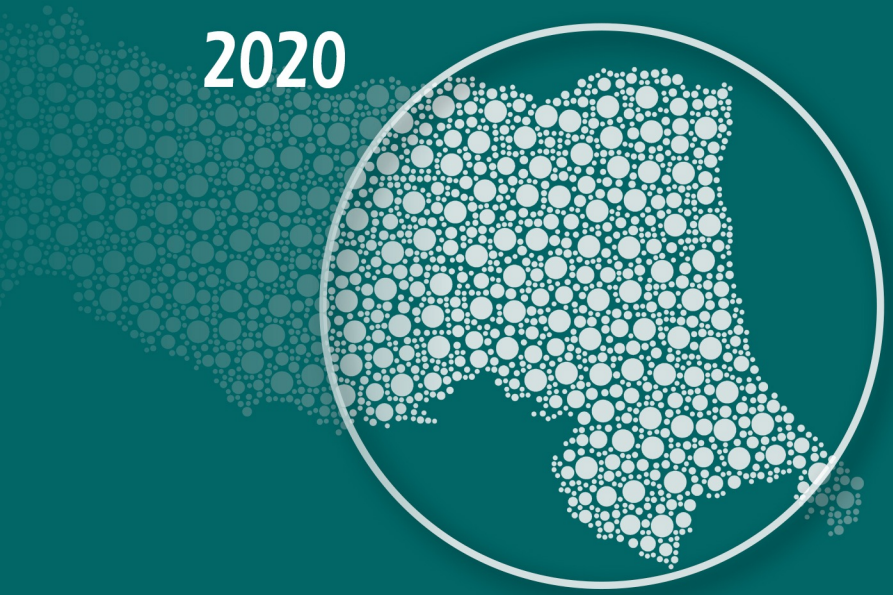

Progetto Ematologia Romagna

Trapianto autologo in tutti i pazienti?

Lucia Pantani

ASSOCIAZIONE ITALIANA
CONTRO LE LEUCEMIE-LINFOMI E MIELOMA
ONLUS

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DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

Background

- In the ’90s, high-dose melphalan plus autologous stem-cell transplantation (ASCT) demonstrated better rates of complete response (CR) and longer overall survival (OS) compared to conventional chemotherapy, primarily in patients younger than 65 years[1]

- The addition of novel agents like IMiDs and PIs as induction therapy before and as consolidation/maintenance therapy after ASCT has led to a further improvement in CR rates, PFS and OS[2]

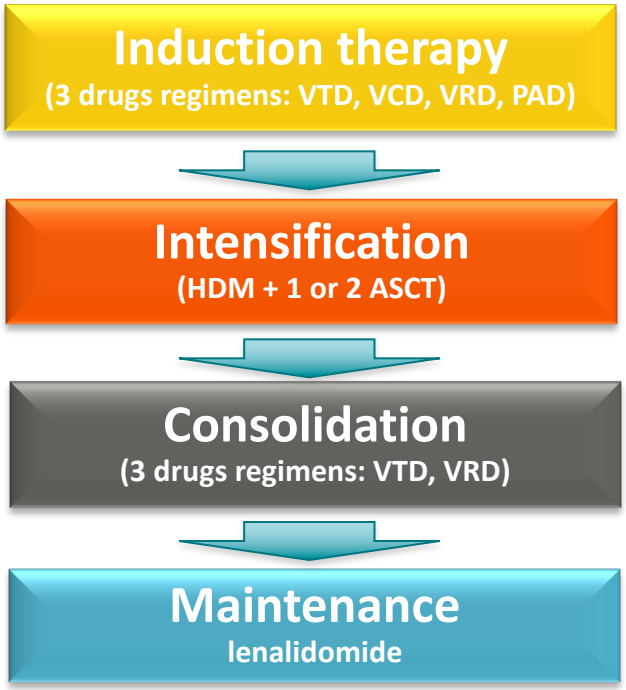
- ASCT is currently considered the standard of care for fit newly diagnosed MM patients

[1]Attal M, N Engl J Med. 1996; 335(2):91–97
Child JA, N Engl J Med. 2003; 348(19):1875-83

[2]Harousseau et al. J Clin Oncol. 2010;28:4621-29
Sonneveld et al. JCO 2012 30(24):2946-55
Cavo et al. Lancet 2010;379:2075-85
Rosinol et al. Blood 2012;120:1589-96

Treatment paradigm for transplant-eligible patients

Sequential blocks of therapy



Continued cytoreduction
Sustained suppression of disease burden

Key endpoints

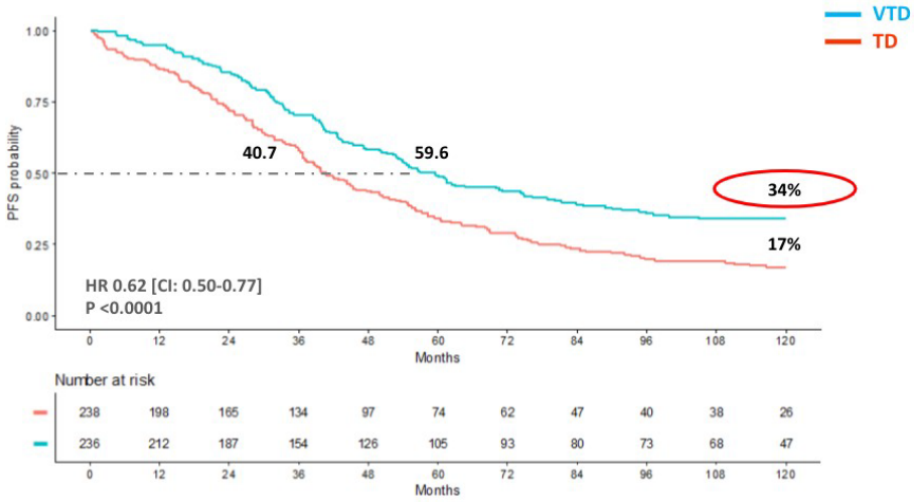
- **Maximize the rate and depth of response, beyond the level of detectable MRD**
- **Sustain MRD negativity and prevent or delay clinical relapse**
- **Increase PFS and OS, possibly offering a chance of cure to a fraction of patients**

Cavo M et al. Blood 2011;117(23):6063-73
Kumar S, et al. Lancet Oncology 2016;17:e328-46
Gay F et al. Haematologica 2018;103(2): 197-211

GIMEMA-MMY-3006 study: long-term analysis

median follow-up surviving patients: 124 months

PFS



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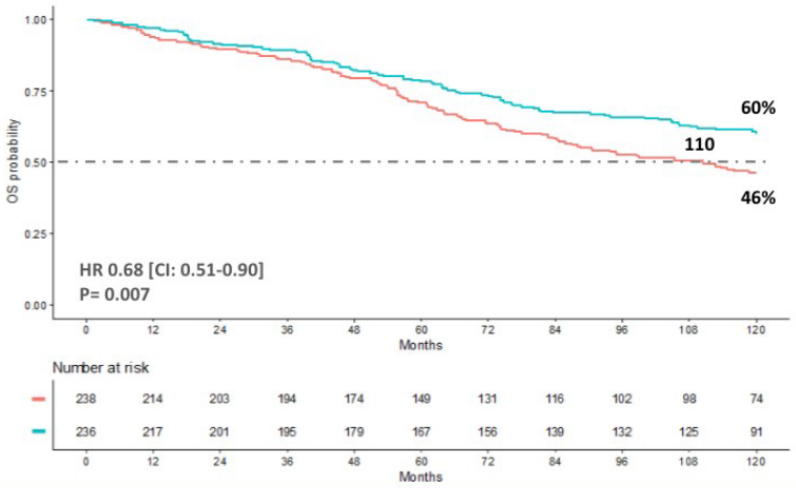


32% reduction in the risk of death with incorporation of VTD into double ASCT

Tacchetti et al, in publishing

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
CLINICAL PRACTICE GUIDELINES
Annals of Oncology 28 (Supplement 4): iv52–iv61, 2017
doi:10.1093/annonc/mdx096
Published online 27 April 2017

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

For younger patients (<65 years or fit patients <70 years in good clinical condition), induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment.

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

J Clin Oncol 2019; 37:1228-1263

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

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 .

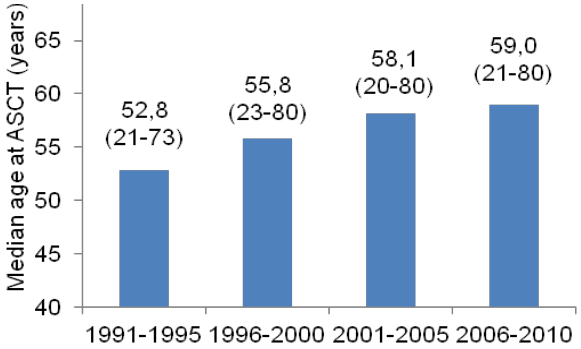
ASCT in patients with renal impairment

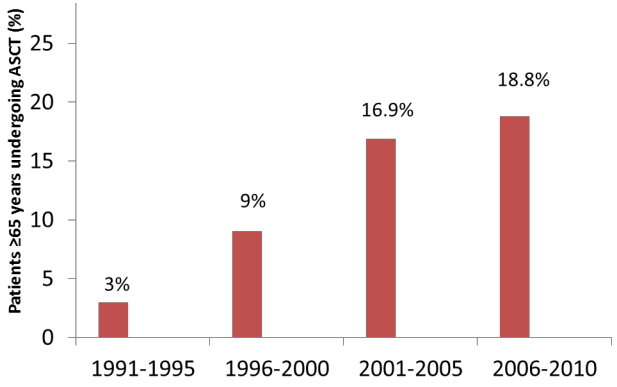
- Several reports have shown that high-dose therapy with stem cell support is feasible in MM and RI, even in dialysis
- RI does not to affect the CD34+ yield or their engraftment
- Melphalan clearance is renal function-dependent as the drug is both secreted and reabsorbed by the renal tubules; HDM 100-140 mg/sm should be used when CrCl is < 60 ml/min
- ASCT is associated with increased mucositis and an increased risk of TRM for pts with RI (>4%) compared with pts without RI at the time of transplantation (<1%)
- Retrospective analyses have reported a ≥ 25% improvement in RI in one third of pts, a 15% to 20% probability of dialysis independence, and a 5-year OS of nearly 35%

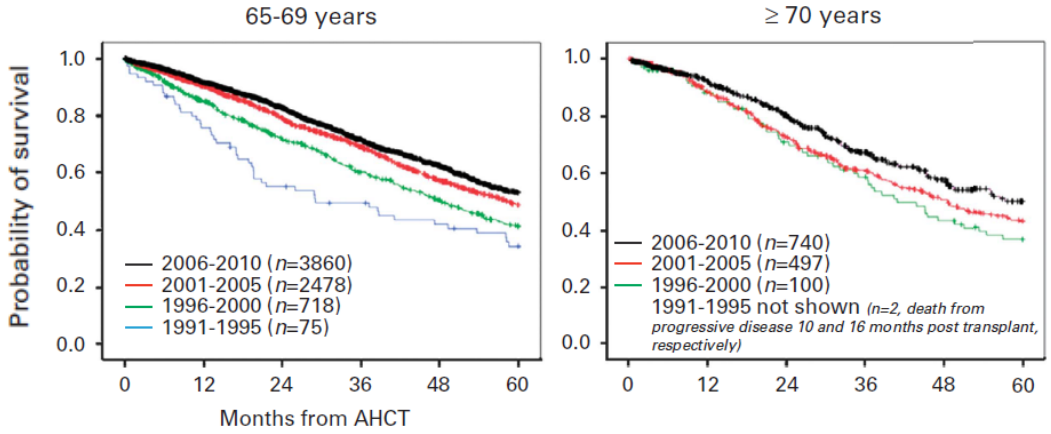
Badros et al. Br J Haematol 2001;114:822-829
San Miguel et al. Hematol J 2000;1:28-36
Lee et al. Bone Marrow Transplant 2004;33:823-828
Parikh et al. Biol Blood Marrow Transplant 2009;15:812-816
Dimopoulos et al, J Clin Oncol,2016;34:1544-57

ASCT in elderly patients

Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: increased use and improved outcomes in elderly patients in recent years







Day-100 all-cause mortality

	60–64		65–69		⩾70	
Calendar period	*%*	*95% CI*	*%*	*95% CI*	*%*	*95% CI*
1991–1995	3.9	2.9–5.3	8.0	6.9–9.3	NA[a]	—
1996–2000	3.6	2.5–5.2	4.1	2.9–5.7	4.0	2.8–5.6
2001–2005	2.4	1.7–3.3	2.7	2.0–3.6	2.4	1.7–3.3
2006–2010	1.8	1.3–2.5	2.1	1.6–2.8	2.4	1.9–3.1

Auner et al. Bone Marrow Transplantation (2015) 50, 209–215

ASCT in elderly patients

Prospective studies of upfront ASCT for *older* patients with NDMM

	Ref. 1	Ref. 2	Ref. 3	Ref. 4	Ref. 5
N° pts	95	126	102	56	434
Age (median)	65 (51-70)	NA	67 (46–74)	67.4 (64–74)	65 (60–72)
Induction (n ° cycles)	VAD (2)	VAD (2)	Bort-based (4)	Bort-based (4–6)	50% Bort-based (4) 50% No induction
High-dose therapy	MEL 100	MEL 100	MEL 100	MEL 200 (64%) MEL 140 (36%)	MEL 140
ASCT (n°)	2	2	2	1	2
Len maintenance	No	No	Yes	No	No
TRM (%)	5	9	5 (<70 ys) 19 (70-75 ys)	0	1.4 (ASCT-1) 0 (ASCT-2)
PFS (median mos or %)	28	19.4	48	76% at 2 ys	20 (induction) 21.4 (no induction)
OS (median mos or %)	58	38.3	68% at 5 ys	88% at 2 ys	53.4 (induction) 55.9 (no induction)

[1]Palumbo et al, Blood 2004; 04:3052-57; [2]Facon et al, Lancet 2007, 370:1209-18; [3]Gay et al, Blood 2013, 122:1376-83;
[4]Garderet et al, Haematologica 2016, 101:1390-97; [5]Straka et al, Haematologica 2016; 101:1398-06.

Up-front ASCT vs novel agent-based intensification therapy

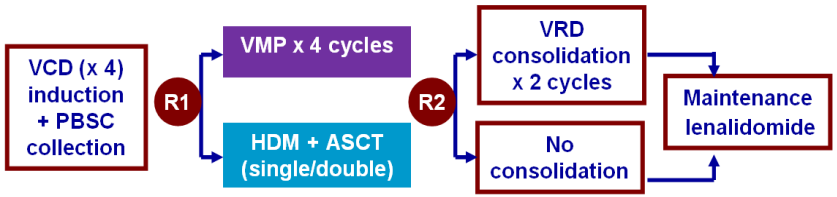
Remarkable results obtained in the non-transplant setting with novel agent-based treatment have raised questions as to the role of upfront *versus* delayed ASCT

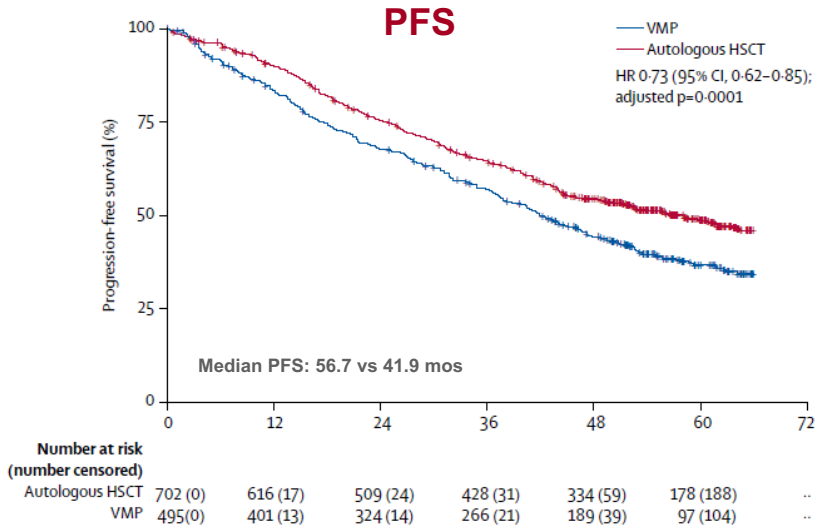
Prospective studies: early vs delayed ASCT

Induction	Intensification phase		Maintenance	PFS (mos) (Control vs ASCT)	OS at 4 years (Control vs ASCT)	N° (%) pts receiving salvage ASCT
	Control Arm (n° pts)	ASCT Arm (n° pts)				
RD x 4 cycles	RCD x 6 cycles (129)	MEL 200 x 1 or 2 (127)	R±P until PD	28.6 vs 43.3 (HR 2.51, p<0.0001)	73% vs 86% (HR 2.40, p=0.004)	43
RD x 4 cycles	MPR x 6 cycles (132)	MEL 200 x 2 (141)	R or observation until PD	22.4 vs 43.0 (HR 0.44, p<0.001)	65.3% vs 81.6% (HR 0.55, p=0.02)	62.8
VRD x 3 cycles	VRD x 8 cycles (331)	MEL 200 x 1 + VRD x 2 cycles (323)	R until PD	36 vs 50 (HR 0.65, p<0.001)	82% vs 81% (p=0.43)	79
VCD x 3-4 cycles	VMP x 4 cycles (495)	MEL 200 x 1 or 2 (702)	R until PD	42 vs 57 (HR 0.73, p<0.001)	71% vs 75% (p=0.36)	63

Gay F, Lancet Oncol 2015;16:1617-29 – Palumbo A, N Eng J Med 2014;371(10):895-905 – Attal M, N Eng J Med 2017;376:1311-20 – Cavo M, Lancet Haematol 2020;7:e456–68

ASCT vs novel agent-based therapy: EMN02/HO95 phase 3 study





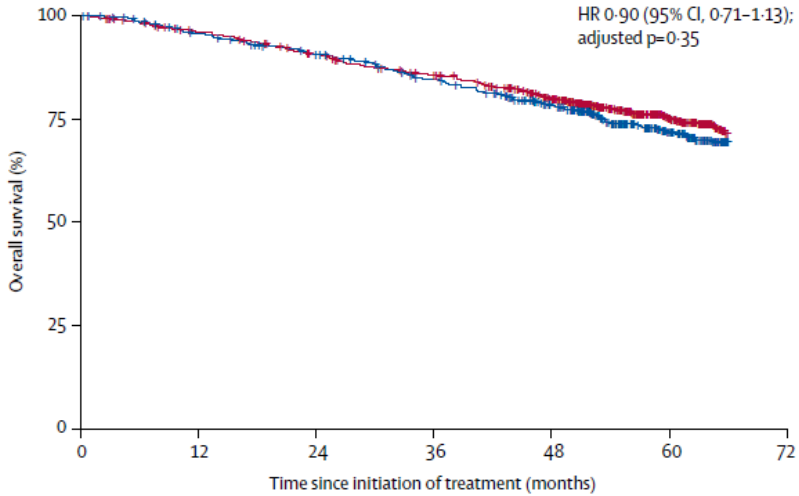
Prespecified subgroup analyses of PFS

SUBGROUPS	Transplant (Median PFS [mos])	VMP (Median PFS [mos])	HR	95% CI
Age ≤ 55 years	61.1	37.2	0.62	[0.48 ; 0.80]
Age > 55 years	56.1	43.5	0.80	[0.66 ; 0.98]
ISS I	NR	50.8	0.74	[0.57 ; 0.96]
ISS II+III	46.0	36.2	0.72	[0.59 ; 0.87]
Standard-risk cytogenetics	NR	46.7	0.70	[0.56 ; 0.87]
High-risk cytogenetics	37.3	20.3	0.63	[0.46 ; 0.88]
R-ISS I	NR	59.2	0.69	[0.47 ; 1.02]
R-ISS II	51.7	37.0	0.72	[0.58 ; 0.88]
R-ISS III	30.0	13.1	0.48	[0.30 ; 0.78]
Hemoglobin ≥ 10.5 g/dL	NR	47.2	0.74	[0.60 ; 0.91]
Hemoglobin < 10.5 g/dL	43.6	33.5	0.72	[0.57 ; 0.91]
Platelet count ≥ 150 x 10^3/mL	61.7	44.0	0.72	[0.61 ; 0.85]
Platelet count < 150 x 10^3/mL	31.3	22.2	0.71	[0.48 ; 1.04]
Plasma cells < 60%	NR	45.9	0.71	[0.57 ; 0.88]
Plasma cells ≥ 60%	45.3	36.2	0.72	[0.57 ; 0.91]
LDH < Upper limit	58.6	42.6	0.72	[0.61 ; 0.86]
LDH > Upper limit	43.4	26.7	0.61	[0.41 ; 0.91]

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

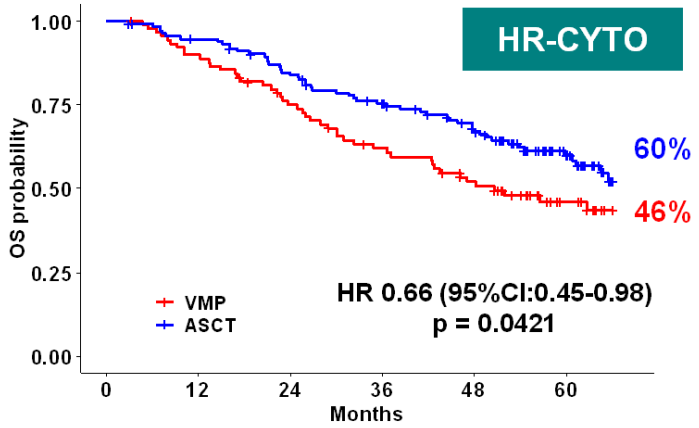
ASCT vs novel agent-based therapy: EMN02/HO95 phase 3 study

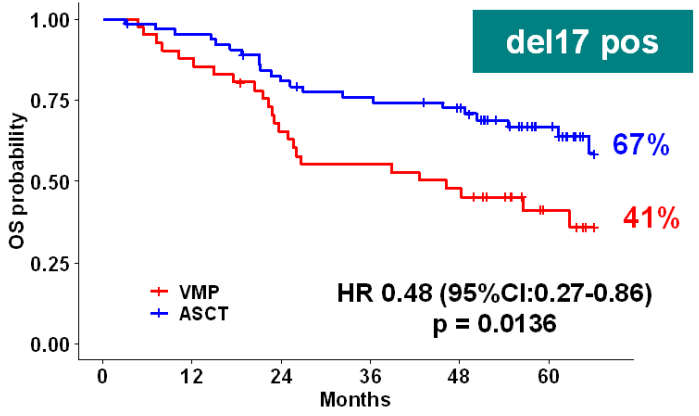
OS



Number at risk (number censored)							
Autologous HSCT	702 (0)	658 (16)	614 (24)	569 (36)	487 (78)	276 (268)	..
VMP	495 (0)	463 (12)	430 (20)	391 (31)	331 (62)	174 (198)	..

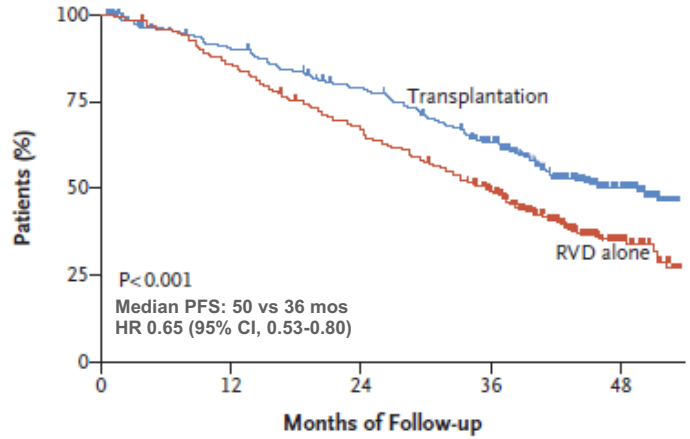
No OS benefit with ASCT,
but the follow-up is still too short





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

ASCT vs novel agent-based therapy: IFM 2009 phase 3 study



No. at Risk

RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

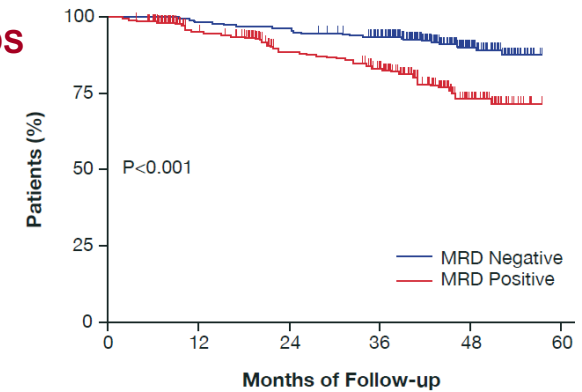
No significant difference in OS

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

MRD (7-colorflow)

OS

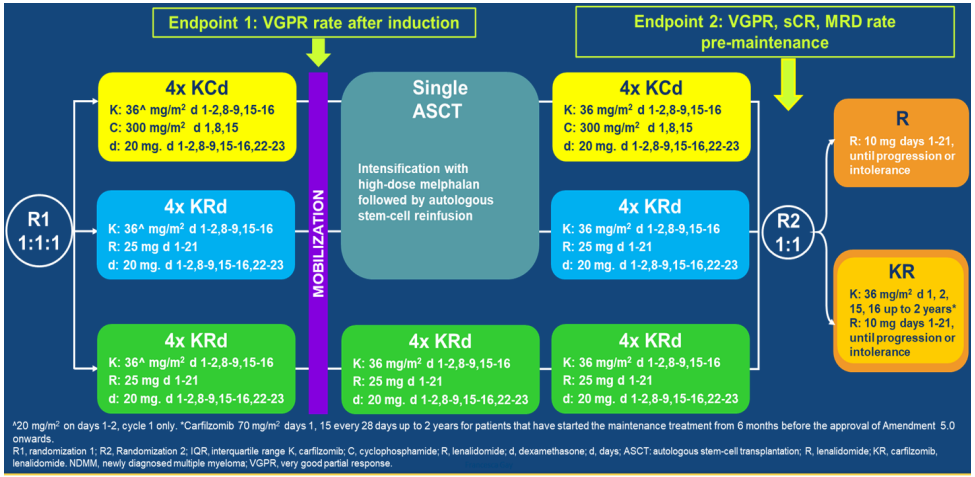


No. at Risk

MRD Negative	0	311	379	347	119	0
MRD Positive	700	358	259	227	65	0

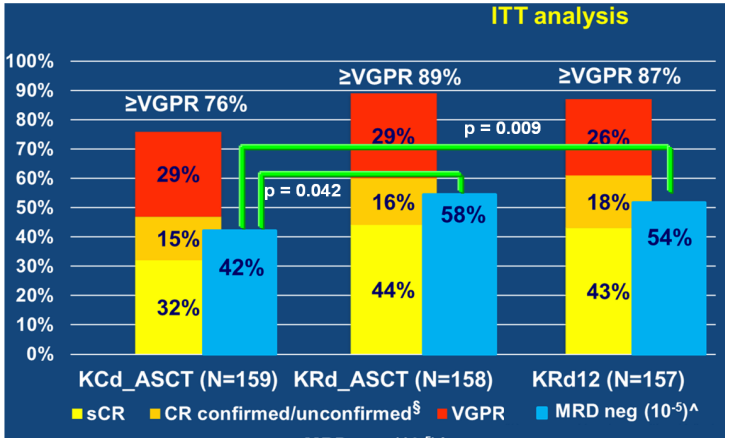
Attal M, et al. NEJM 2017; 376: 1311-1320

ASCT vs novel agent-based therapy: FORTE phase 2 trial



	KRd_ASCT	KRd_12	p
Pre-maintenance MRD negativity			
Overall	158 (58%)	157 (54%)	-
RISS II/III	92 (51%)	94 (49%)	-
Persistent 1-year MRD negativity			
Overall*	72 (90%)	64 (78%)	na
RISS II/III	41 (90%)	33 (72%)	na
Early relapse (≤18 mos from random1)			
Overall	12 (7.6%)	26 (16.6%)	0.015
RISS II/III	11 (12%)	22 (23.4%)	0.05

*available pts: 77% and 75%,respectively



Multivariate Logistic Regression Model

	OR	95% CI	P-value
R-ISS II/III vs R-ISS I	3.78	1.71-8.35	0.001
KRd-ASCT vs KRd12	0.41	0.19-0.88	0.022
MRD negative (10^{-5})	0.21	0.12-0.40	<0.001

Increased risk of early relapse

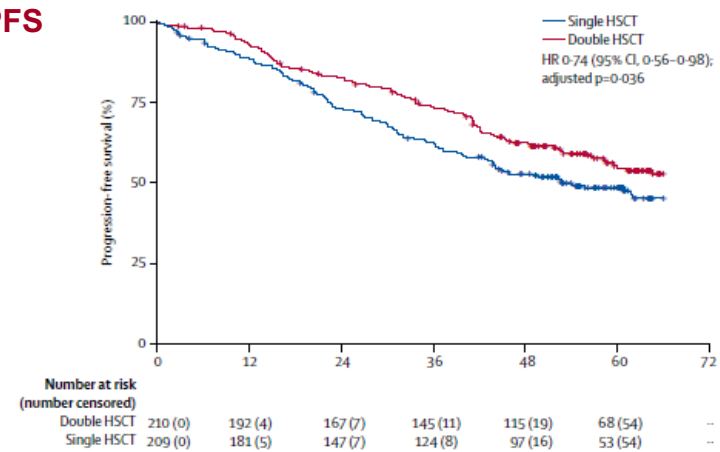
Reduced risk of early relapse

Gay F, et al. J Clin Oncol. 2019;37 Suppl:8002. Presented at ASCO 2019.

Single vs double ASCT

EMN02/HO95 phase 3 study

PFS



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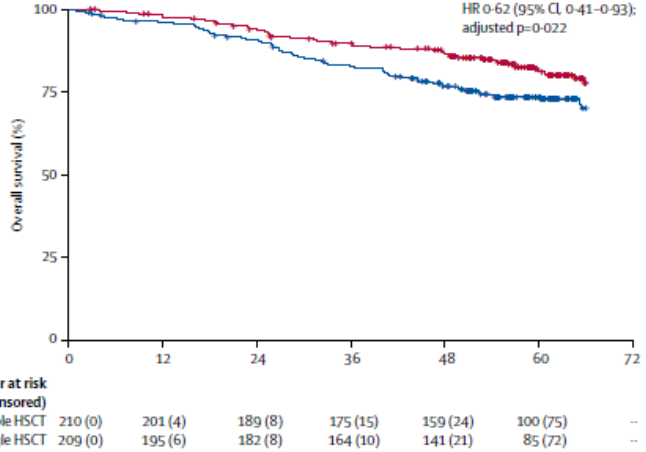
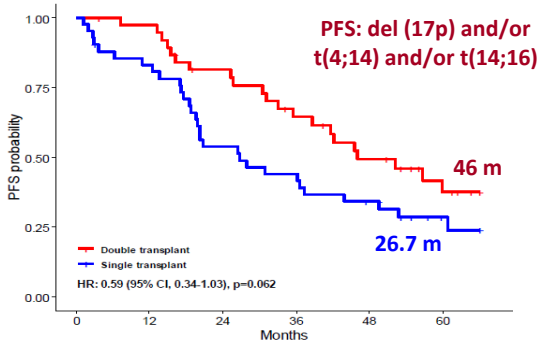
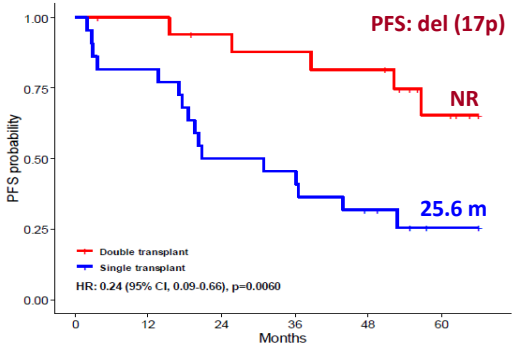
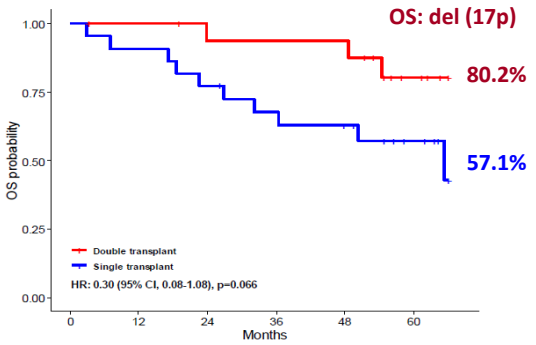




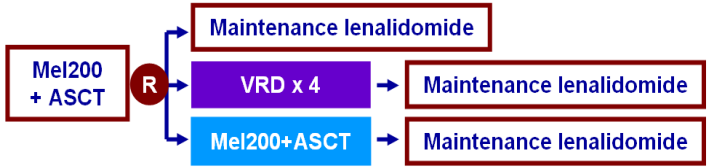




Cavo et al. Lancet Haematol 2020;7:e456–68

Single vs double ASCT

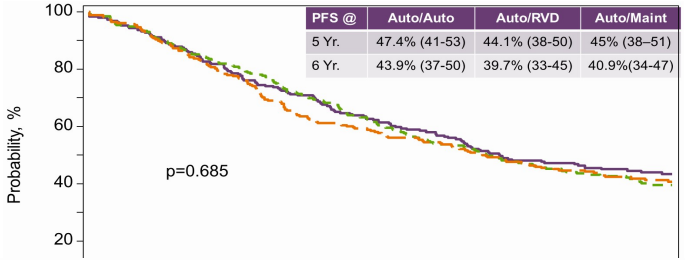
BMT CTN 0702 ph.2 trial (STaMINA)



	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

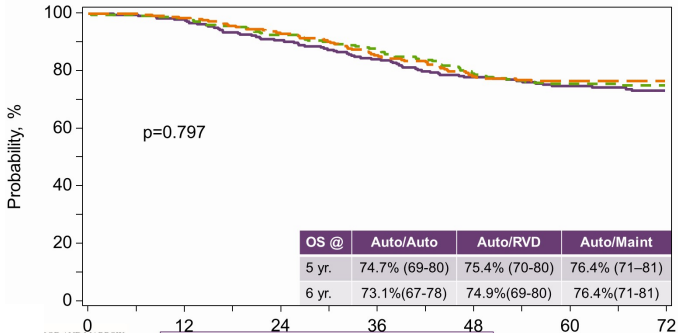
Cavo M, IMWG 2019

PFS

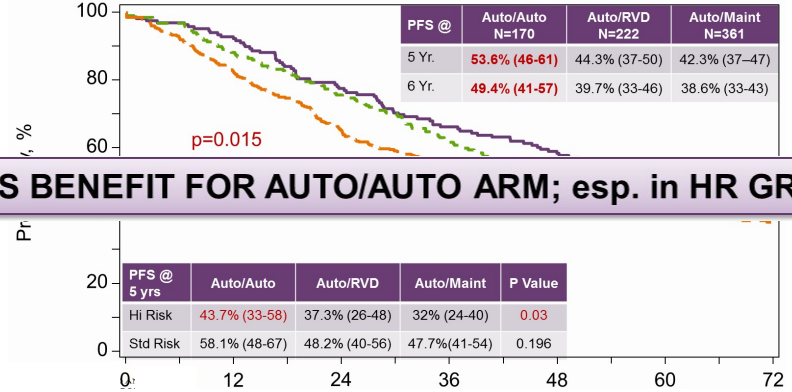


NO DIFFERENCE BETWEEN STUDY ARMS

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

Single vs double ASCT

Pooled analysis of 3 ph.3 EU studies

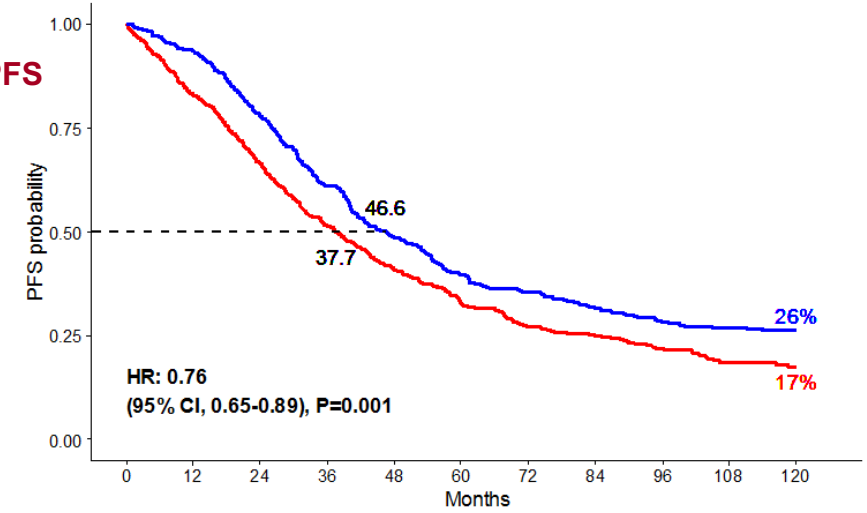
- **GIMEMA MMY-3006** Cavo, Lancet 2010
- **PETHEMA/GEM** Rosinol, Blood 2012
- **HOVON65MM/GMMG-HD41** Sonneveld, JCO 2012

- 909 pts (501 ASCT-1 vs 408 ASCT-2)
- median age 58 years
- high risk cytogenetics*: 18% vs 23%
- ISS II/III stage: 64% vs 56%
- bortezomib-based induction
- median follow up of **117** months

* del(17p) ≥ 20% and/or t(4;14) ≥ 10% of PCs

Survival by single vs double ASCT

PFS



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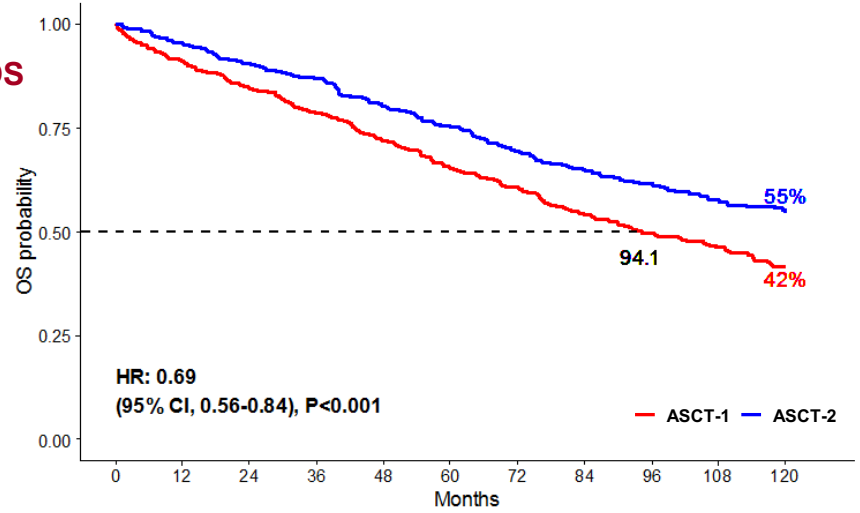


Cavo M, ASH 2018 (Abstract 124), Oral presentation

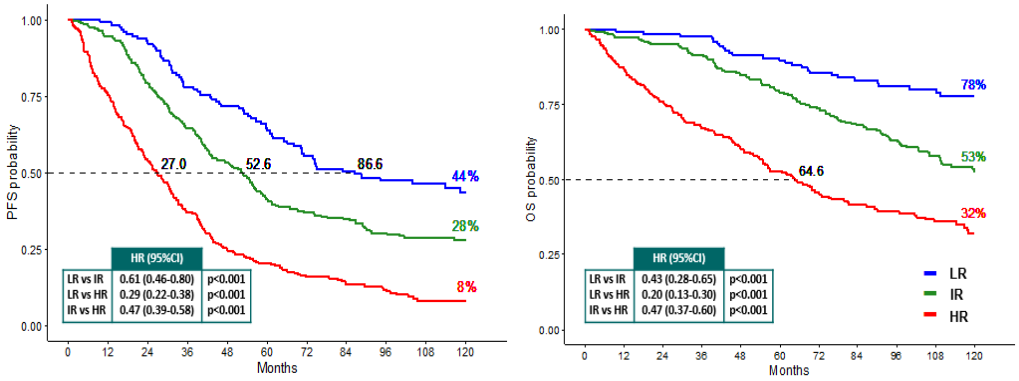
Single vs double ASCT

Pooled analysis of 3 ph.3 EU studies

MULTIVARIATE COX REGRESSION ANALYSIS (not including therapy)			
Variables affecting PFS	**HR**	**95% CI**	**P value**
High-Risk cytogenetic	1.565	1.235-1.985	<0.001
ISS II-III	1.427	1.159-1.758	0.001
Best response <CR	1.831	1.497-2.241	<0.001

			RISK SCORE LEVELS		
HR-cyto	Best <CR	ISS II-III	LOW (0/3)	INTERMEDIATE (1/3)	HIGH (≥2/3)
Total pts, nr (%)			132 (20,1%)	277 (42,2%)	248 (37,7%)

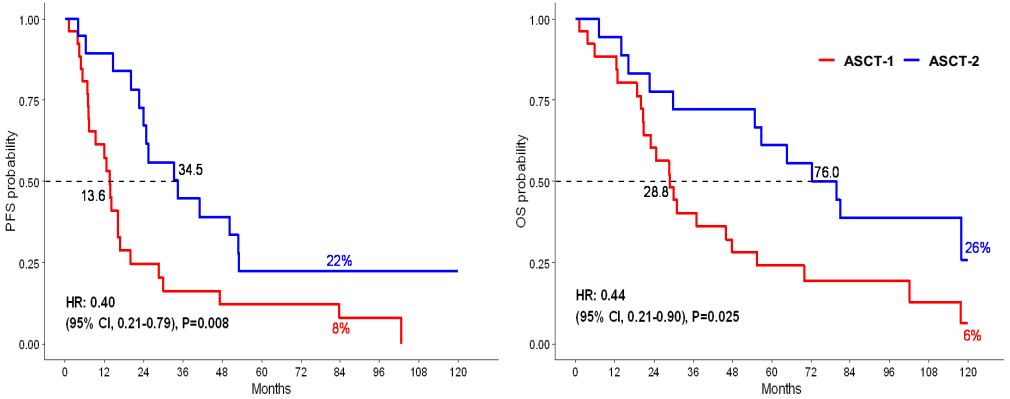
Survival according to risk



	ASCT-1		ASCT-2				
	N pts	Median PFS	N pts	Median PFS	HR	95% CI	P-value
Low-Risk	55	74	77	NR	0.66	0.41-1.07	0.093
Intermediate-Risk	133	49.8	144	53.9	0.87	0.65-1.17	0.357
High-Risk	112	20.2	136	31.7	0.71	0.54-0.93	0.008

	N pts	Median OS	N pts	Median OS	HR	HR	P-value
Low-Risk	55	NR	77	NR	0.91	0.42-1.98	0.810
Intermediate-Risk	133	110.2	144	NR	0.79	0.54-1.14	0.210
High-Risk	112	47.8	136	79.8	0.58	0.42-0.80	0.001

PFS and OS by ISS II-III + HR-Cyto + best < CR



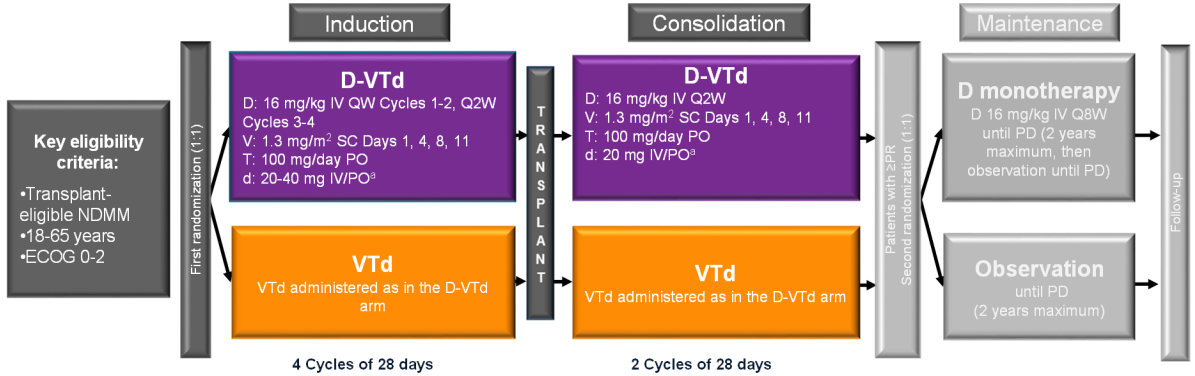
Cavo M, ASH 2018 (Abstract 124), Oral presentation

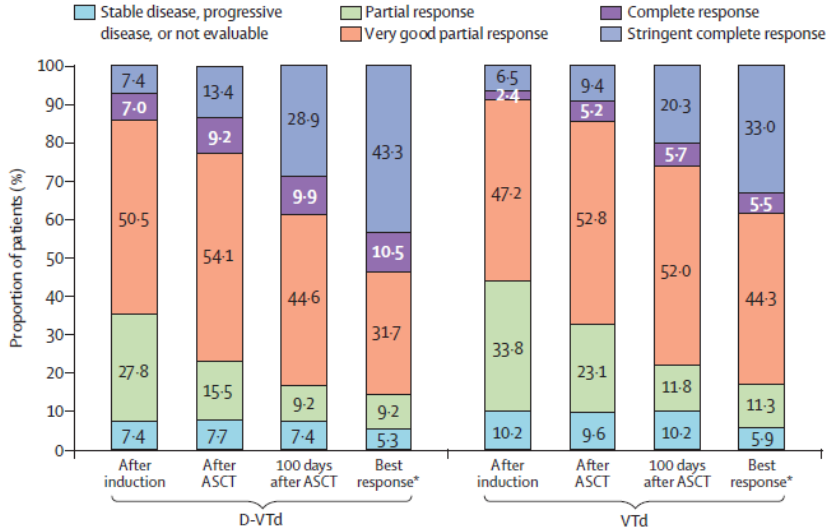
ASCT in the context of new novel combinations

CASSIOPEIA phase 3 trial

Primary endpoint:
- sCR rate (post consolidation)

Secondary endpoints:
- MRD-negative rate
- PFS and OS from 1st randomization





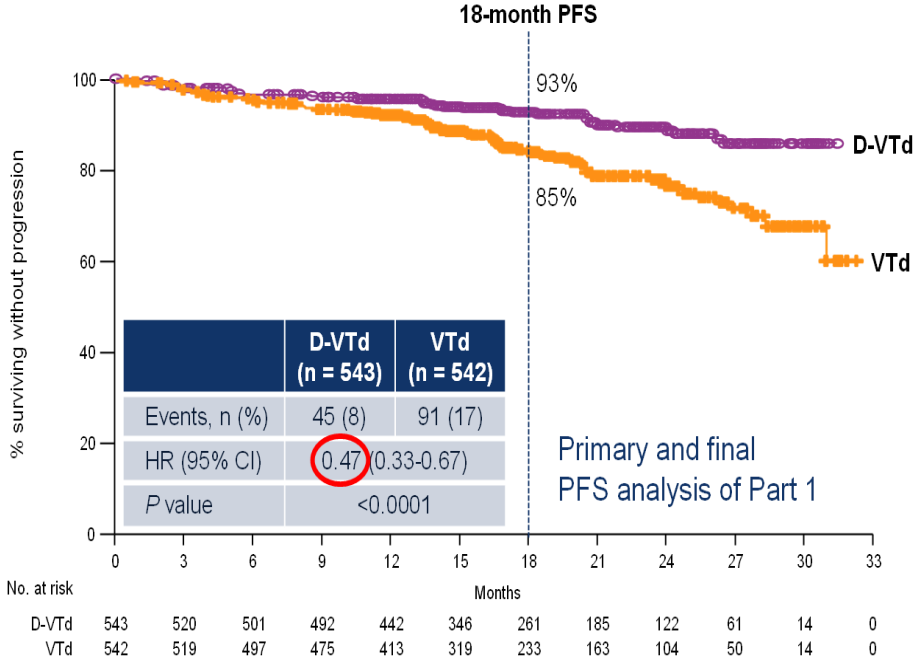
Responses and MRD status 100 days after ASCT

	D-VTd (n=543)	VTd (n=542)	p value*
Overall response			
Stringent complete response	157 (29%)	110 (20%)	0·0010
Complete response or better	211 (39%)	141 (26%)	<0·0001
Very good partial response or better	453 (83%)	423 (78%)	0·024
MRD-negative status (10^{-5})†			
MRD negative regardless of response	346 (64%)	236 (44%)	<0·0001
MRD negative and complete response or better‡	183 (34%)	108 (20%)	<0·0001
MRD negative and very good partial response or better‡	338 (62%)	231 (43%)	<0·0001

Moreau P, Lancet 2019; 394: 29-38

ASCT & novel combinations: CASSIOPEIA phase 3 study

PFS from 1st randomization

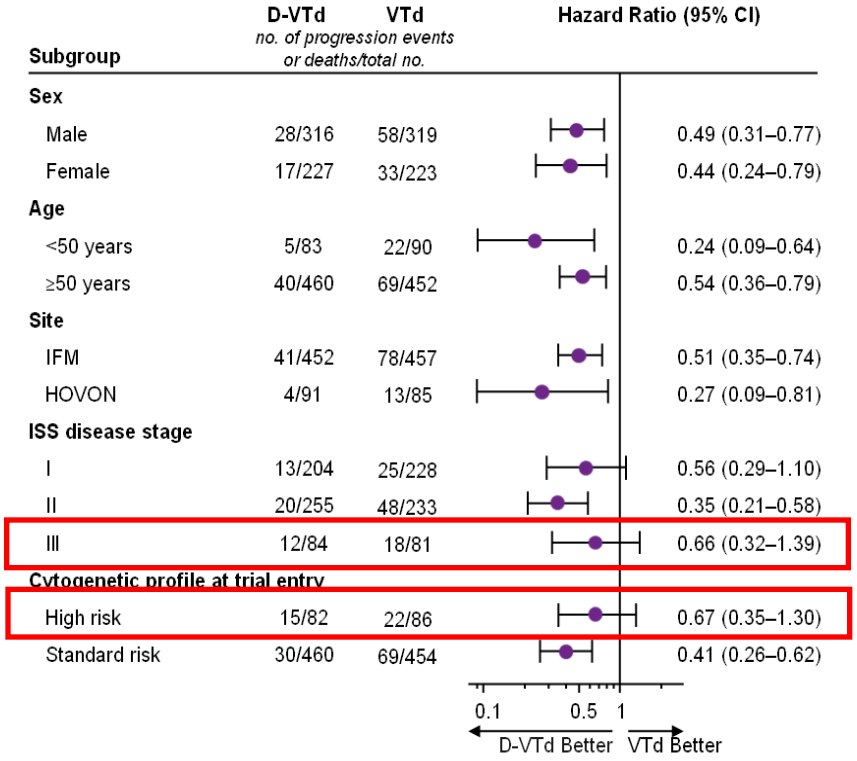


	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	<0.0001	

Primary and final PFS analysis of Part 1

53% reduction in the risk of progression or death in the D-VTd arm

PFS in prespecified subgroups



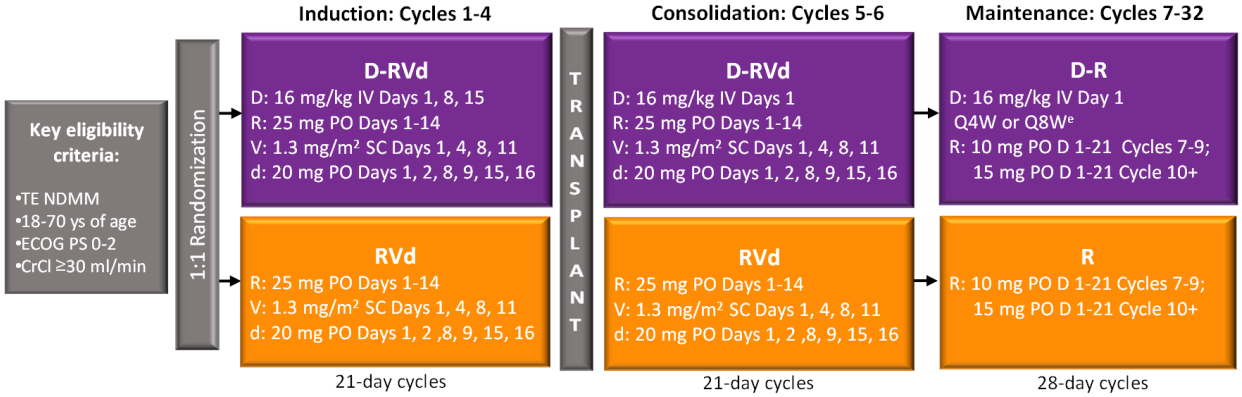
Moreau P, Lancet 2019; 394: 29-38

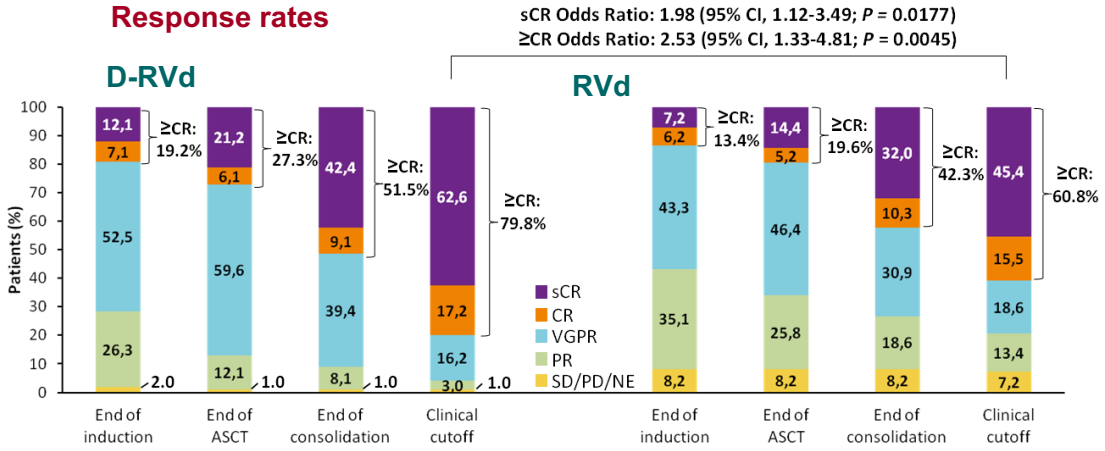
ASCT & novel combinations: GRIFFIN phase 2 study

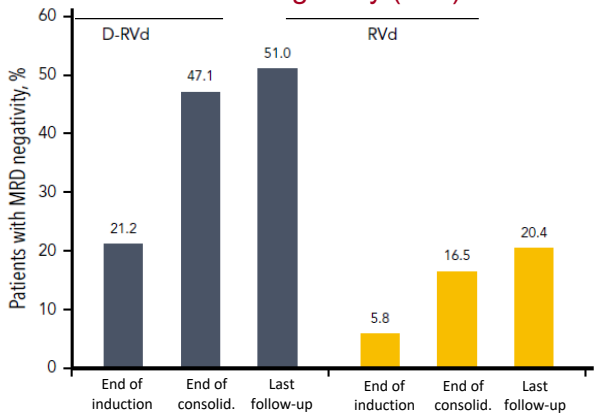
GRIFFIN phase 2 trial

Primary endpoint:
- sCR rate (post consolidation)

Secondary endpoints:
- MRD-negative rate (NGS)
- ORR, DoR
- PFS and OS





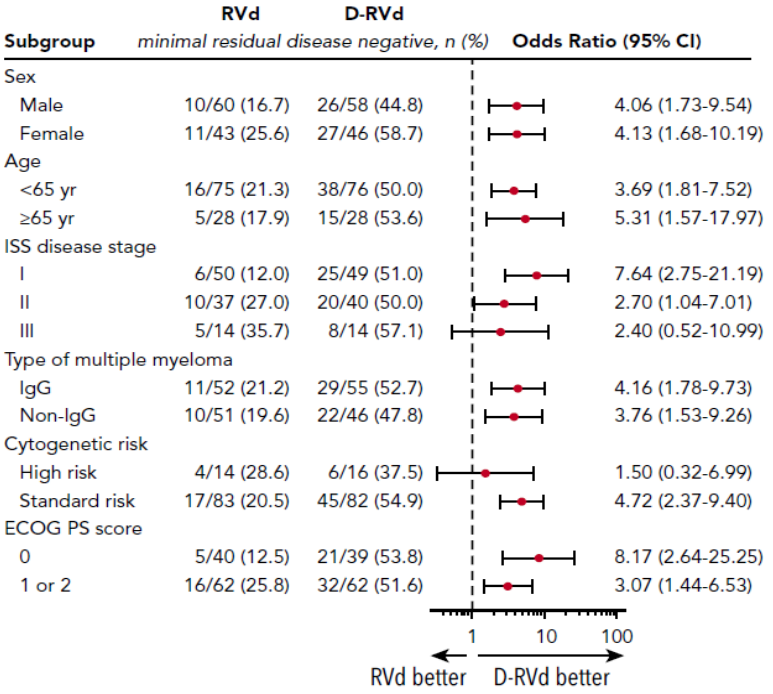


Voorhees PM, Blood. 2020;136(8):936-945

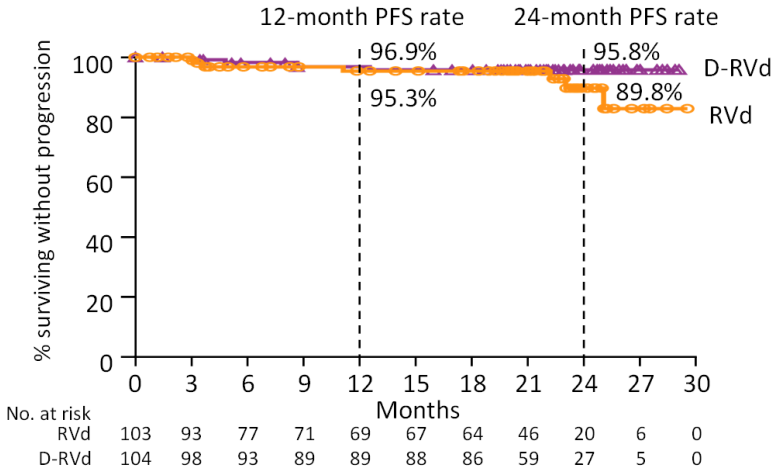
ASCT & novel combinations: GRIFFIN phase 2 study

MRD-negative (10^{-5}) status*	D-RVd, n (%)	RVd, n (%)	Odds ratio (95% CI)†	P‡
Intent-to-treat population				
MRD-negative	53/104 (51.0)	21/103 (20.4)	4.07 (2.18-7.59)	<.0001
MRD-negative with ≥CR	49/104 (47.1)	19/103 (18.4)	3.89 (2.07-7.33)	<.0001
In patients achieving ≥CR	49/79 (62.0)	19/59 (32.2)	3.57 (1.72-7.44)	.0006
MRD-evaluable population	53/77 (68.8)	21/65 (32.3)	4.47 (2.19-9.11)	<.0001

MRD status at last follow-up (median 22 mos) and subgroup analysis of MRD negativity (10^{-5})



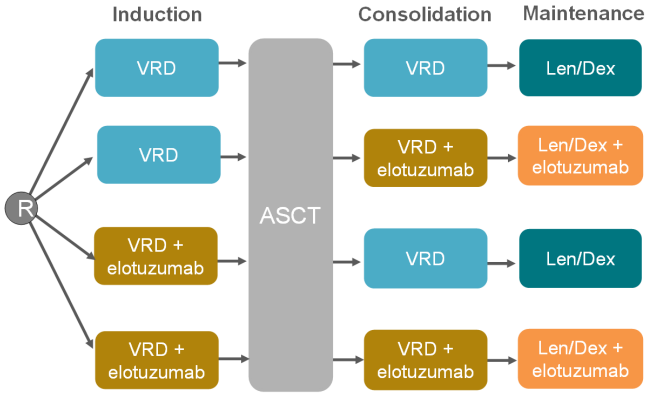
Progression Free Survival



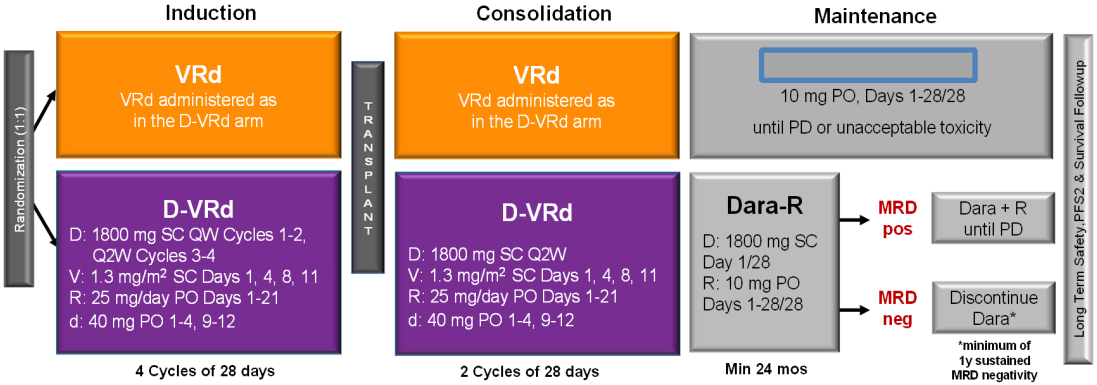
Voorhees PM, Blood. 2020;136(8):936-945

Ongoing trials

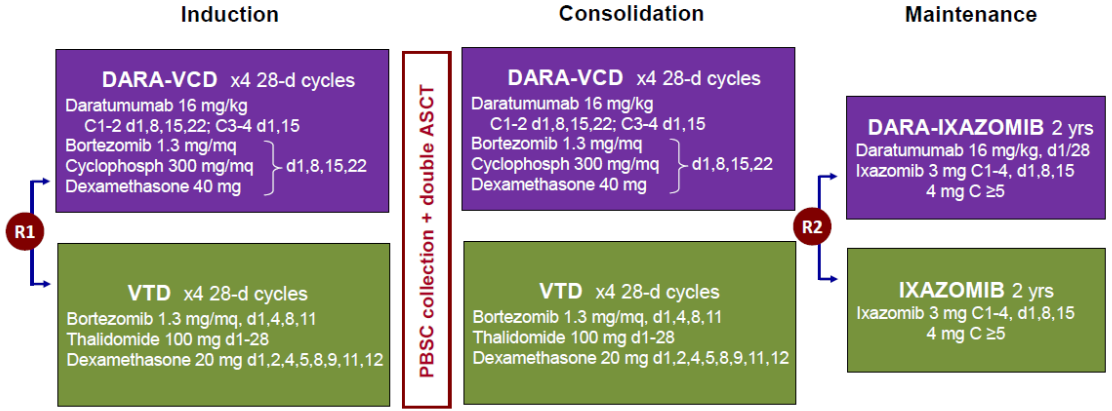
GMMG-HD6 phase 3 trial (NCT02495922)



PERSEUS phase 3 trial (NCT03710603)



EMN18 phase 3 trial (NCT03896737)



Main inclusion criteria

- NDMM ≤ 65 years
- LVEF ≥ 40%, creatinine cl. ≥ 30 mL/minute
- measurable disease

Primary end-points:

- PFS of Dara-VCD vs VTD and dara-ixa vs ixa
- MRD negativity rate pre and during maintenance by NGS

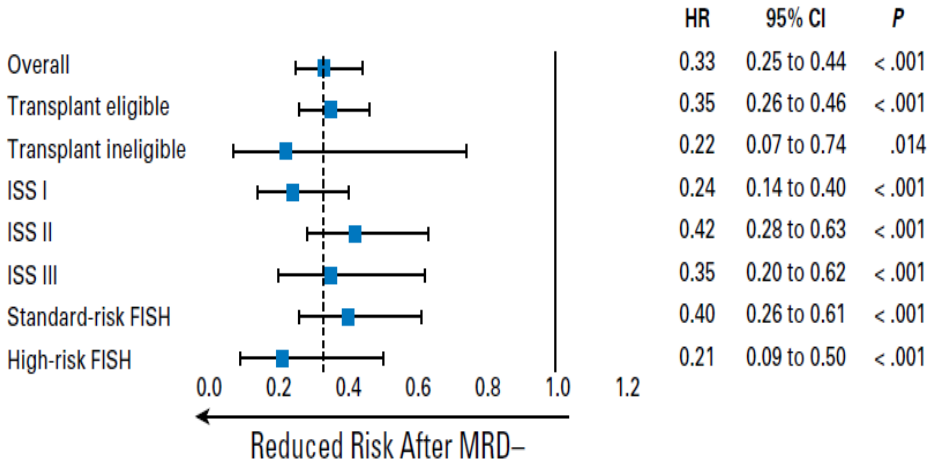
Risk- and MRD status- adapted therapies

Correlation between quality of response and better survival

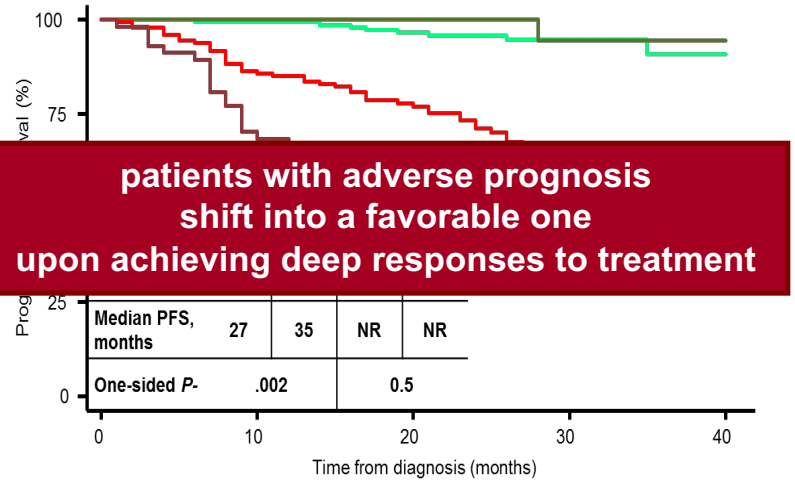
→ MRD negativity as a surrogate marker for PFS and OS

Can MRD-response modulate patients' risk at diagnosis?

OS according to achievement of MRD negativity among patient subgroups



Progression-free survival according to FISH and NGF



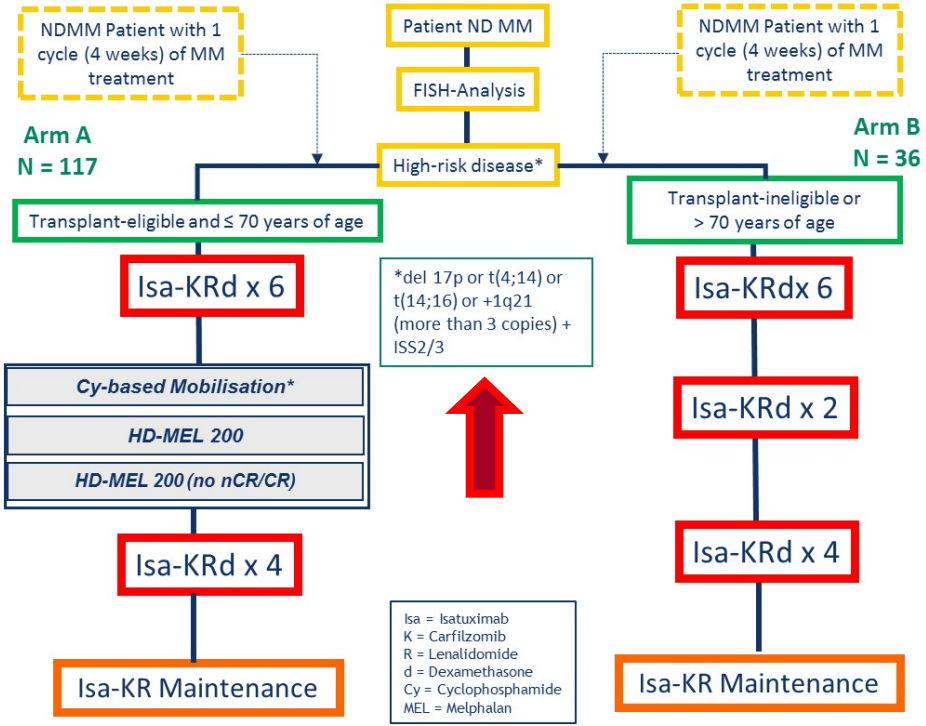
patients with adverse prognosis shift into a favorable one upon achieving deep responses to treatment

Lahuerta JJ, et al. JCO 2017;35(25):2900-2910

Paiva B et al. ASH 2017

Risk- and MRD status- adapted therapies: GMMG-CONCEPT trial

Isa-KRd in front-line treatment of high-risk MM



Primary endpoint: MRD-negativity /flow, 10-5, after consolidation
Secondary endpoint: Progression Free Survival

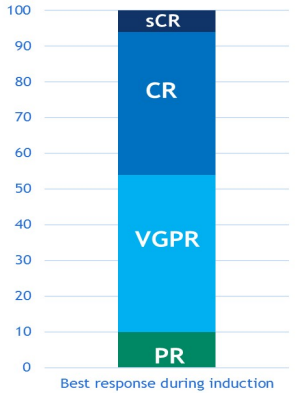
Interim analysis: 50 pts

Characteristic	N=50
Median age (range), years	58 (42-82)
Arm A	58 (42-69)
Arm B	77 (72-82)
male/female	21/29
ECOG performance status	
0	21 (42%)
1	23 (46%)
2	6 (12%)

Characteristic	N=50
ISS	
Stage II	28 (56%)
Stage III	22 (44%)
High-risk cytogenetics**	
Del 17p*	26 (52%)
t(4;14)	19 (38%)
t(14;16)	5 (12%)
> 3 copies +1q21	21 (42%)

Best response to therapy, 6 induction cycles

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Weisel KC et al., ASCO. 2020; oral presentation

Risk- and MRD status- adapted therapies: MASTER phase 2 trial

MRD response-adapted Dara-KRd sequential therapy in transplant-eligible NDMM patients

Key inclusion criteria
- NDMM*
- ECOG PS 0-2
- CrCl ≥ 40 mL/min

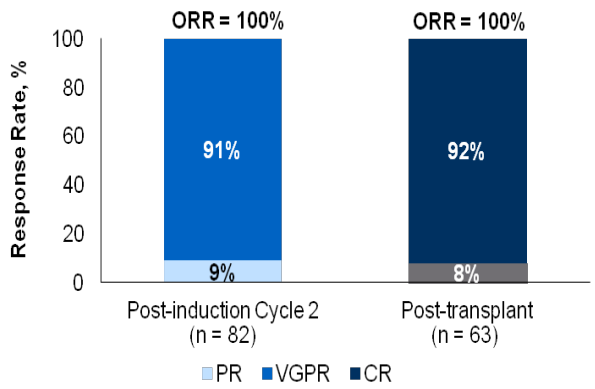
→ **Induction** Dara-KRd x 4 cycles → **AHCT** → **Consolidation** Dara-KRd x 4 cycles → **Consolidation** Dara-KRd x 4 cycles → ***Lenalidomide maintenance***

Dara-KRd dosing: D 16 mg/m^2 on days 1,8,15,22 (days 1,15 of Cycles 3-6; Day 1 Cycle > 6); K 56 mg/m^2 days 1,8,15; R 25 mg days 1-21; d 40 mg PO Days 1,8,15,22. *1 VCD cycle permitted.

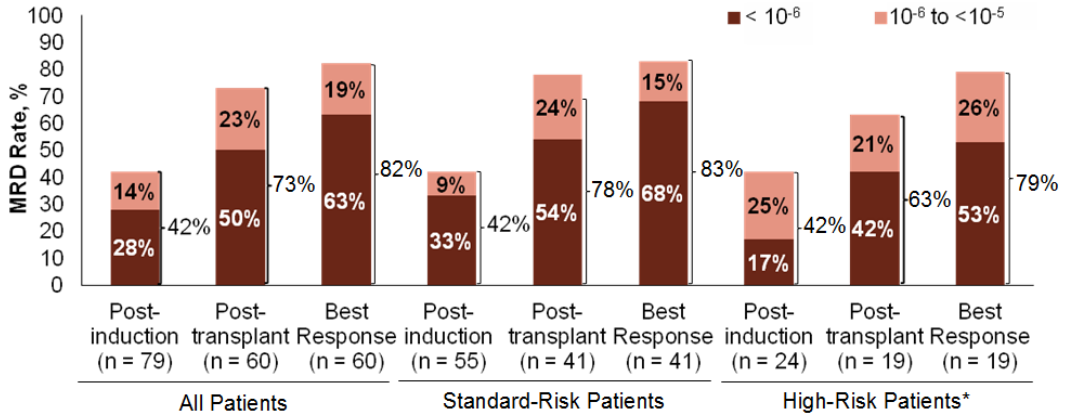
MRD assessment after each treatment phase; pts with confirmed (2nd) MRD-negative status (< 10^{-5}) entered treatment-free observation phase with MRD assessment at 24 and 72 wks after EOT

Primary Endpoint: MRD-negative remission

Response rates



MRD rates



*del17p, t(4;14) or t(14;16)

Costa LJ et al, EHA 2020

Conclusions

- Upfront ASCT is currently the gold standard intensification therapy for fit NDMM patients
- Double ASCT following short-term induction improves outcomes, especially in patients with high-risk cytogenetic abnormalities
- Modern induction and post-ASCT consolidation therapies (PI+IMiDs, with or without an added mAb) ultimately result in high rates of MRD negativity
- New highly-effective novel 4-drug combinations could further question the role of upfront ASCT, especially in low risk patients
- Treatment based on risk profile and MRD status as the first step towards individualized therapy