Highlights from IMW 2019

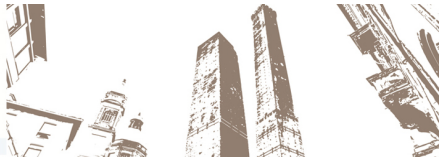
19-20 novembre 2019
Bologna
Royal Hotel Carlton

Paola Tacchetti

Azienda Ospedaliero-Universitaria S.Orsola-Malpighi
Ematologia "Seràgnoli", Bologna

Il ruolo del trapianto autologo nell'era dei nuovi farmaci

DISCLOSURE



Paola Tacchetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
Janssen							x
Celgene						x	x
Amgen						x	x
Takeda						x	x
BMS							x
Oncopeptides							x
AbbVie							x

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.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Multiple Myeloma

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.

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

J Clin Oncol 37:1228-1263

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

Delayed initial SCT may be considered in select patients

Moreau P, Ann Oncol, 2017;28(suppl_4):iv52-iv61 - NCCN Guidelines Version 1,2019 Multiple Myeloma - Mikhael J, J Oncol Pract. 2019;15(5):279-286.

Treatment paradigm for ASCT-eligible patients with MM

Treatment phases

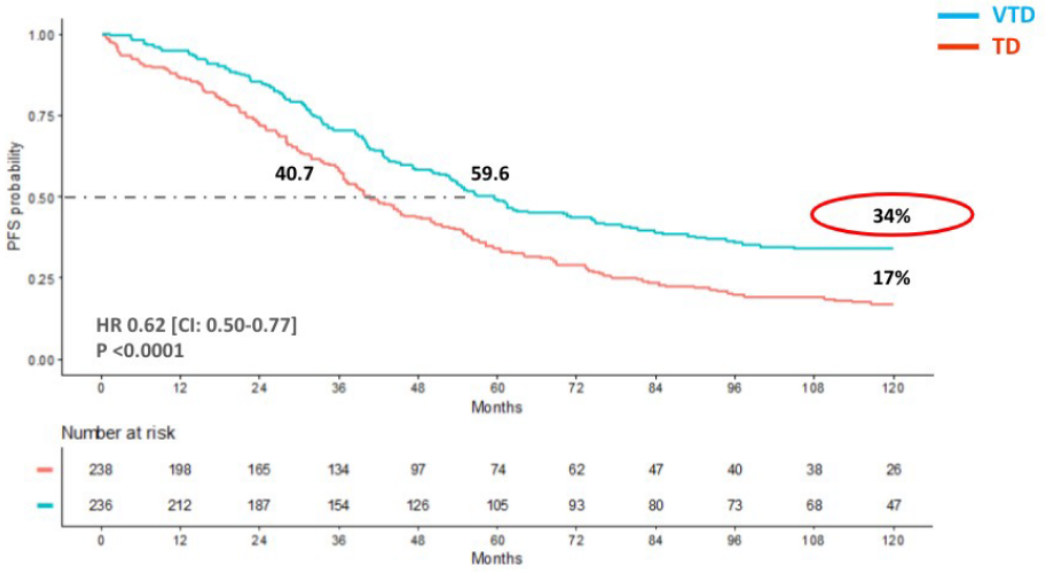
Key endpoints

- 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

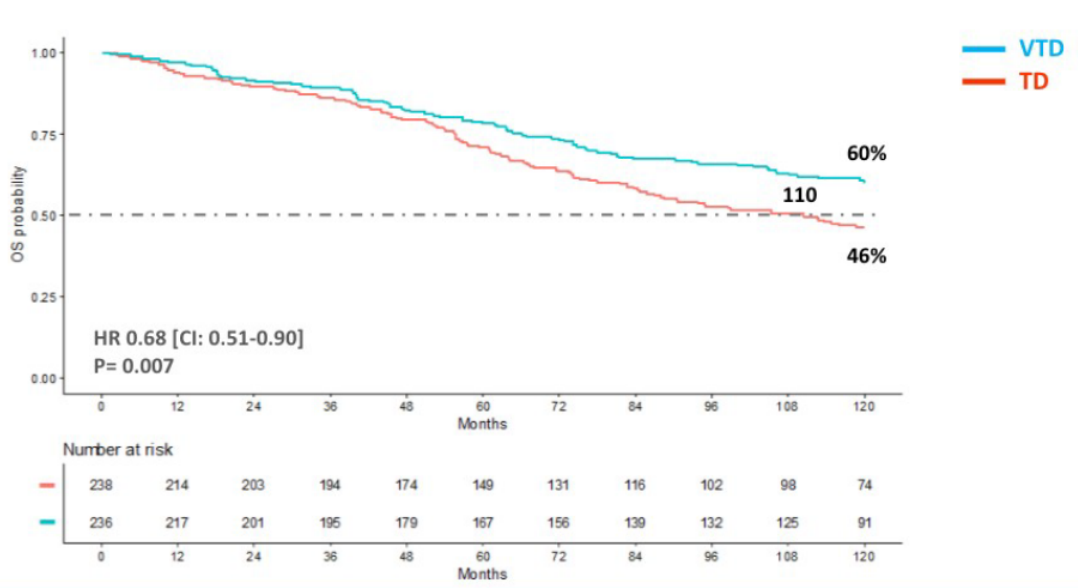
Cavo M et al. Blood 2011;117(23):6063-73
Cavo M et al. Blood 2012;120(1):9-19
Kumar S, et al. Lancet Oncology 2016;17:e328-46
Cavo M. IMW 2019

GIMEMA-MMY-3006 study: long-term analysis (10-year follow-up)

PFS



OS



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

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TD, thalidomide + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone..

Tacchetti P, et al., ASH 2018 (Abstract 125), Oral presentation

KEY TOPICS

- **Up-front ASCT vs novel agent-based intensification therapy**
- Single vs Double ASCT
- ASCT in the context of new novel combinations

Up-front ASCT vs novel agent-based intensification therapy

Prospective studies : early vs delayed ASCT

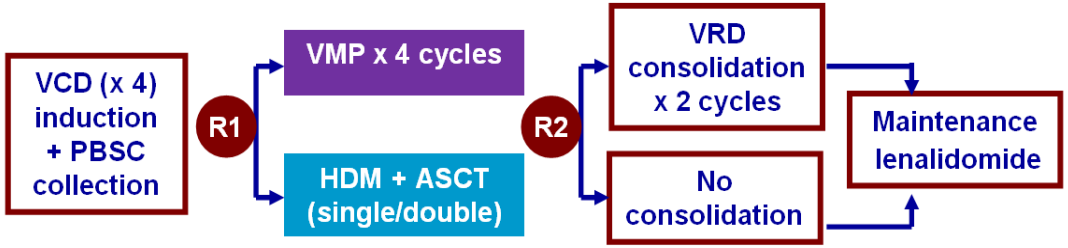
Induction	Intensification phase		Maintenance	PFS (mos) (Control vs ASCT)	OS at 4 years (Control vs ASCT)	N° (%) pts receiving salvage ASCT
	Control Arm (n° pts)	ASCT Arm (n° pts)				
RD x 4 cycles	RCD x 6 cycles (129)	MEL 200 x 1 or 2 (127)	R±P until PD	28.6 vs 43.3 (HR 2.51, p<0.0001)	73% vs 86% (HR 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

ASCT: autologous stem cell transplantation; MEL: melphalan; OS, overall survival; PFS, progression-free survival; PD: progression disease; R: lenalidomide; P: prednisone; VRD: bortezomib, lenalidomide, dexamethasone; RD: lenalidomide, dexamethasone; RCD: lenalidomide, cyclophosphamide, dexamethasone; MPR: melphalan ,lenalidomide, prednisone; HR: hazard ratio.

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, ASH 2017, Oral presentation.

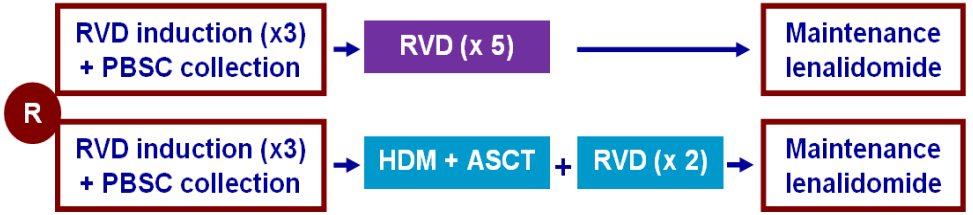
ASCT upfront vs bortezomib-based intensification therapy

EMN02/HO95 phase 3 study: VMP vs ASCT



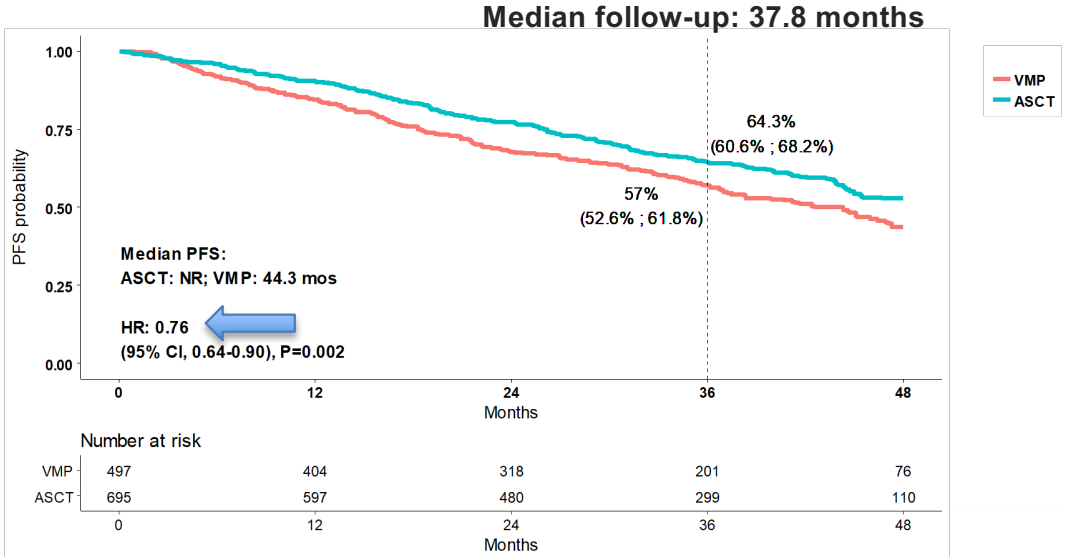
Cavo M, et al. ASH 2017 (Abstract 397), Oral presentation

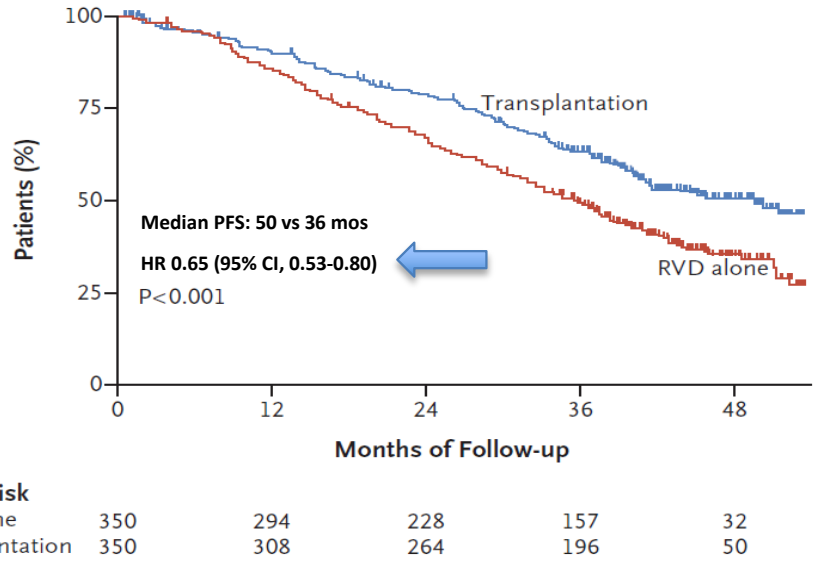
IFM 2009 phase 3 study: RVD vs ASCT



Attal M, et al. N Engl J Med 2017; 376:1311-20

Statistically significant PFS benefit with upfront ASCT





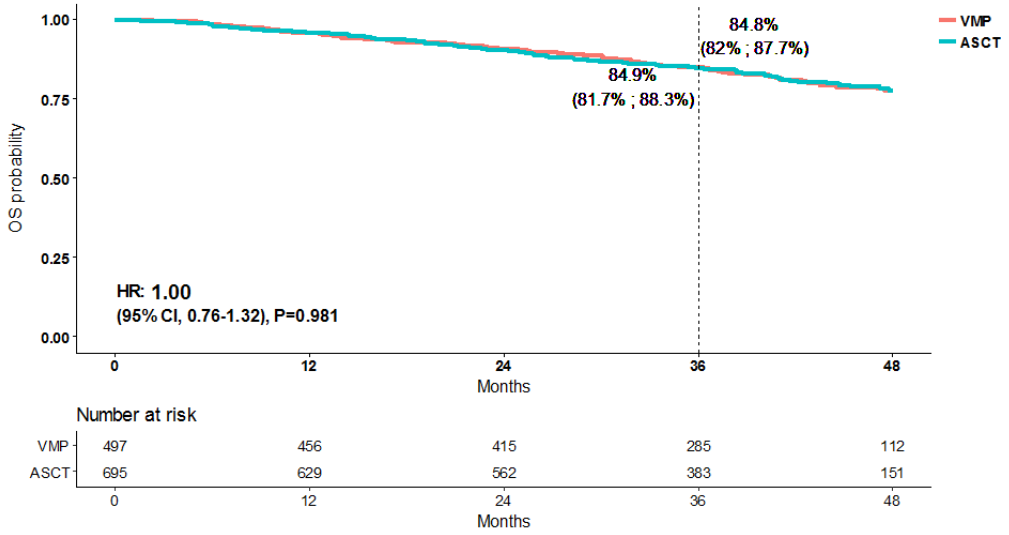
No. at Risk

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

ASCT upfront vs bortezomib-based intensification therapy

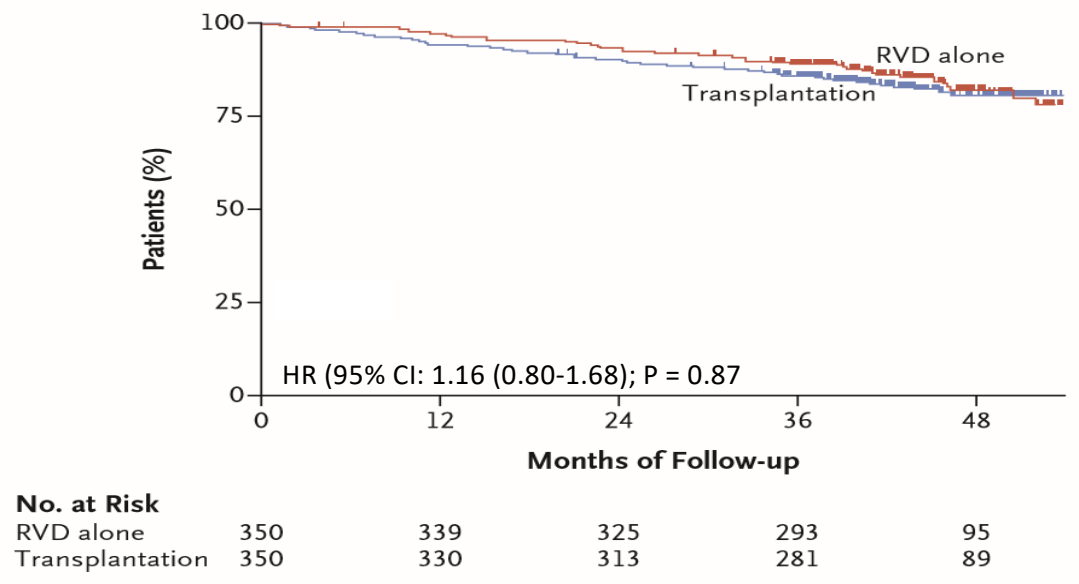
No OS benefit with ASCT, but the follow-up is still too short

EMN02/HO95 phase 3 study: VMP vs ASCT



Cavo M, et al. ASH 2017 (Abstract 397), Oral presentation

IFM 2009 phase 3 study: RVD vs ASCT

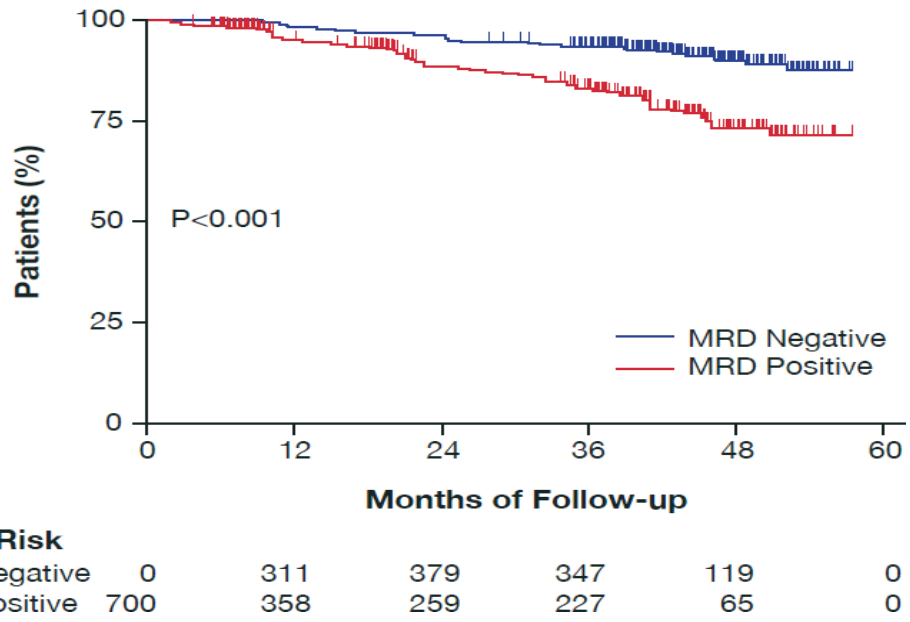


Attal M, et al. N Engl J Med 2017; 376:1311-20

IFM/DFCI 2009: OS according to minimal residual disease

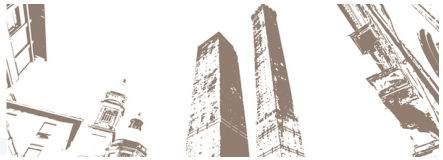
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	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-color flow)



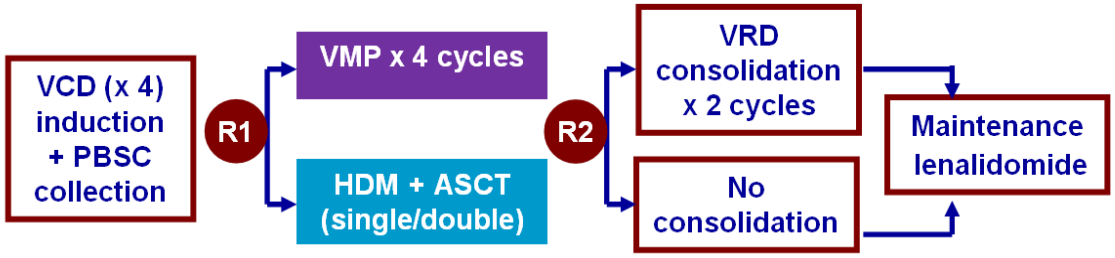
Attal M, et al. N Engl J Med 2017; 376:1311-20

KEY TOPICS

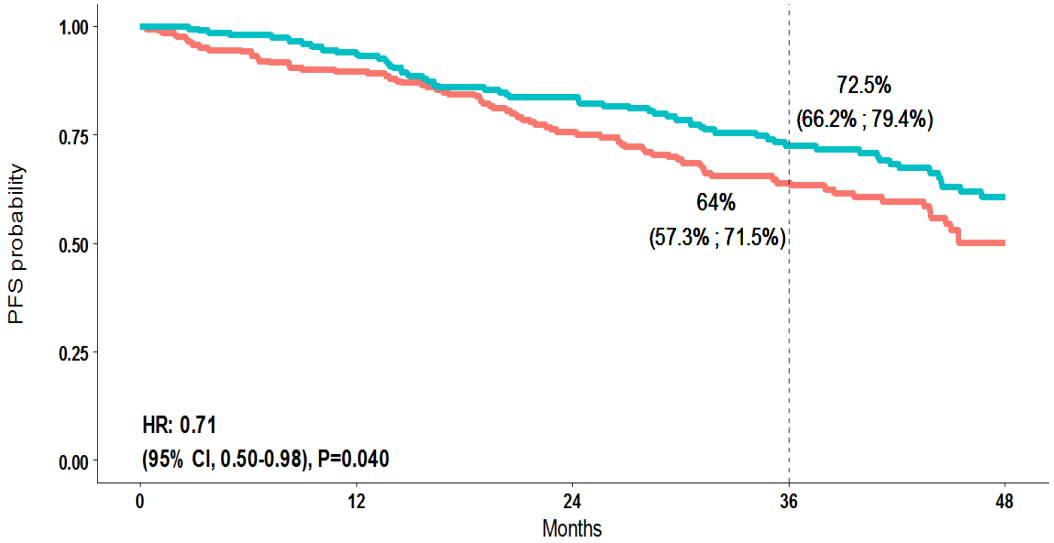


- Up-front ASCT vs novel agent-based intensification therapy
- **Single vs Double ASCT**
- ASCT in the context of new novel combinations

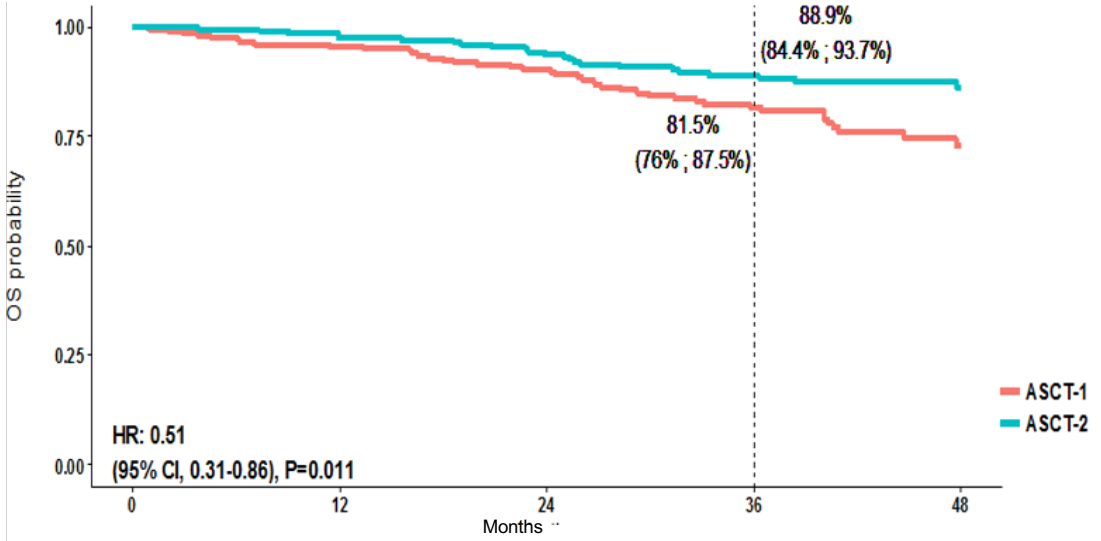
Single vs double ASCT: *EMN02* trial



PFS: ITT

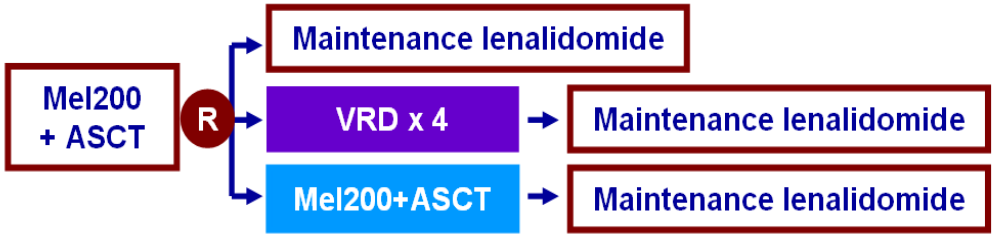


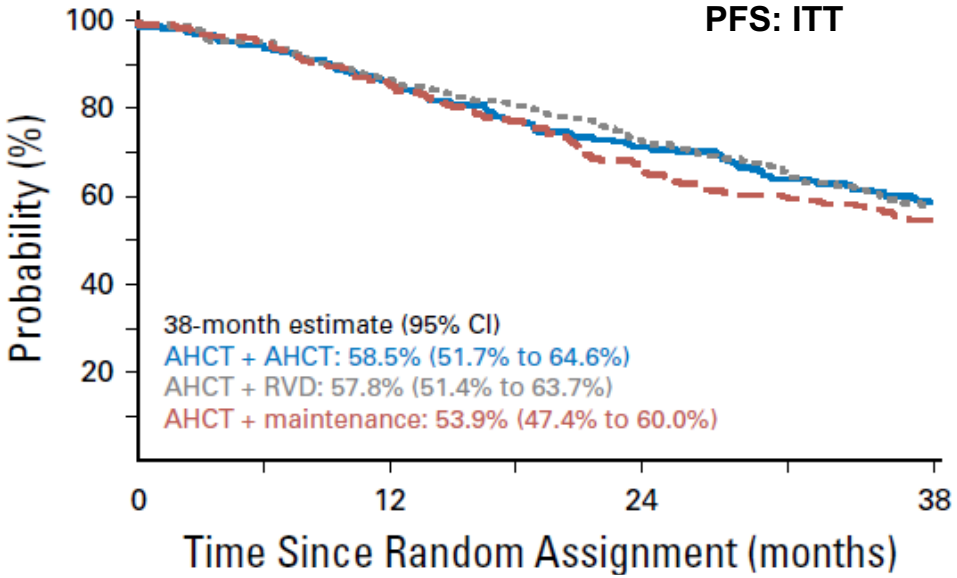
OS: ITT

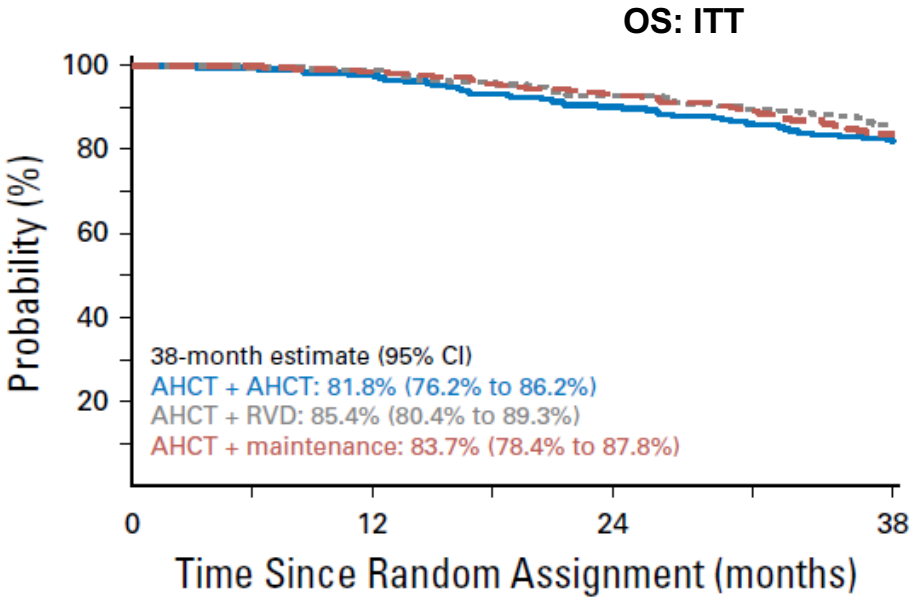


Cavo M, et al. ASH 2017 (Abstract 401), Oral presentation

Single vs double ASCT: *BMT CTN 0702* trial

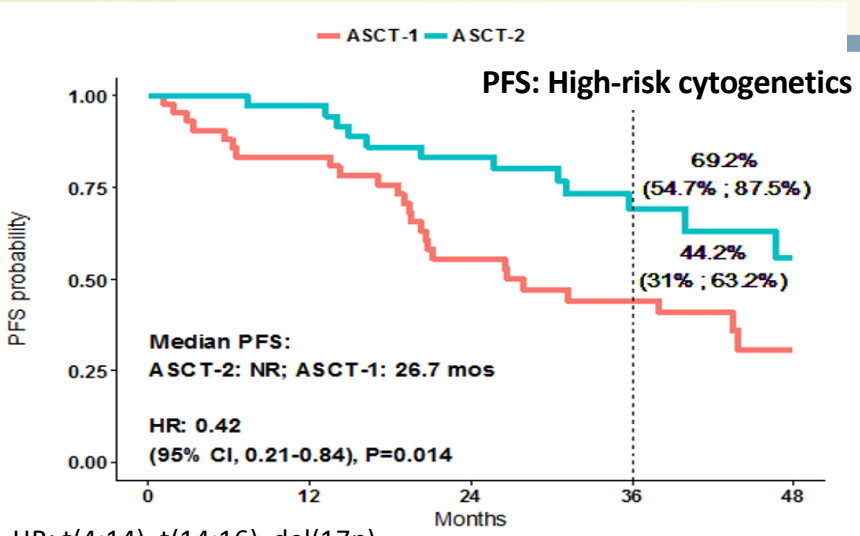




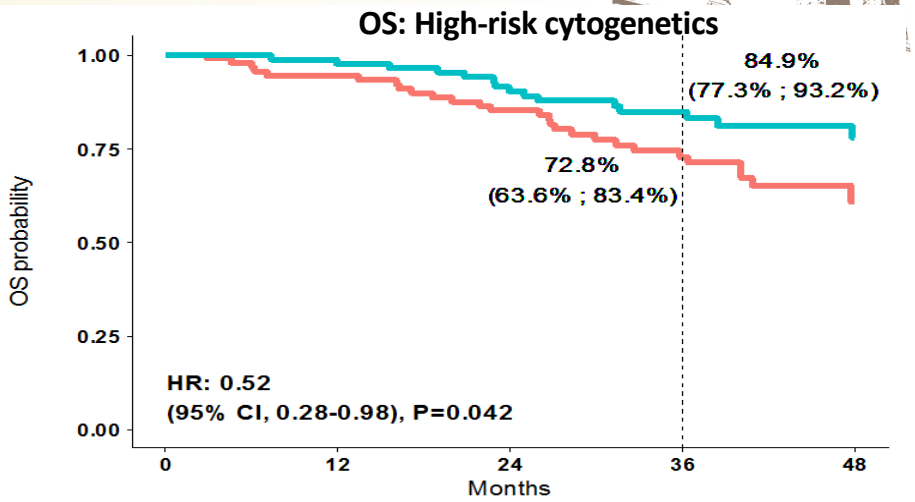


Stadtmauer EA et al, JCO 2019, 37, 589-597

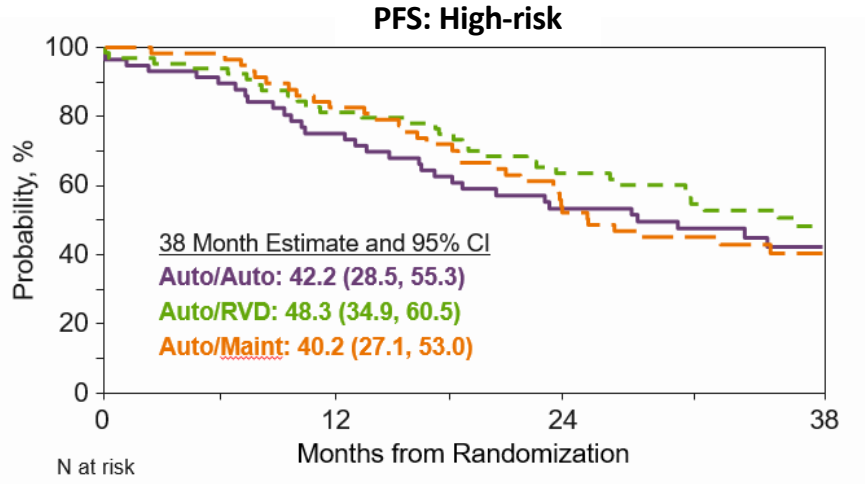
Single vs double ASCT: *EMN02* and *STAMINA* studies

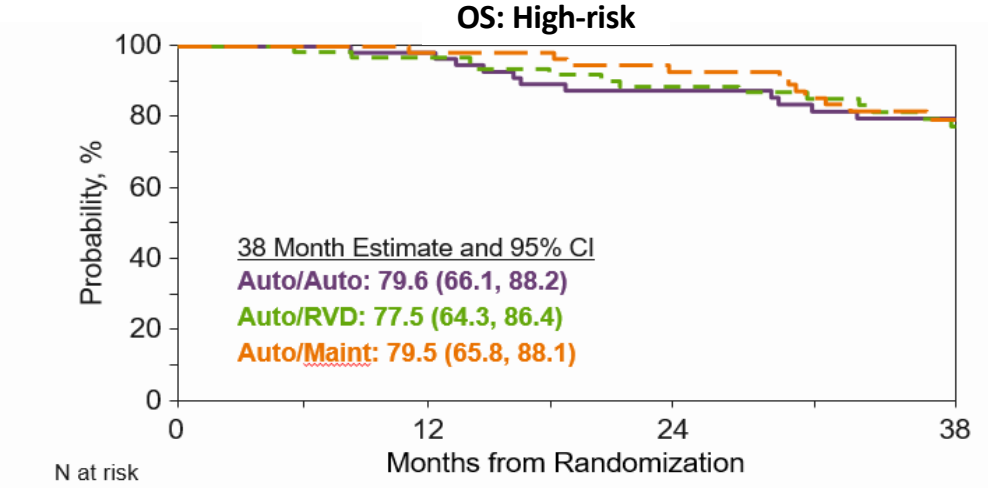


HR: t(4;14), t(14;16), del(17p)



Cavo M, et al. ASH 2017 (Abstract 401), oral presentation

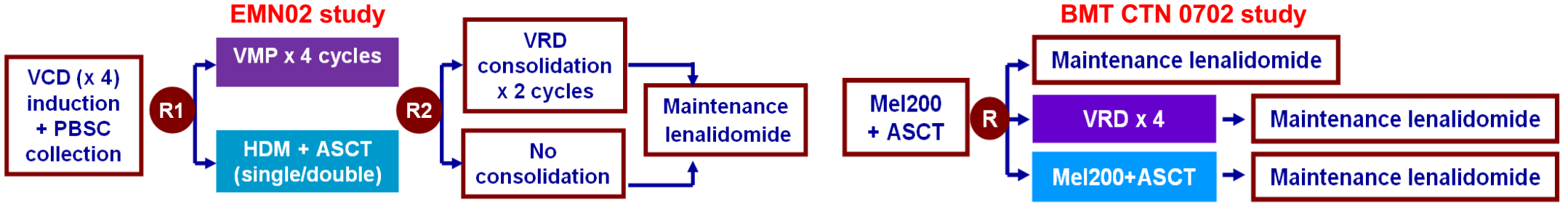




HR: b2M >5.5 mg/L, t(4;14), t(14;20), t(14;16), del(17p) by FISH or standard Cg, del(13) by standard Cg, or aneuploidy

Stadtmauer EA et al, JCO 2019, 37, 589-597

EMN02 and BMT CTN 0702: study inconsistencies



Cavo M, et al. ASH 2017 (Abstract 401), Oral presentation

Stadtmauer EA et al. J Clin Oncol 2019;37(7):589-597

	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

*Different criteria

Cavo M, IMWG 2019

Single vs double ASCT: analysis of 3 phase 3 EU studies

10-year follow-up

GIMEMA MMY-3006

Cavo M et al. Lancet 2010;376:2075-85

RANDOM
n=474

INDUCTION (3x 21-d cycles)

INDUCTION VTD

INDUCTION TD

MOBILIZATION

TRANSPLANTATION
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

CONSOLIDATION VTD
2x 35-d cycles

CONSOLIDATION TD
2x 35-d cycles

MAINTENANCE DEX

PETHEMA/GEM

Rosinol et al. Blood 2012;120:1589-96

RANDOM
n=386

INDUCTION (6x 28-d cycles)

VBMCP/ VBAD/B

VTD

TD

MOBILIZATION

TRANSPLANTATION MEL 200 (ASCT-1)

RANDOM

MAINTENANCE (3 years)

IFN-α2b

VT

T

HOVON65MM/GMMG-HD41

Sonneveld et al. JCO 2012;30:2946-55

RANDOM
n=827

INDUCTION (3x 28-d cycles)

INDUCTION PAD

INDUCTION VAD

MOBILIZATION

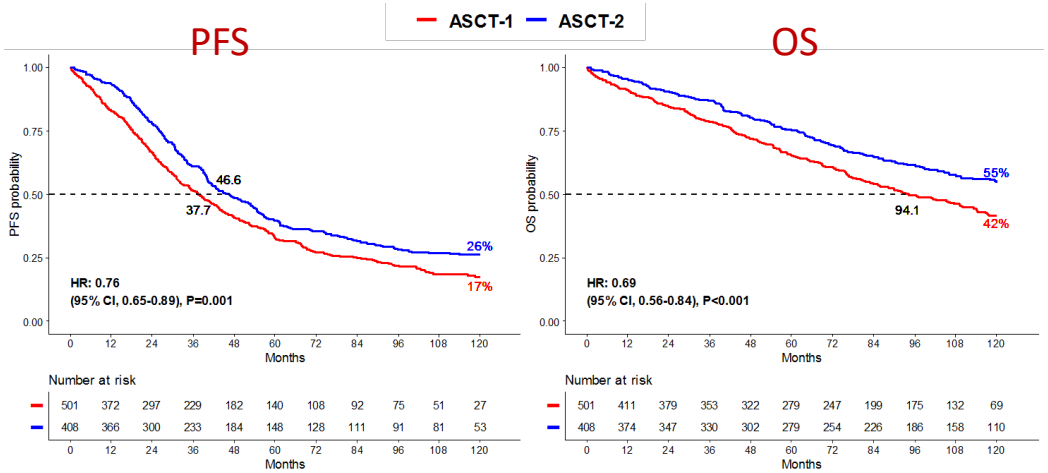
TRANSPLANTATION *
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

* HOVON single / GMMG double ASCT

MAINTENANCE V (2 years)

MAINTENANCE T (2 years)

Single vs double ASCT: analysis of 3 phase 3 EU studies



PFS and OS by treatment

	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	**0.012**

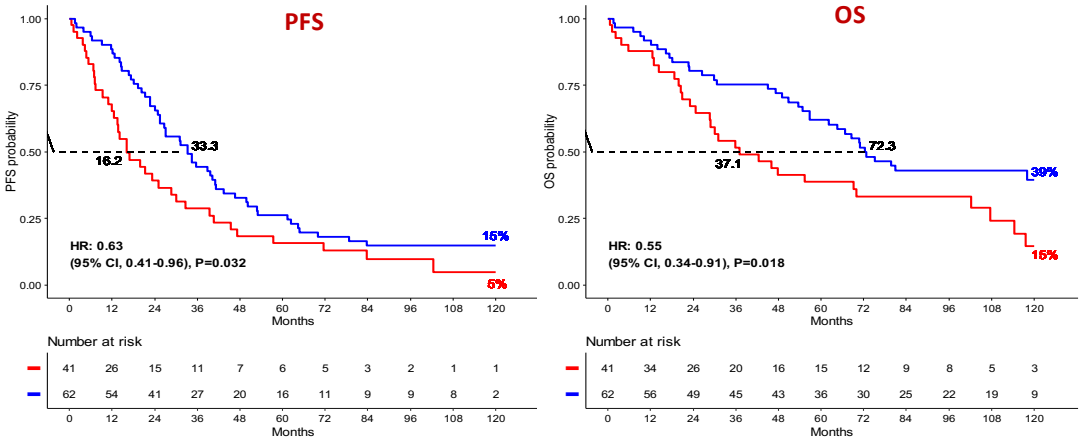
	N pts	Median OS	N pts	Median OS	HR	HR	P-value
Low-Risk	55	NR	77	NR	0.91	0.42-1.98	0.810
Intermediate-Risk	133	110.2	144	NR	0.79	0.54-1.14	0.210
High-Risk	112	47.8	136	79.8	0.58	0.42-0.80	**0.001**

MULTIVARIABLE COX REGRESSION ANALYSIS (excluding 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 <CR	1.831	1.497-2.241	<0.001

*CR: complete remission, time dependent variable

			RISK SCORE LEVELS		
HR-cyto	Best <CR	ISS II-III	LOW (0/3)	INTERMEDIATE (1/3)	HIGH (≥2/3)
No	No	No	132 (100%)		
		Yes		156 (56,3%)	
	Yes	No		98 (35,4%)	
		Yes			138 (55,7%)
Yes	No	No		23 (8,3%)	
		Yes			54 (21,8%)
	Yes	No			11 (4,4%)
		Yes			45 (18,2%)
Total pts, nr (%)			132 (20,1%)	277 (42,2%)	248 (37,7%)

PFS and OS by stage ISS II-III and HR-FISH



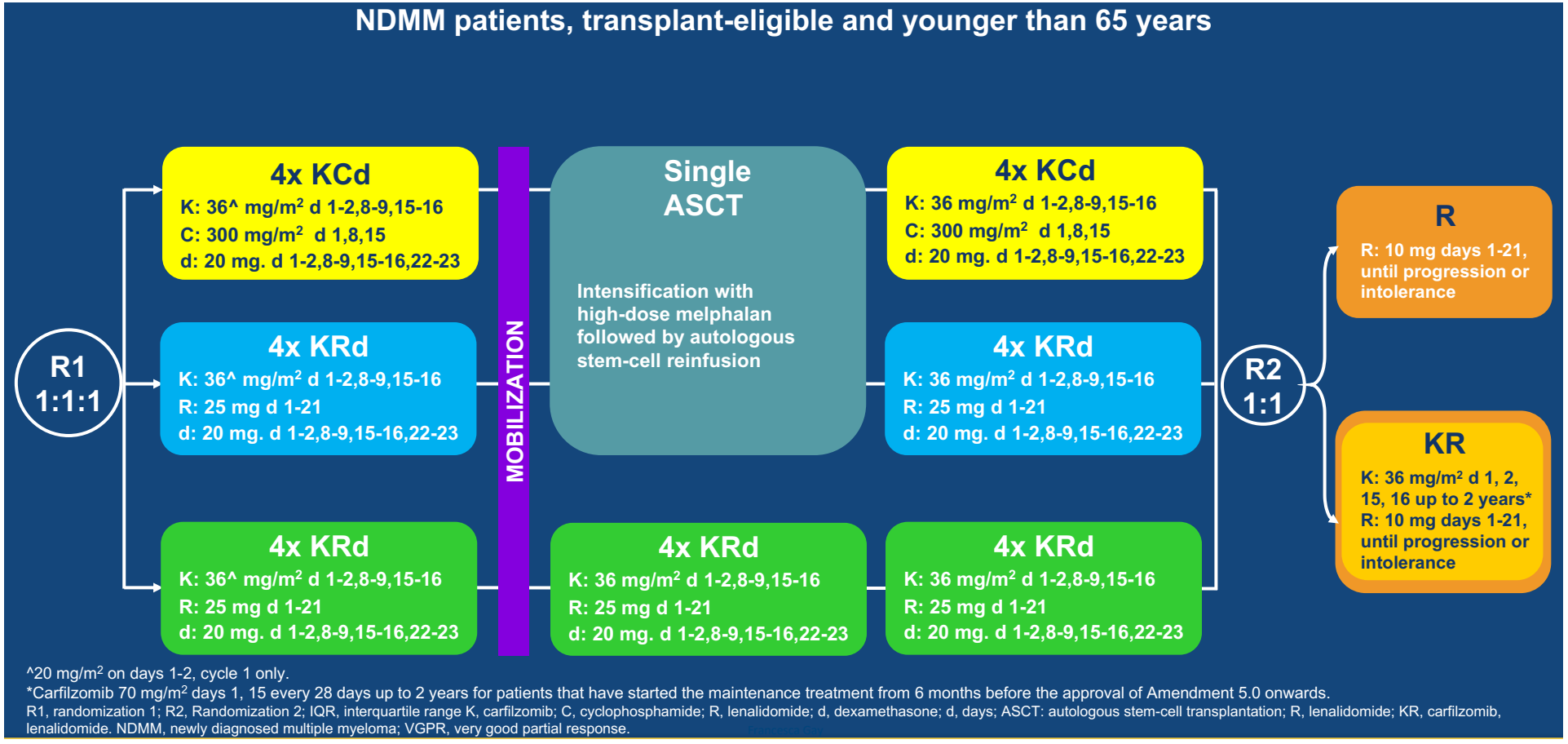
HR Cg: t(4;14) and/or del(17p) (cut-off levels ≥10% and ≥20%, respectively) by FISH

Cavo M, et al. ASH 2018 (Abstract 124), Oral presentation

KEY TOPICS

- Up-front ASCT vs novel agent-based intensification therapy
- Single vs Double ASCT
- **ASCT in the context of new novel combinations**

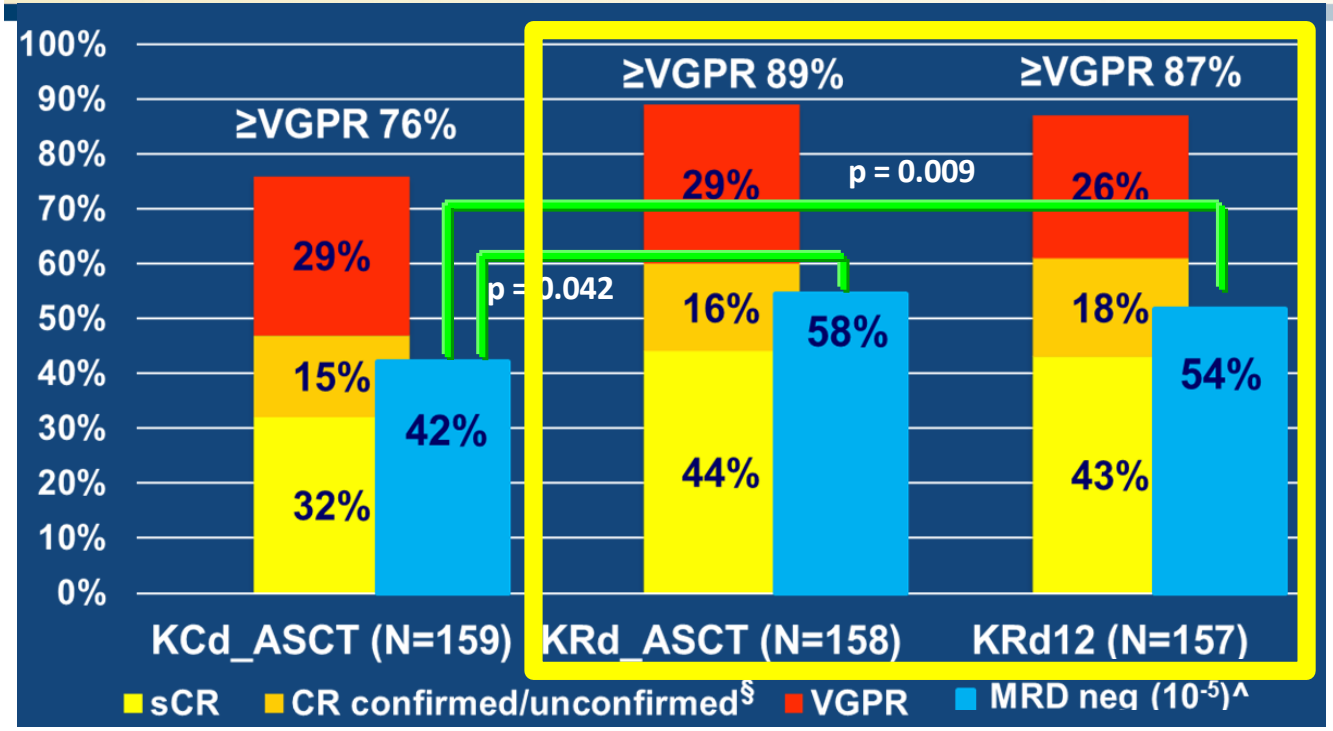
FORTE study: trial design



^20 mg/m² on days 1-2, cycle 1 only.
*Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.
R1, randomization 1; R2, Randomization 2; IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT: autologous stem-cell transplantation; R, lenalidomide; KR, carfilzomib, lenalidomide. NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response.

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

FORTE study: efficacy analysis by risk status



Median follow-up: 25 months

Early relapse (≤18 mos from random1)			
	KRd_ASCT	KRd_12	p
Overall	12 (7.6%)	26 (16.6%)	0.015
R ISS II/III	11 (12%)	22 (23.4%)	0.05

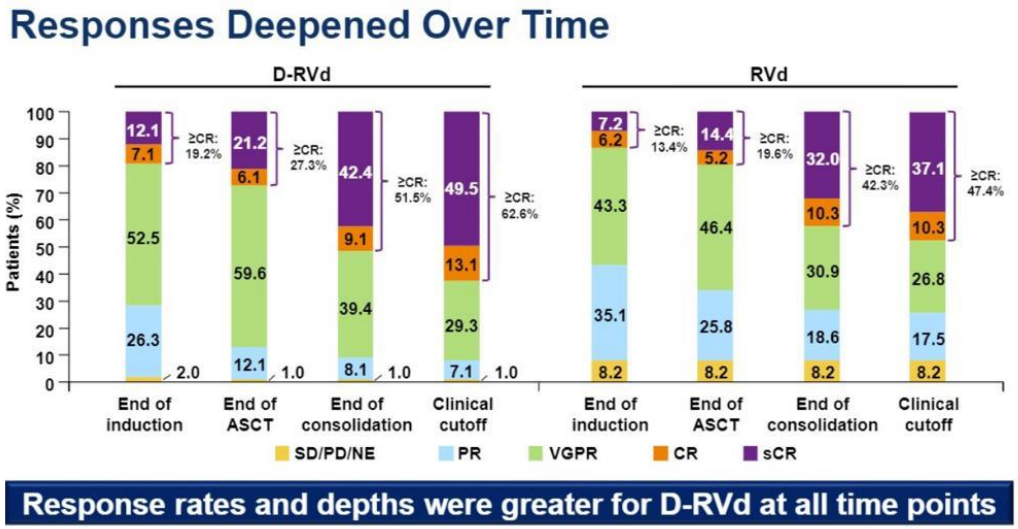
Multivariate Logistic Regression Model

	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

Gay F et al, ASCO 2019 Abs 8002 oral presentation

Modern induction and post-ASCT consolidation therapies including mAb

GRIFFIN ph2 trial

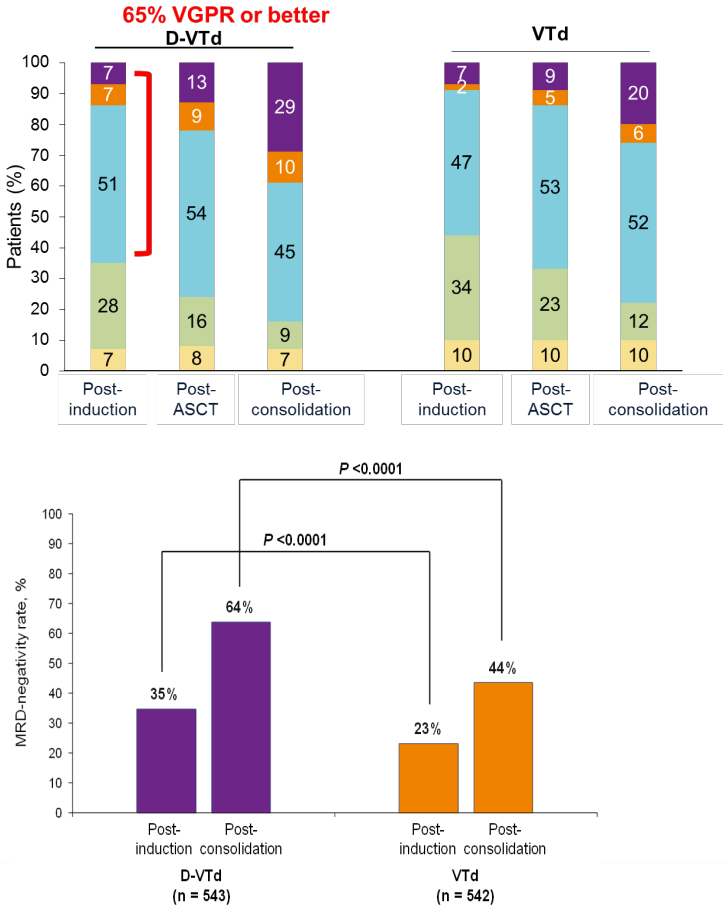


Response rates and depths were greater for D-RVd at all time points

MRD negativity rate (NGS, 10^{-5}): 59% vs 24%
(End of consolidation, pts ≥CR)

Voorhees P et al. IMWG 2019

CASSIOPEIA ph3 trial



Moreau et al. The Lancet 2019; Avet-Loiseau H, et al. IMW 2019,Oral presentation

Highlights from IMW 2019

Summary

- **Upfront ASCT remains the gold standard** intensification therapy, even in MRD-ve patients (at high risk?)
- **Double ASCT following short-term induction therapy improves outcomes**, a benefit retained in high-risk patients
- **Future directions and open questions with new highly-effective novel 4-drug combinations:**
  - **Upfront ASCT:** place for new trials in low-risk patients vs highly-effective novel combinations based on MRD status
  - **Double ASCT:** role in the future with routine use of quadruplets? Treatment based on risk profile and MRD?

Acknowledgements

Seràgnoli Institute of Hematology

Myeloma Research Unit
Michele Cavo

Clinical Research Unit
Elena Zamagni
Paola Tacchetti
Lucia Pantani
Katia Mancuso
Serena Rocchi
Ilaria Rizzello
Alessio Fusco
Gabriella De Cicco
Francesco De Felice
Margherita Ursi

Data Management
Federica Pedali
Giorgia Lazzarini
Francesca Trombetta
Alessandra Scatà
Simona Barbato
Claudio Mostaccio
Giada Giulia Riso

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Lab of Cytogenetics
Nicoletta Testoni
Giulia Marzocchi

Lab of Molecular Biology
Carolina Terragna
Marina Martello
Vincenza Solli
Andrea Poletti
Luca Cifarelli

Lab of Cellular Biology
Enrica Borsi

Statistical Analysis
Luca Dozza