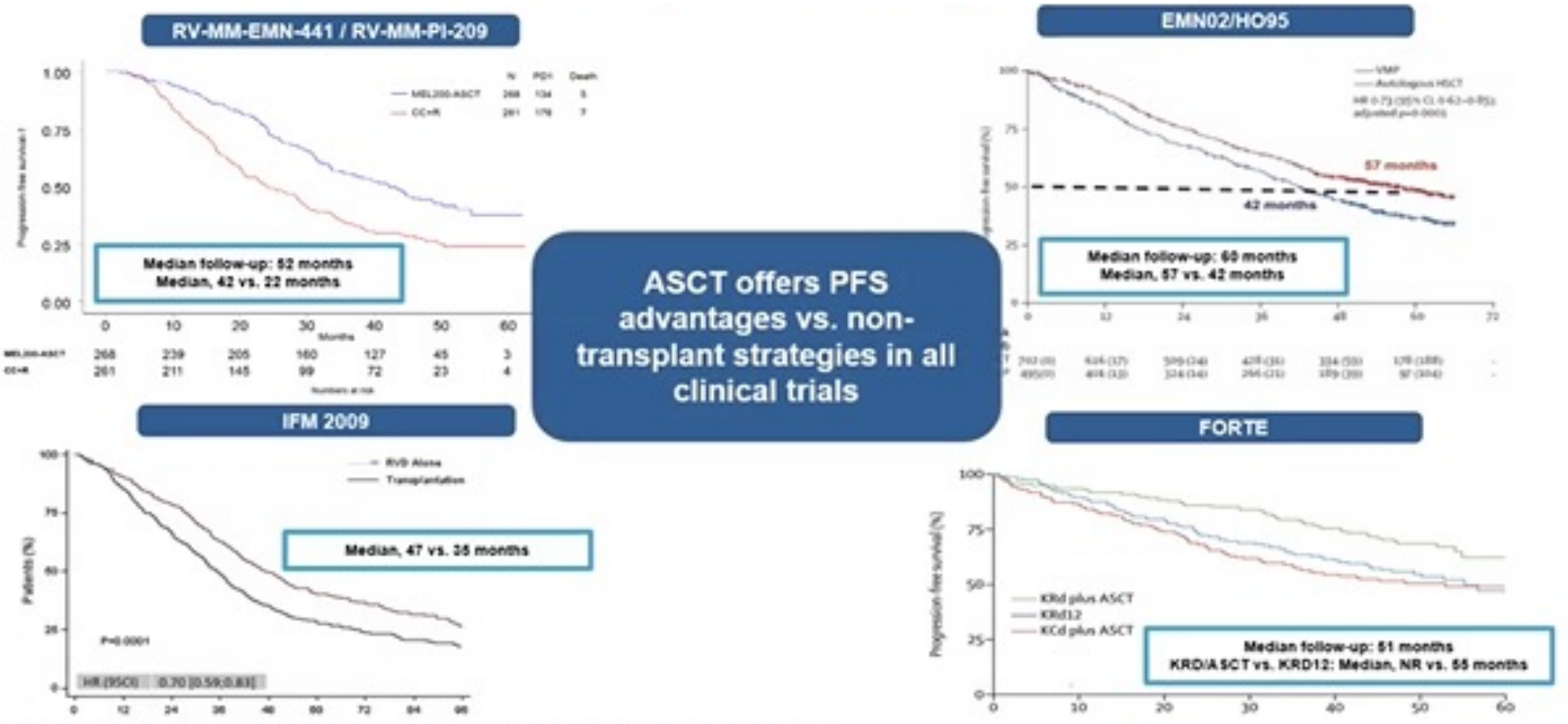
Benefit of KRd_ASCT observed in all pts subgroups:

- ISS I, FISH standard risk, LDH ≤ULN: 3-y PFS: 80-84%

- ISS II/III, FISH high risk, LDH >ULN: 3-y PFS: 69-72%

Gay et al. ASH meeting 2020

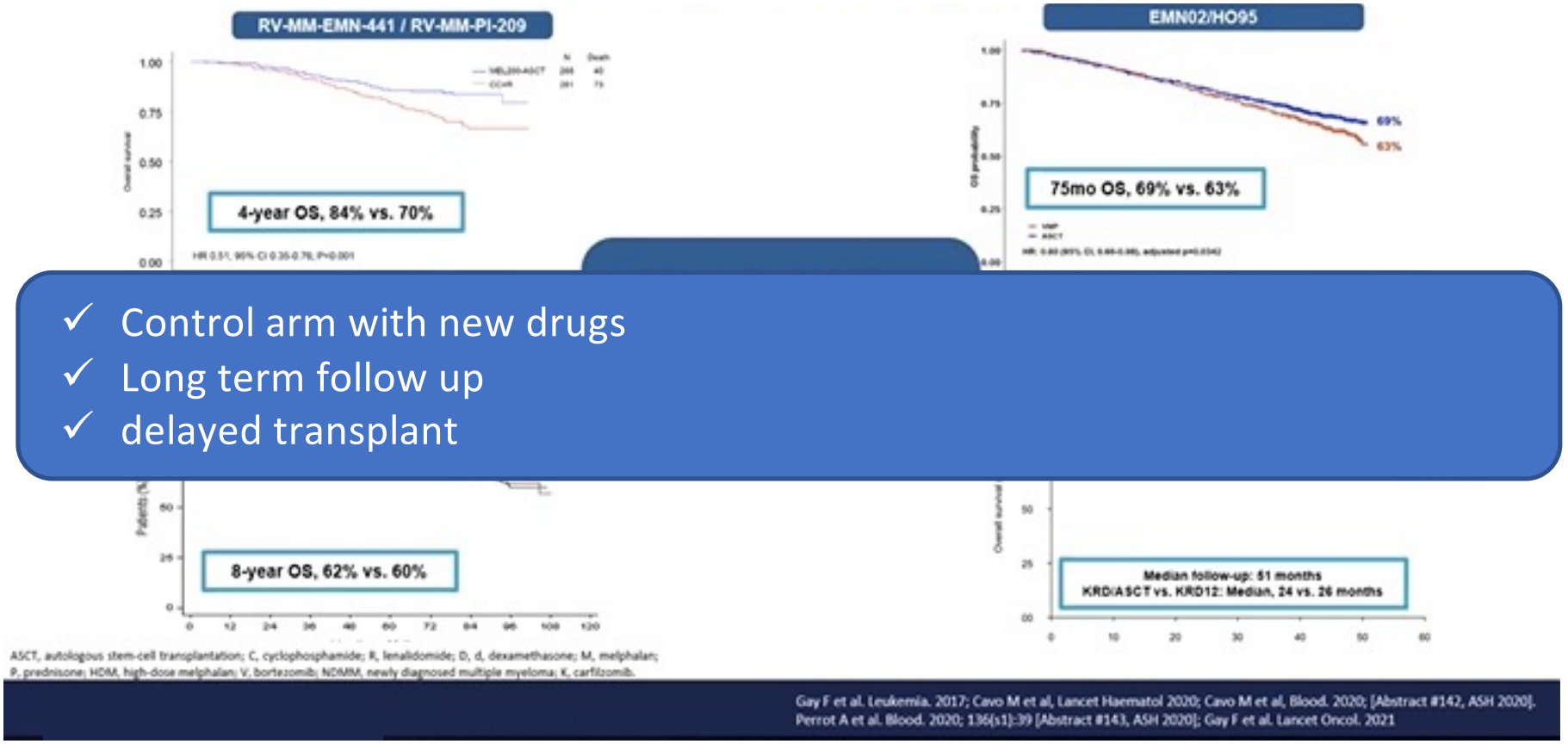
ASCT vs. non-transplant strategies: PFS results



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.

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

ASCT vs. non-transplant strategies: OS results



- ✓ Control arm with new drugs
- ✓ Long term follow up
- ✓ delayed transplant

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.

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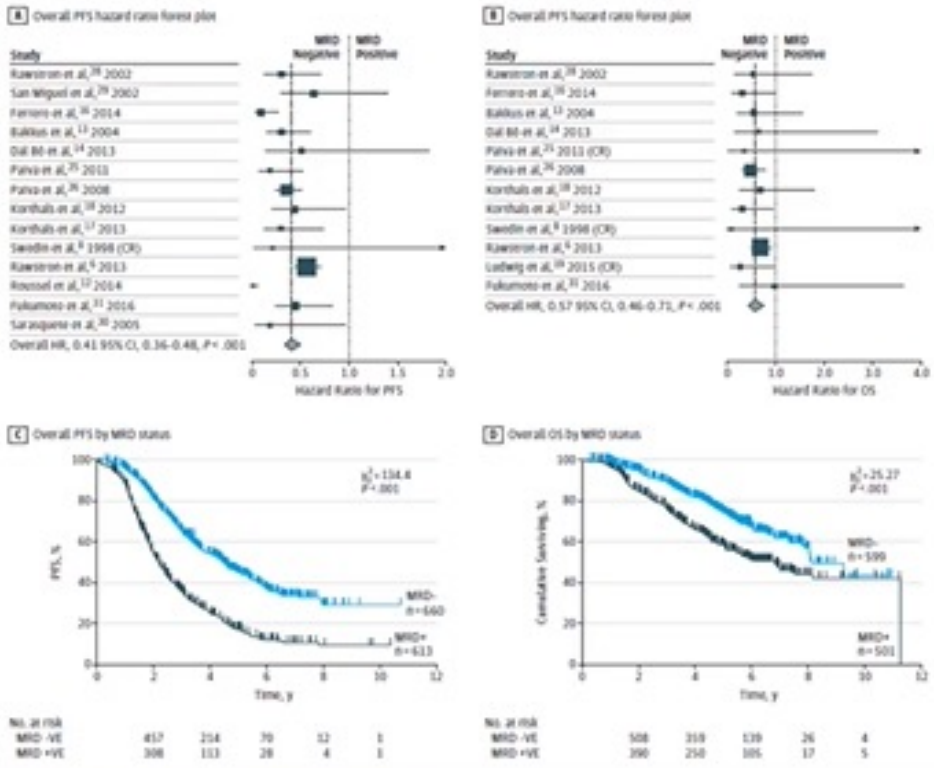
Overall effect of MRD status on PFS and OS



Is OS the best endpoint?

→ We need a long follow-up to assess OS

→ MRD negativity offers PFS and OS advantage

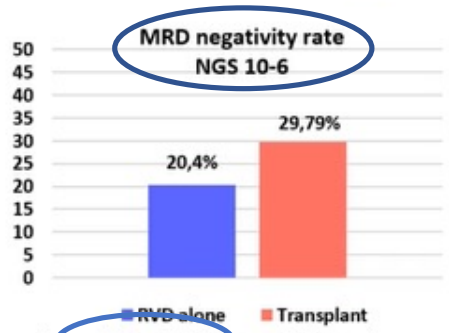
MRD is likely the best surrogate

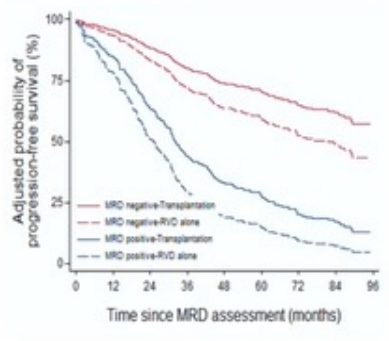
MRD: negativity; PFS: progression free survival; OS overall survival.

Munshi NC et al. JAMA Oncol. 2017 Jan 1;3(1):28-35.

ASCT vs. non-transplant strategies: MRD negativity benefits

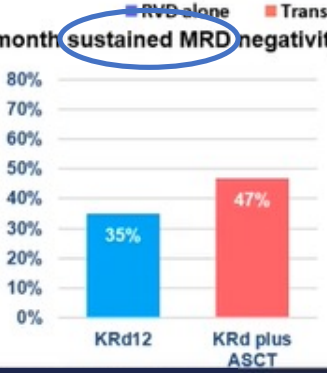
IFM 2009





MRD negativity in ASCT arm vs. other arm → longest PFS

FORTE



3-years PFS	MFC_NEG
KRd_ASCT vs KRd12	88% vs 76% HR 0.48 (p=0.01)

HDM-ASCT increased the rate of 12-month sustained MRD negativity, as compared with KRd without ASCT.

MRD: negativity; PFS: progression free survival; OS overall survival.

Perrot A et al. Blood. 2020; 136(s1):39 [Abstract #143, ASH 2020].
Gay F et al. Blood. 2020; 136(s1): 35-37 [Abstract #141, ASH 2020, oral presentation].

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%
Neutropenia	8%	93%	26%	80%	29%	78%	47%	92%	43%	86%
Thrombocytopenia	1%	22%	5%	70%	16%	83%	14%	20%	20%	82%
LATE TOXICITY										
Mucositis	NA	NA	NA	NA	0%	16%	0	17%	0	5%
Infections	1%	16%	6%	19%	5%	25%	9%	20%	9%	18%
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

Early vs delayed ASCT: is the timing relevant in term of efficacy?

Ref.	Year	Study type	Induction regimen (early vs. late)	Response (early vs. late)	PFS (early vs. late)	OS (early vs late)
Fernand et al.[1]	1998	P	VAMP x 3-4 cycles and ASCT vs. VMCP until plateau and ASCT at relapse	85.7% vs 55.%	39 mo vs 13 mo	64.6 mo vs 64 mo (p=0.92)
Gay et al.[2]	2017	P	HDM-ASCT vs CC-R	//	PFS1: 42 vs 24 mo (P=0.001)	4y: 84 vs 70% (p=0.001)
Cavo et al. EMN02[3]	2020	P	HDM-ASCT vs VMP	CR: 44% vs. 40% (*p* = 0.03)	54 vs 45·5 (p=0.014)	75mo: 69% vs. 63% (*p* = 0.03)
Attal et al. IFM2009[4]	2017	P	VRD x 3 cycles and ASCT + VRD x 2 cycles vs- VRD x 8 cycles and ASCT at relapse	CR 59% vs 48% (p=0.05)	47 mo vs 35 mo (p< 0.01)	4y: 62 vs 60% (p=NS)
Richardson et al. DETERMINATION[5]	2022	P	VRD x3 + ASCT + 2 VRD vs. VRD x8	≥CR 46.8 VS. 24 (p=NS)	67.5 vs 46.2 mo (p< 0.01)	5y: 81 vs. 79% (p=NS)

CR, complete response; NR, not reached; NS, nonsignificant; P, prospective; r, retrospective; R, Revlimid; RD, Revlimid, dexamethasone; Ref., reference; T, thalidomide; TD, thalidomide, dexamethasone; V, Velcade; VAMP, vincristine, Adriamycin, melphalan, prednisolone; VGPR, very good partial response; VMCP, vincristine, melphalan, cyclophosphamide, prednisolone; VRD, Velcade, Revlimid, dexamethasone

1 Fermand JP et al., Blood. 1998; 2 Gay F et al. Leukemia. 2017; 3 Cavo et al Lancet 2020; 4 Attal M et al., 5 IFM 2009 Study N Engl J Med 5 Richardson PG et al. N Engl J

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Fernand et al.[1]	1998	P	VAMP x 3-4 cycles and ASCT vs. VMCP until plateau and ASCT at relapse	77% of relapsed patients in the VMCP arm received salvage ASCT		
Gay et al.[2]	2017	P	HDM-ASCT vs CC-R	53% of relapsed patients in the CC+R alone arm received salvage ASCT		
Cavo et al. EMN02[3]	2020	P		lapsed patients in the VMP alone arm received salvage ASCT		
Attal et al. IFM2009[4]	2017	P	VRD x 3 cycles and ASCT + VRD x 2 cycles vs- VRD x 8 cycles and ASCT at relapse	77% of relapsed patients in the RVd alone arm received salvage ASCT		
Richardson et al. DETERMINATION[5]	2022	P	VRD x3 + ASCT + 2 VRD vs. VRD x8	28% of relapsed patients in the RVd alone arm received salvage ASCT		

Feasible but not in all patients

omplete response; NR, not reached; NS, nonsignificant; P, prospective; r, retrospective; R, Revlimid; RD, Revlimid, dexamethasone; Ref., ence; T, thalidomide; TD, thalidomide, dexamethasone; V, Velcade; VAMP, vincristine, Adriamycin, melphalan, prednisolone; VGPR, very good al response; VMCP, vincristine, melphalan, cyclophosphamide, prednisolone; VRD, Velcade, Revlimid, dexamethasone

1 Fermand JP et al., Blood. 1998; 2 Gay F et al. Leukemia. 2017; 3 Cavo et al Lancet 2020; 4 Attal M et al., 5 IFM 2009 Study N Engl J Med 5 Richardson PG et al. N Engl J

Is there still a role for delayed ASCT?

KARMMA 3

Ide-cell in patients with 2-4 prior lines of therapy

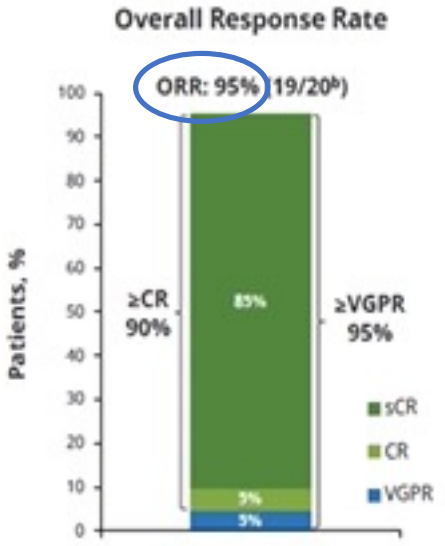
mPFS rate 13.3 months

ORR: 71%

CAR: chimeric antigen receptor; AE: adverse event; LOT: line of therapies; ORR: overall survival; NR: not reached

CARTITUDE-2 Cohort A

Cilta-cel in patients with early relapse (1-3 LOT) and Len-ref (n=20)

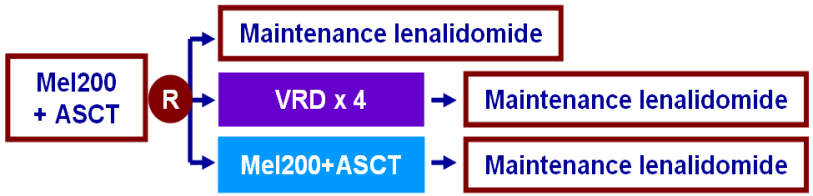


- Median DOR was NR
- **15-month PFS rate was 70%** (95% CI, 45.1–85.3)

Rodriguez Otero P et al, NEJM 2023
Cohen AD et al. IMS 2022. Oral presentation.

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

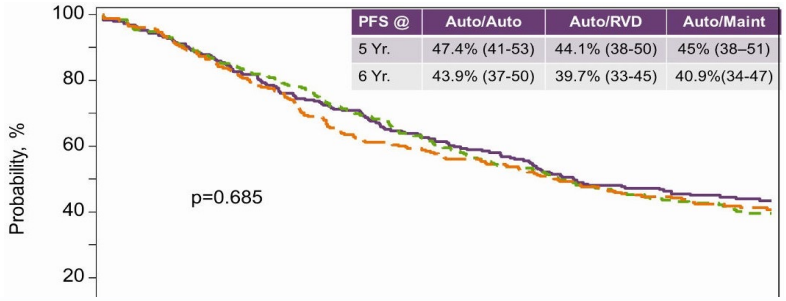
BMT CTN 0702 ph.2 trial (STaMINA)



	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

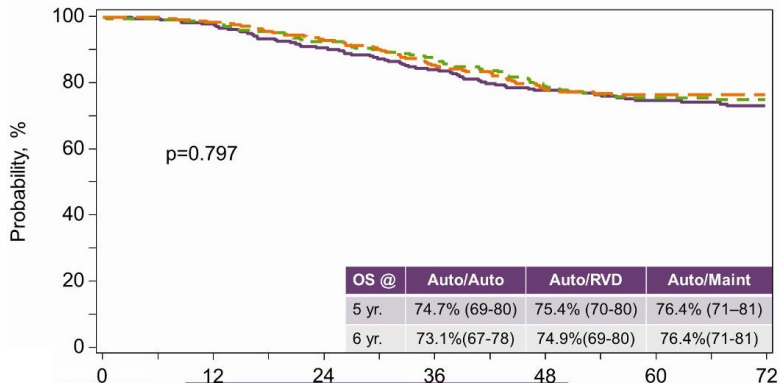
2019

PFS

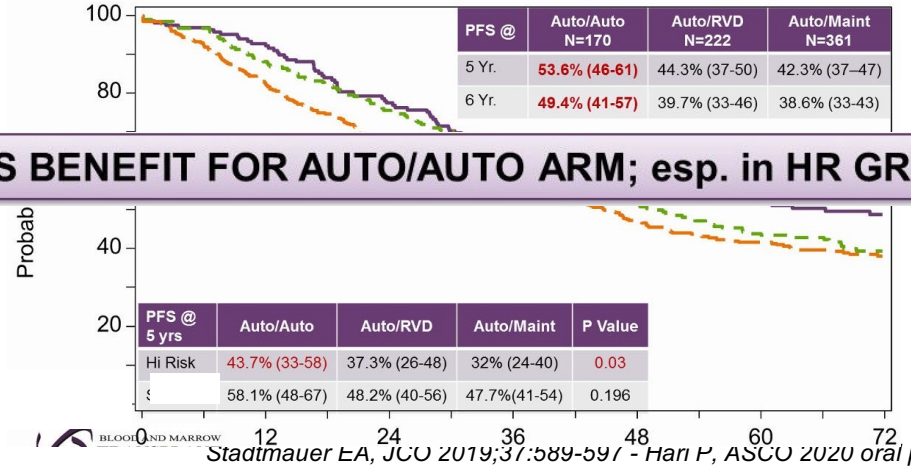


NO DIFFERENCE BETWEEN STUDY ARMS

OS



STaMINA: PFS by Treatment Received

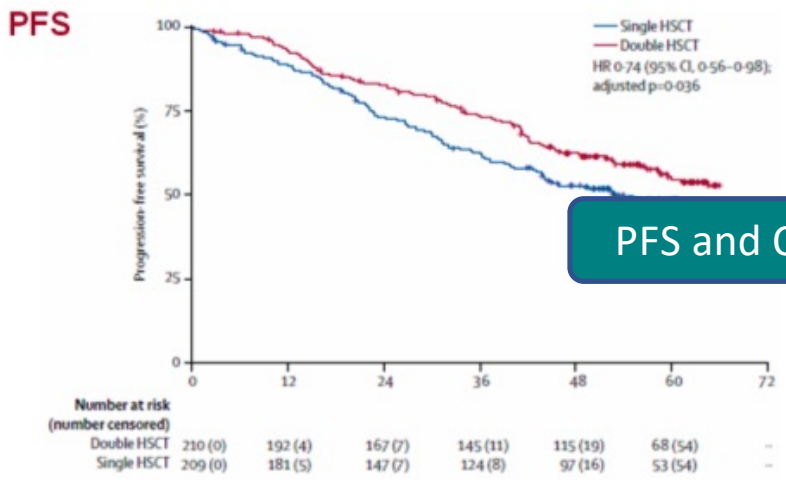


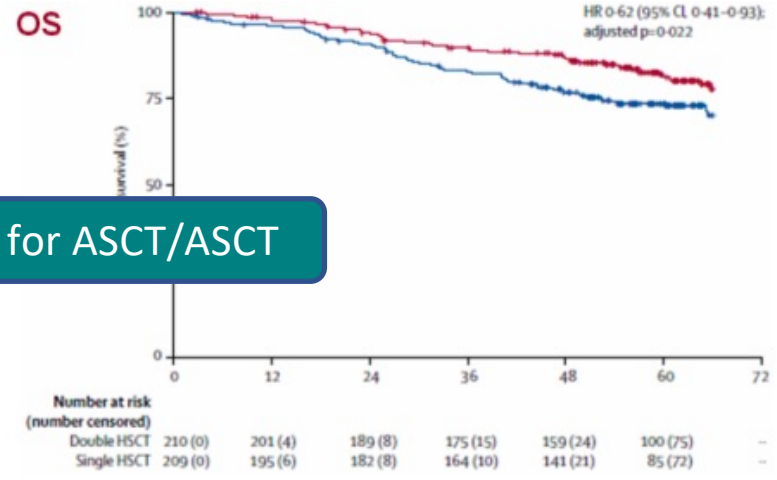
PFS BENEFIT FOR AUTO/AUTO ARM; esp. in HR GROUP

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

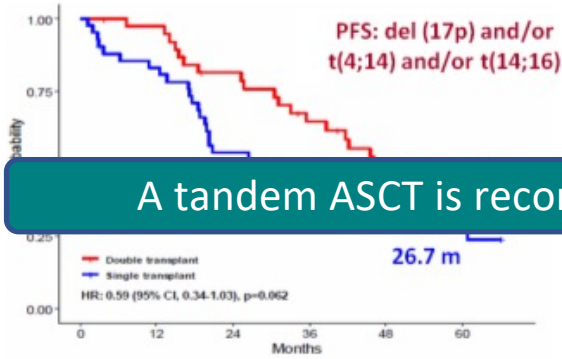
Second ASCT (tandem) as consolidation therapy: more is always better?

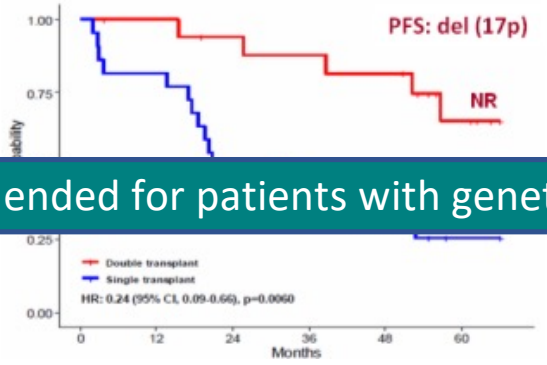
EMN02/HO95 phase 3 study

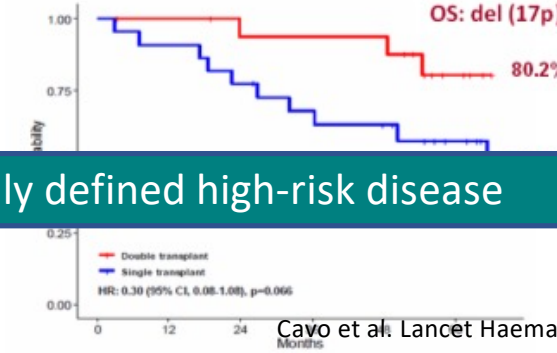




PFS and OS benefit for ASCT/ASCT







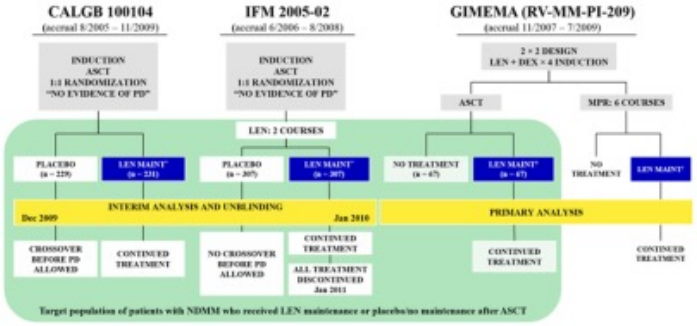
A tandem ASCT is recommended for patients with genetically defined high-risk disease

Cavo et al. Lancet Haematol 2020;7:e456–68

MAINTENANCE: Lenalidomide post ASCT

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

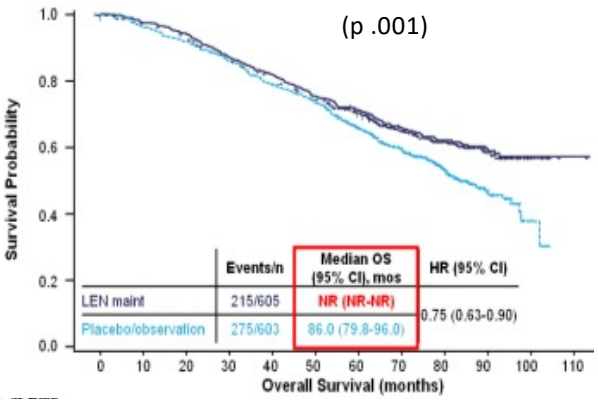
Meta-analysis

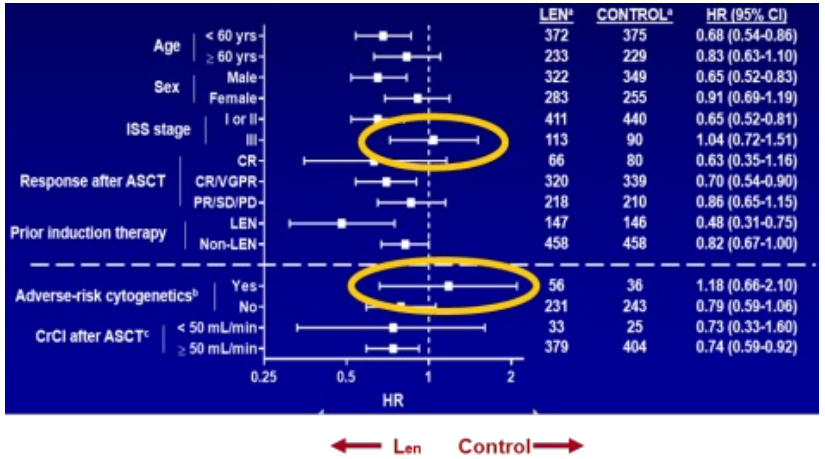


McCarthy, et al. JCO 2017;35:3279-89

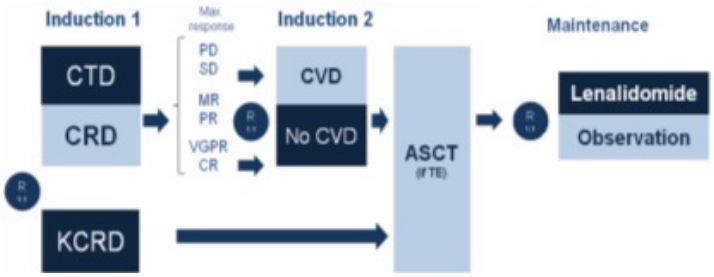
OS

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



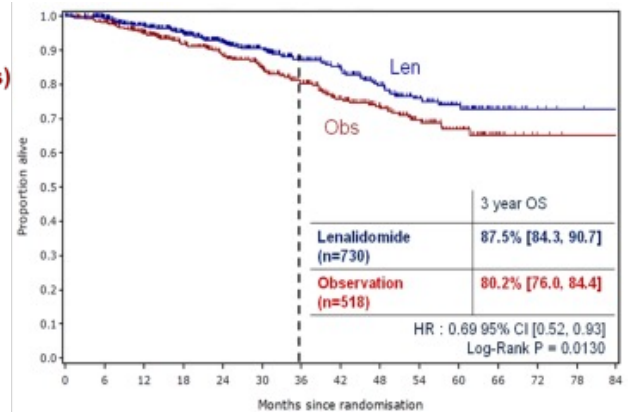


Myeloma XI trial



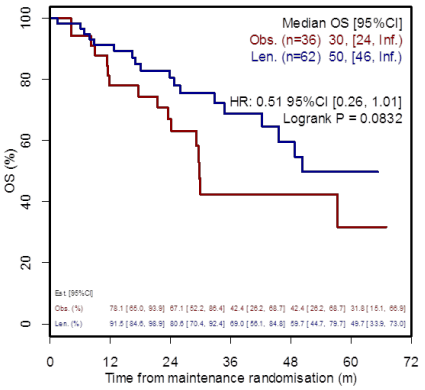
Jackson et al. Lancet Oncol 2019;20:57-73

OS
(TE pts)



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

OS



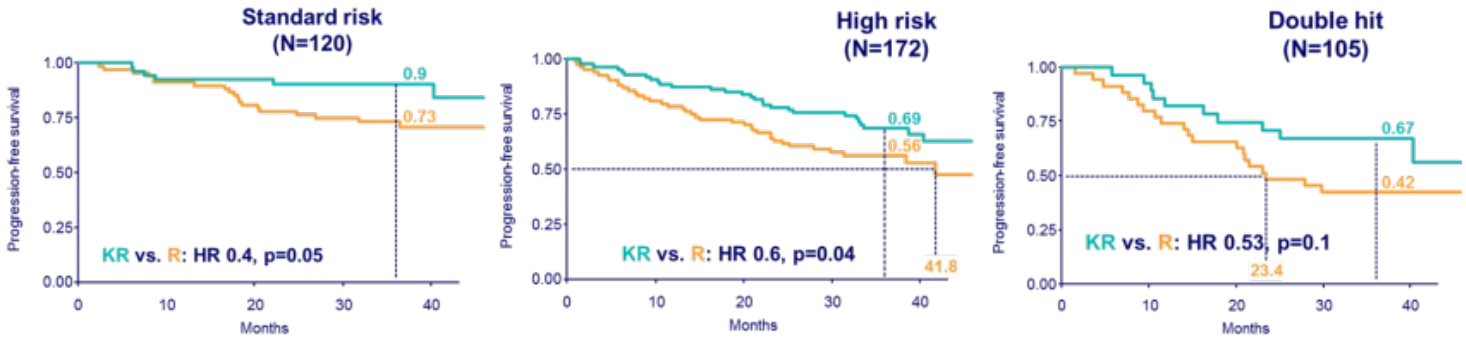
MAINTENANCE: other options

HOVON-65/GMMG-HD4 phase 3 trial: btz induction and maintenance

		PFS at 60 months, %			OS at 60 months, %		
FISH	n	Bortezomib arm	p	Standard arm	Bortezomib arm	p	Standard Arm
del(17p) yes/no	39/312	22% vs 27%	0.47	5% vs 24%	65% vs 72%	0.48	18% vs 66%

Sonneveld et al. JCO 2012; Goldschmidt et al. Leukemia 2018; Neben et al. Blood. 2012

FORTE ph 2 trial: carfilzomib plus lenalidomide



Mina R et al. EHA 2021

ASCT-eligible NDMM: Practical considerations

Induction therapy for 4 to 6 cycles should be planned in ASCT-eligible NDMM patients

- The 4-drug combination **DaraVTd** is the current standard of care
- Beware of PN (DaraVRd in the future?)

Upfront ASCT remains the gold standard intensification therapy

Double ASCT improves outcomes especially in patients with **high-risk cytogenetic abnormalities**. Role in the future with routine use of quadruplets?

Lenalidomide is the standard maintenance therapy, Btz maintenance can be considered for HR patients, some patient subgroups might benefit from combos (not yet approved)

Future directions: New combo, Immunotherapy, New clinical trials are aimed at addressing the issue of MRD status and Risk assessment as driver of first-line therapy

The **main challenges** will be to better understand the biology of MM and to make every possible effort for improving the outcome of this heterogeneous disease by personalized precision therapies

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Grazie per l'attenzione!