Mieloma Múltiple

Combinaciones quimioterápicas en hemopatías malignas

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FEHH
FUNDACIÓN ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

Tratamiento Antineoplásico en Hematología: Mucho que aprender, mucho que recordar

Madrid, 23 de octubre de 2014

MM Efficacy with Different Regimens of Oral Melphalan

The Southwest Cancer Chemotherapy Study Group Experience (1959-1965)

Regimen	№	Responses, %
Continuous Melphalan	35	19
Intermittent Melphalan	69	35
Intermittent Melphalan	158	42
Continuous Melphalan & Prednisone every other day	28	65
Melphalan & Prednisone, both intermittent	51	73

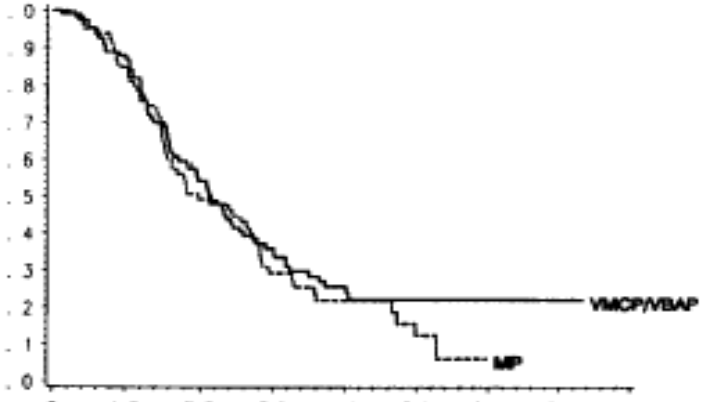
In all groups: Median OS 24 m. In responders 50 m.

Alexanian R et al. JAMA 1969;208:1680-5

VMCP/VBAP vs. MP

Respuestas 59% vs. 47%

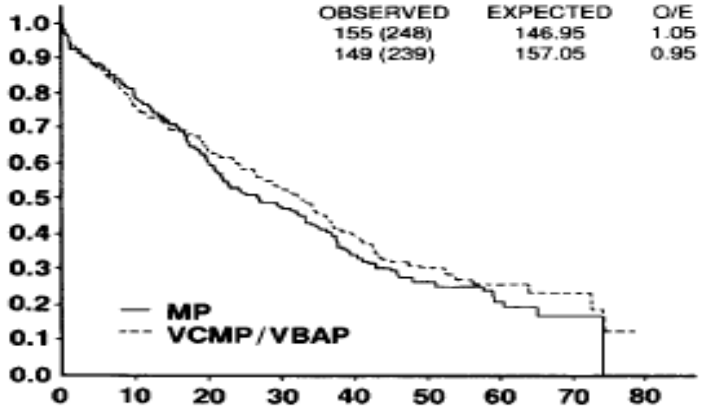
Boccadoro M. JCO 1994



VMCP/VBAP vs. MP

Respuestas 63% vs. 52%

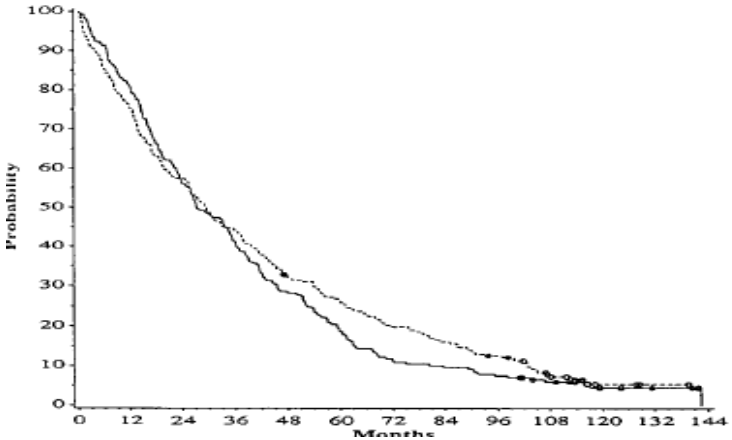
Bladé J. JCO 1994



VBMCP vs. MP

Respuestas 72% vs. 51%

Oken MM (ECOG). Cancer 1997



MELPHALAN: DOSE – RESPONSE CORRELATION

Reference	Melphalan mg/m²	Stem cell support	Case n	Deaths related %	Response %	CR %	PFS mo.	OS mo.
Barlogie B. Blood 1988 72: 2015-2019	70-100	No	43	30	44		3	5
Barlogie B. Bone Marrow Transplant 1993;11(S1):37-44	70	No	23	26	34	4	3	4
Cunningham D. J Clin Oncol 1994; 12:764-8	140	No	63	13	82	32	18	47
Barlogie B. Oncology 1994;8:89-03	140+TBI	BM	73	5		20*	16	42
Cunningham D. J Clin Oncol 1994; 12:759-63	200	BM	53	1.8	90	75**	20+	63%, 5 y.
Moreau P. Blood 2002 91:731-35	200	PBSC	142	0	94%	35*	21	66%, 45 m.

*CR IF -, ** EEF -

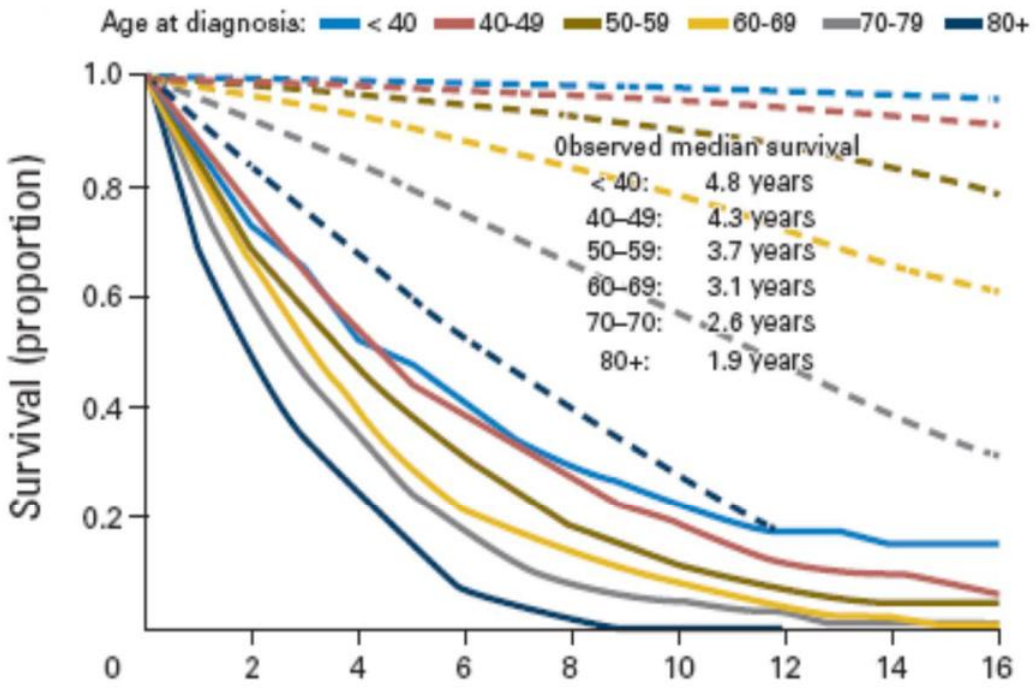
HDT / ASCT vs Standard dose therapy

A comparison which has lost its significan

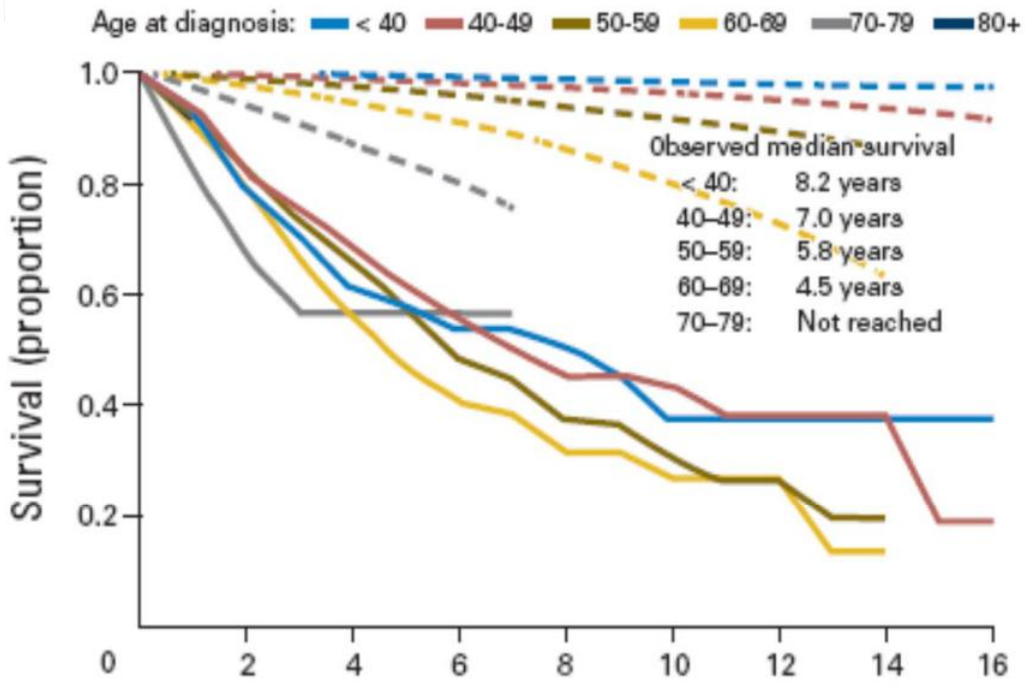
Study	Pts	HDT Regimen	Age	CR %	EFS, median, m	OS, median, m
IFM90 (NEJM 1996)	200	MEL140+ TBI	≤65	5 vs. 22	18 vs. 28	44 vs. 57
MRC VII (NEJM 2003)	401	MEL200	≤65	8 vs. 44	19 vs. 31	42 vs. 54
IMMSG M97G (Blood 2004)	194	MEL100	50-70	6 vs. 25	16 vs. 28	42 vs. 58+
MAG91 (JCO 2005)	190	MEL200/BUMEL	55-65	20 vs. 36	19 vs. 25	45 vs. 42
PETHEMA (Blood 2005)	164	MEL140+TBI/MEL200	≤65	11 vs. 30	34 vs. 42	67 vs. 65
US Interg. S9321 (JCO 2005)	516	MEL140+TBI	<70	11 vs. 11	21 vs. 25	53 vs. 58

Patterns of Long-term Survival in MM patients

Conventional or High Dose Chemotherapy



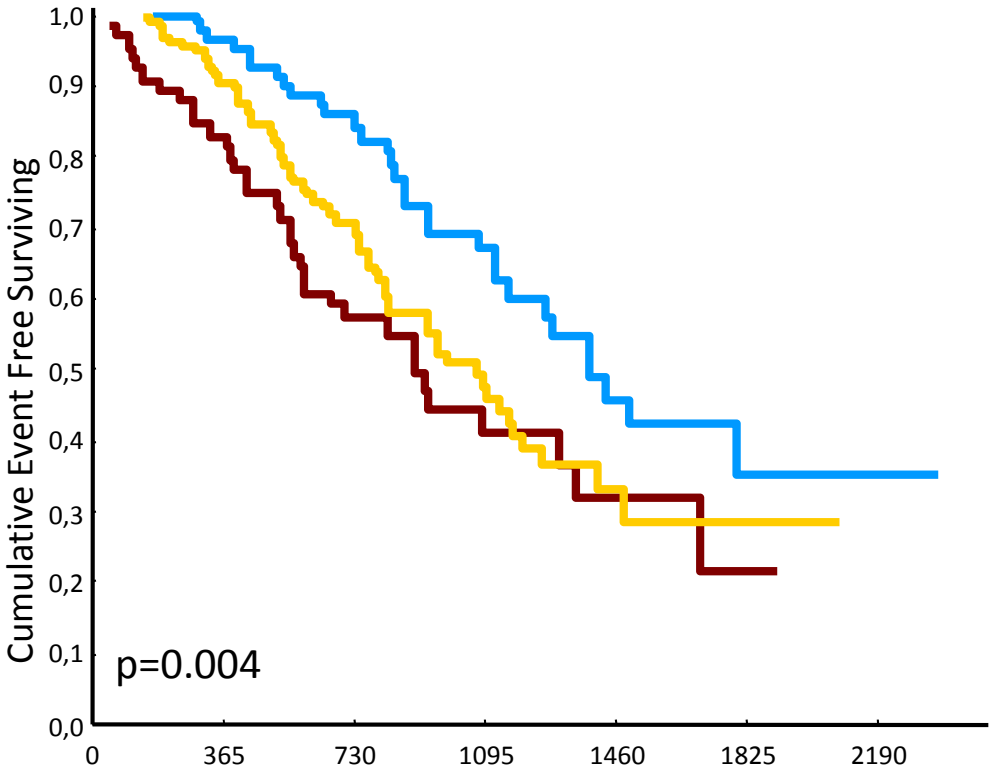
Conventional Chemo

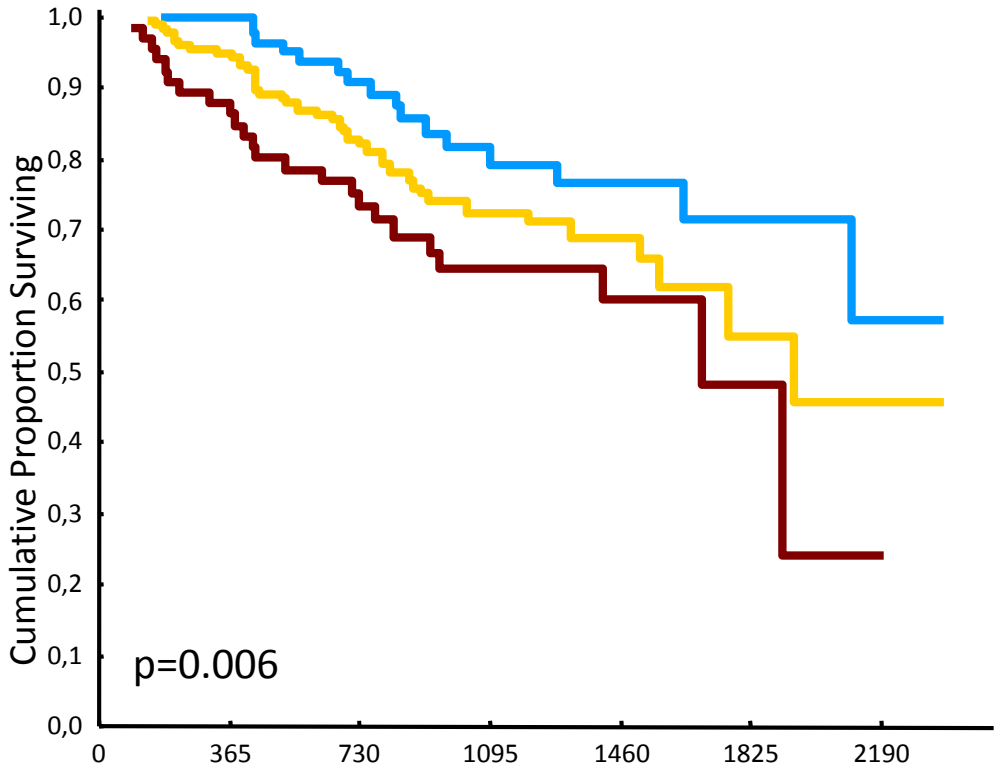


HDT/ASCT

Ludwig H et al. JCO 2010; 28:1599-605

CR EP Negative Include nCR+CR (≥nCR)





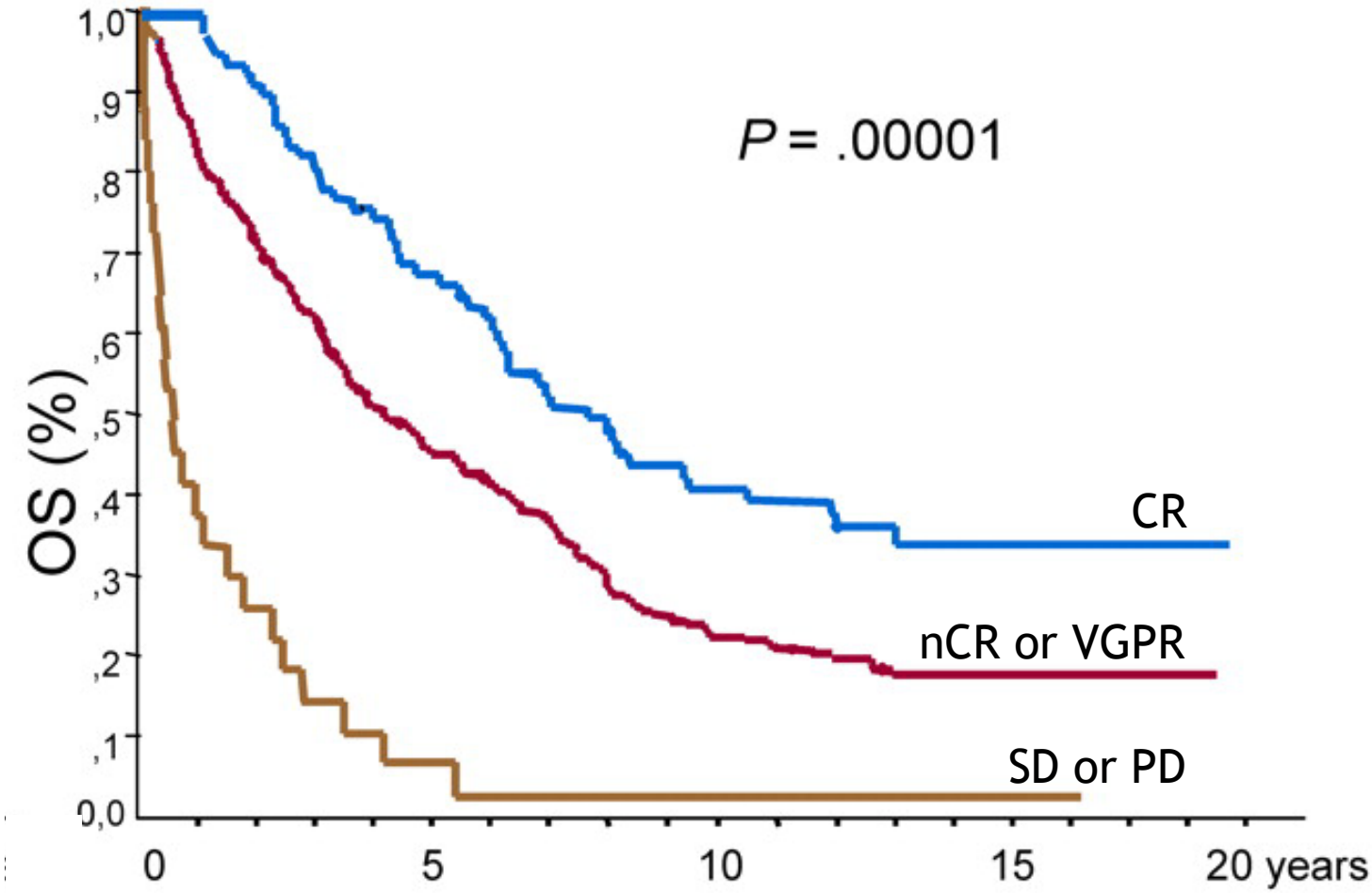
Days from Transplantion

	≥CR o CR EPnegative, n 150	CR IF negative, n 84	nCR (EF-, IF+), n 66
Medians EFS, m.	43	46	30
Medians OS, m.	70	NR	56

Lahuerta JJ et al. Br J Haemat 2000

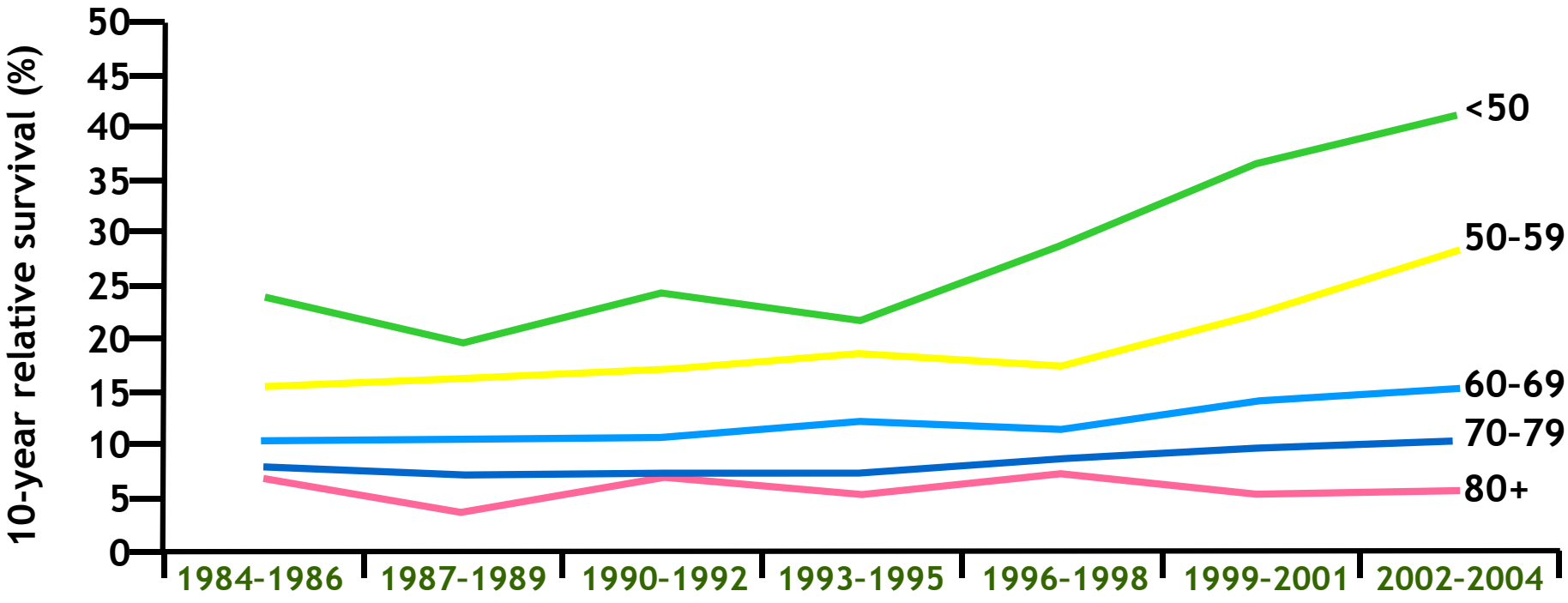
The MM is a Curable Disease

The GEM 1992-99 Series: 10 Years Later



Martínez-López et al. Blood 2011

Period estimates of 10-yr survival by major age groups



Project 10-year relative survival expectations of MM patients diagnosed in 2006-2010

<45	55.3%
45-49	39.4%
50-54	32.1%

Brenner H, Gondos A, Pulte D. *Blood 2008. Haematologica 2009*

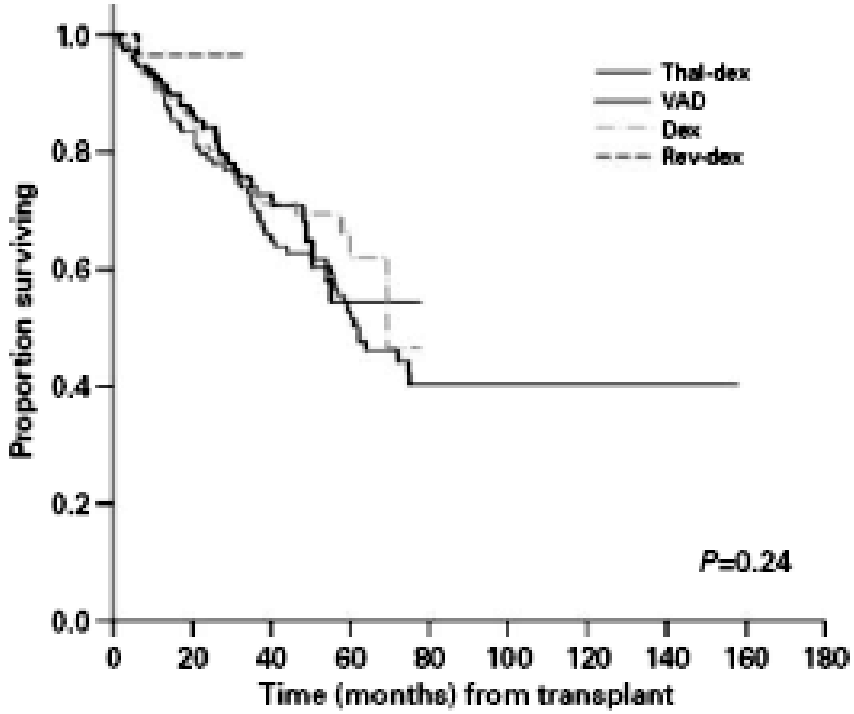
3rd landmark:
Transplantation and New Drugs

¿Synergistic Effect Induction-Transplant?

Suboptimal Induction Regimens

"For patients undergoing early ASCT for myeloma, the nature of initial treatment utilized has no long-term impact on the outcome of ASCT…"

	DEX	VAD	TAL-DEX
OR, pre-Tx	¿	¿	¿
OR, post-Tx	96	97	98
CR pos-Tx	45	49	38
PFS (2 years), %	54	55	47
OS (4 years), %	64	65	72



Kumar SK et al. Bone Marrow Transplant 2008: 41:1013-9

Pre and Post-ASCT CR Rate: "Novel" Induction Regimens:

20-25% of aditional CR

		Response to Induction (%)		Response to ASCT (%)		Aditional CR (%)
Author, Phase	Scheme	≥nCR+CR	CR	≥nCR+CR	CR	
Cavo M, III Blood 2012	TD		5		23	27
	VTD		19		38	25
Harousseau, III JCO 2010	VAD	6		18		12
	BD	15		35		20
Jakubowiak JCO 2009, II	PAD	37		57		20
Rosiñol, III Blood 2012	TD		14		38	23
	VBMCP/VBAD/BD		21		24	26
	VTD		35		46	21

- The ASCT is not competitive with induction.
- CR postransplant depends on the effectiveness of the induction therapy

Continuous Therapy in MM

In MM, across of the frontline therapeutic sequence, the progressive increase of the response involves:

- **More possibilities of conversions from post-induction nCR/VGPR to CR post-ASCT.** The effect of transplantation provides an additional 20-25% of CR. Improved response post-transplantation is correlated with Survival[1]

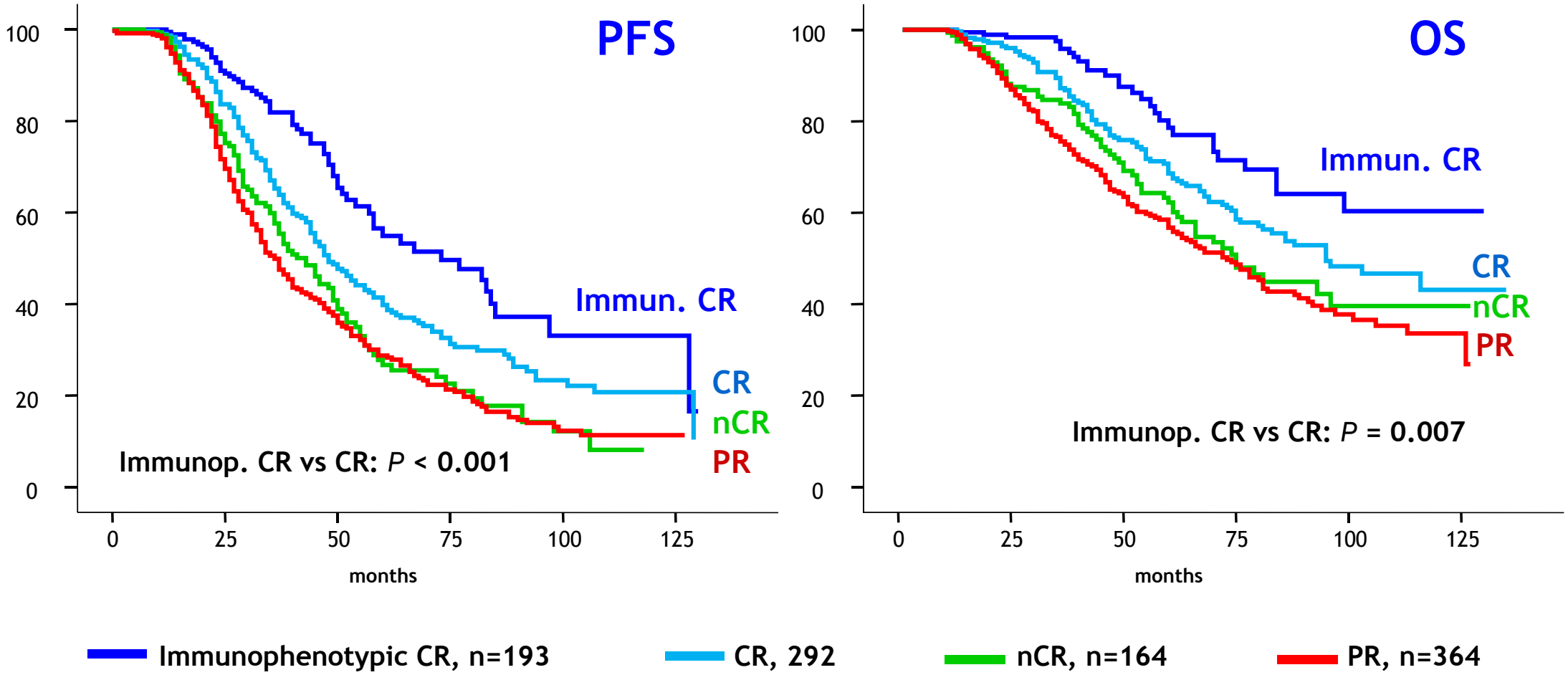
- **Conversions from CR to Molecular/Immunophenotypic Remission**. Molecular or Immunophenotypic Remissions are associated with significant improvements in PFS and OS[2-4]

- **Better PFS and OS rates in patients in Immunophenotypic remission "overtreated"** with transplant[5]

1. Lahuerta JJ et al. J Clin Oncol. 2008; 10:5775-82
2. Ladetto M et al. ASH2011; abstr 827
3. Paiva B et al. Blood 2010. 116; abstr 1910
4. Paiva B et al. EHA2011; abstr O468
5. *Paiva B et al. Blood. 2008, 112: 4017-4023*

Immunophenotypic Remission

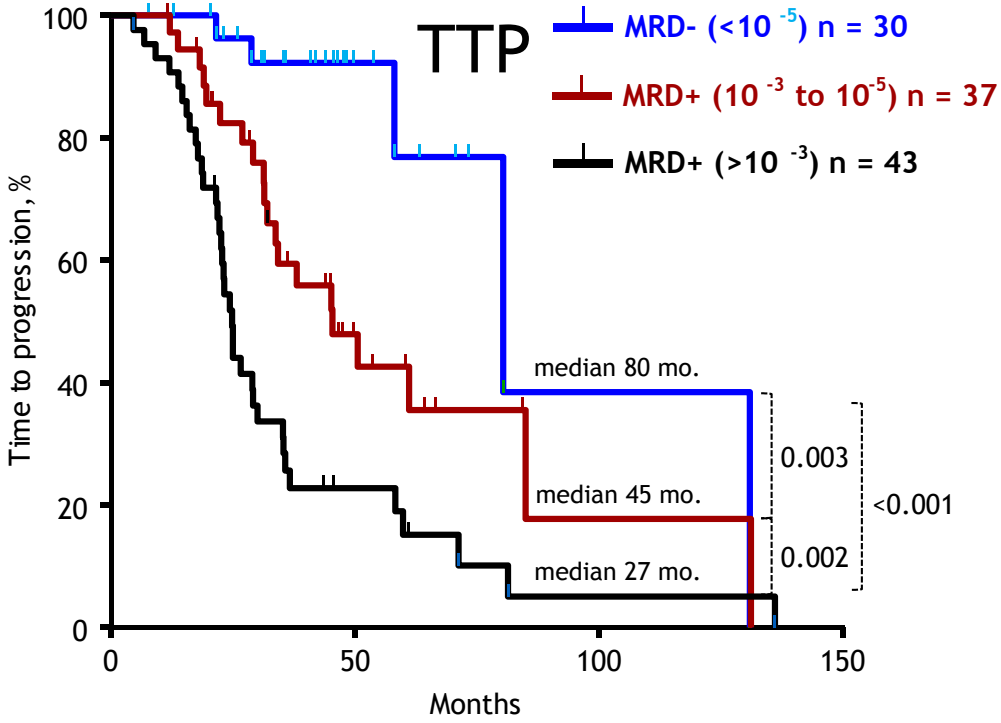
The better the quality of the response the longer the survival: GEM2000 & 2005

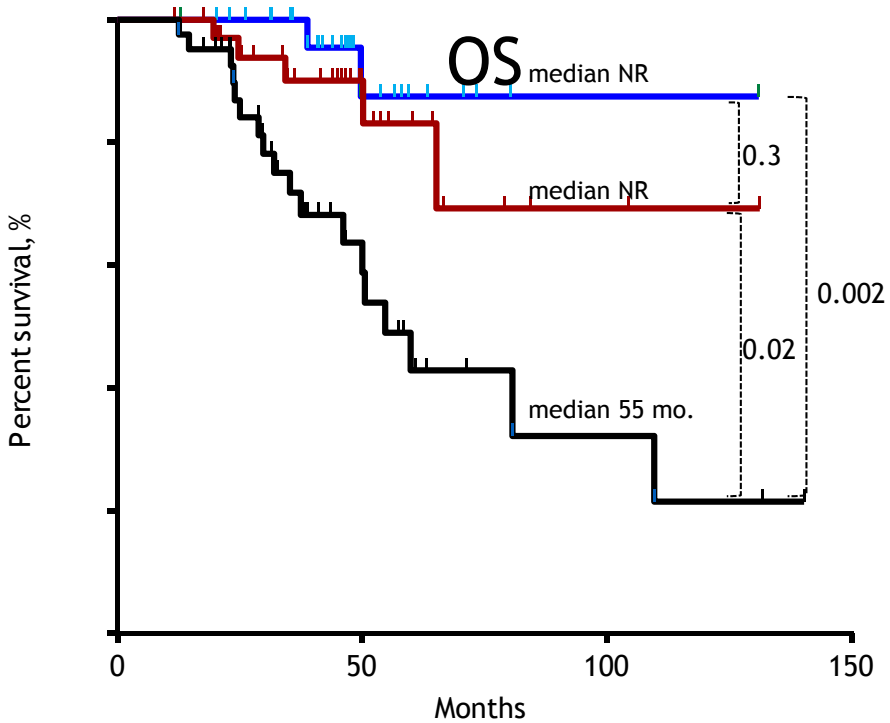


Median f/u: 46 months (updated)

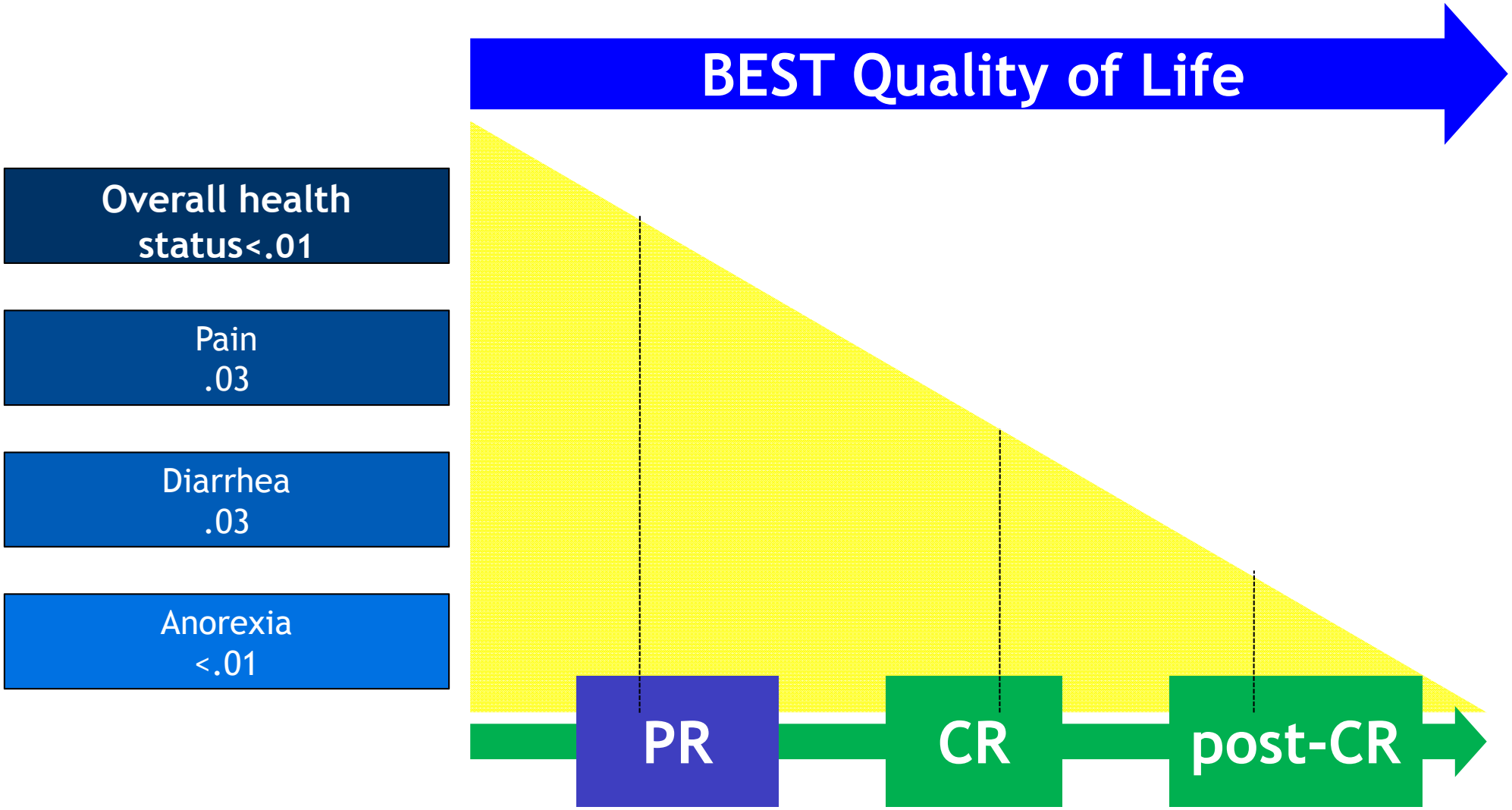
Paiva et al. Blood. 2008, JCO 2011

Prognosis of achieving MRD- by sequencing depending of MRD level





Martinez-Lopez et al Blood. 2014 May 15;123(20):3073-9.



Dhawan R. XII International Myeloma Workshop 2009. Abst A352

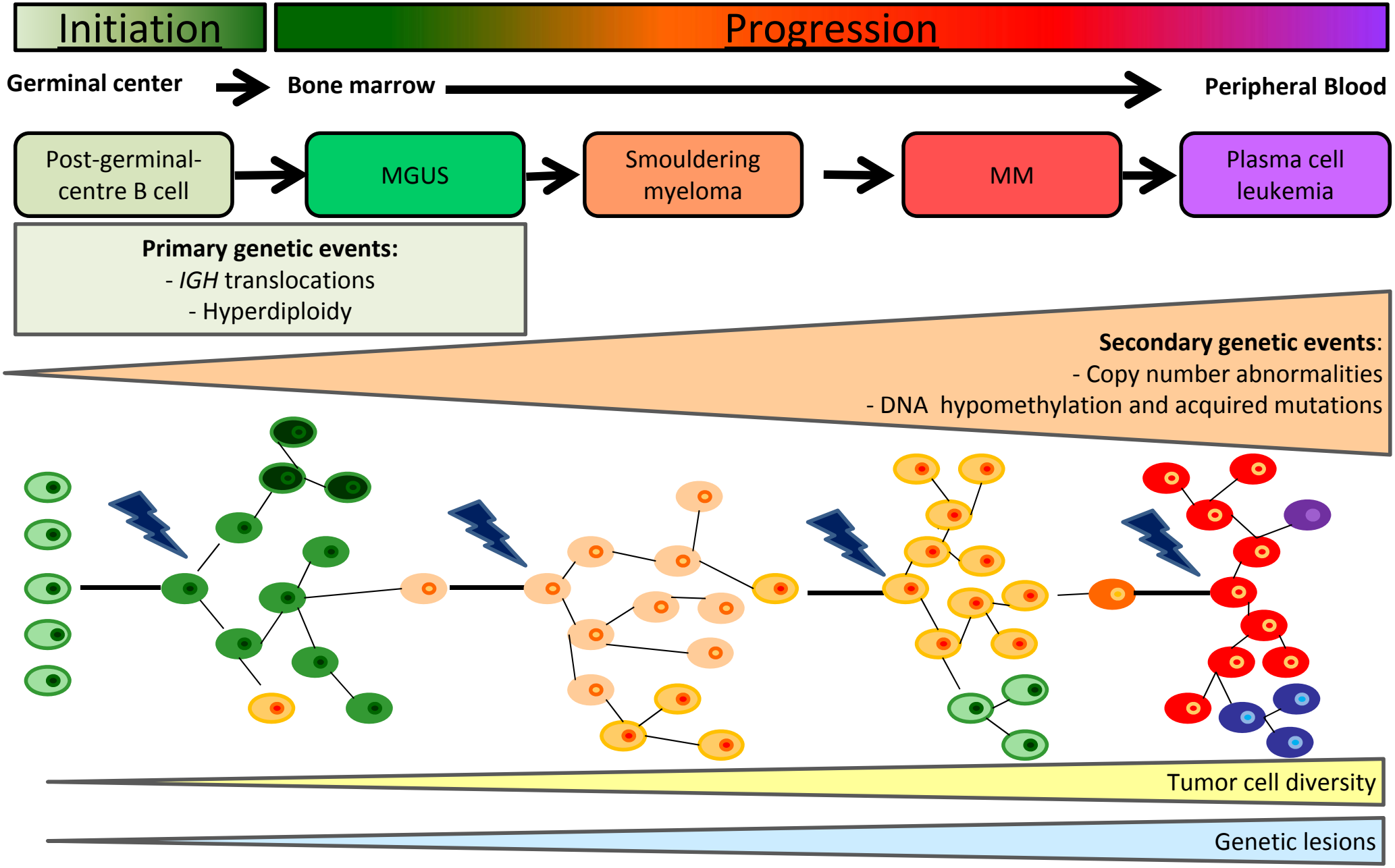
In MM there is a clear association between optimal response and long-term outcome (PFS and OS)

….CR and immunophenotypic or molecular remissions should be a treatment endpoint

MM: ¿Cure or Control?

- The optimal treatment of MM is based on the additive effect of a therapeutic sequence including induction, transplant, consolidation and maintenance.

- The composition of treatment depends on the biological integrity of the patient and their tolerance to toxicity



Morgan G (modified by Gutierrez N), Nature 2012

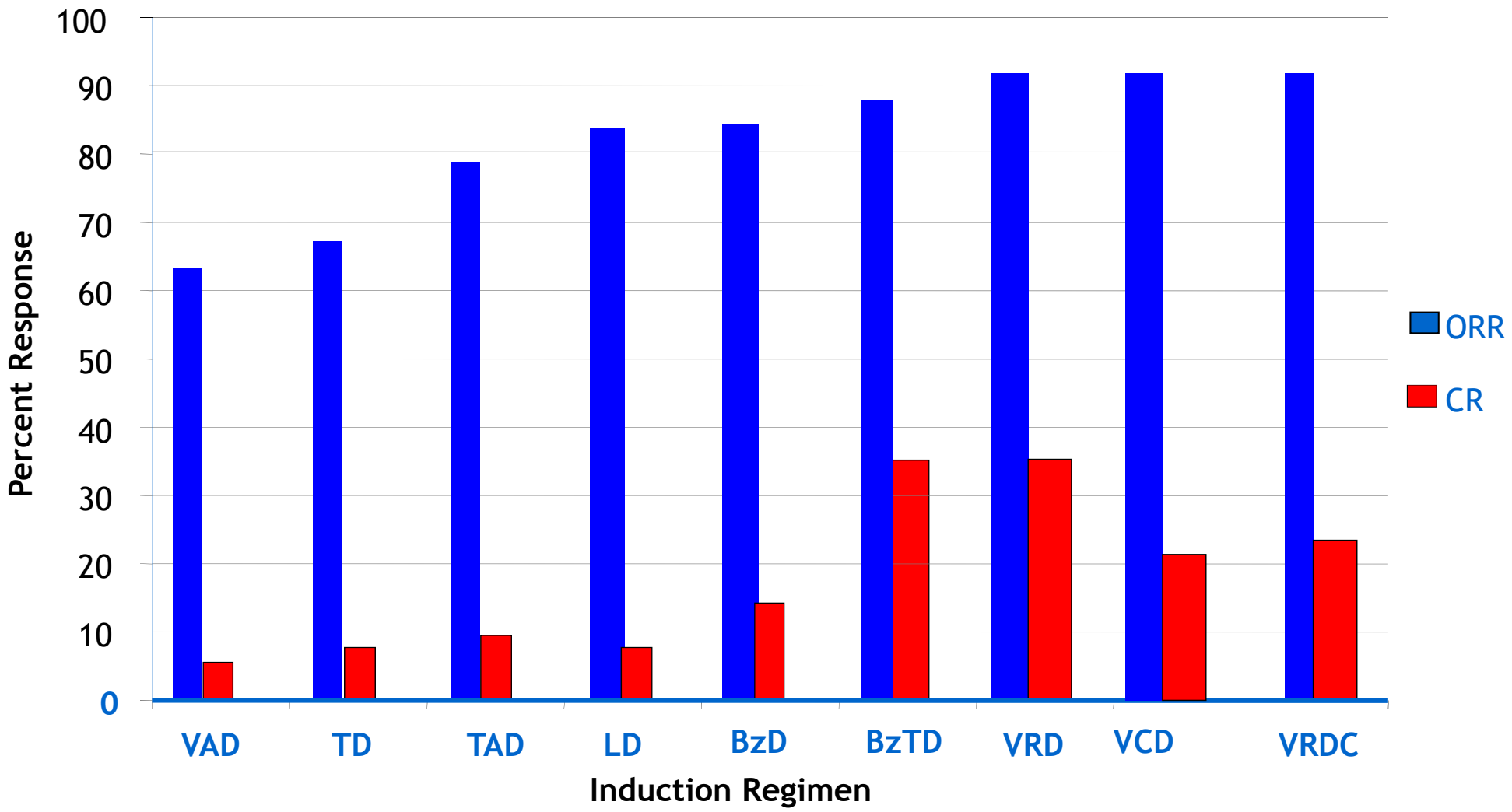
Multiple Myeloma: Basic Clinical Settings

Stratification by Treatment Intensity

- **Candidate for ASCT:** Optimal treatment strategy, with the cure at the horizon
- **Elderly and biologically fit:** Induction and maintenance: improved survival and quality of life. Some patients may achieve an operative cure
- **Elderly and frail:** Attenuated treatments for improving the quality of life, reduce toxicity and disease control
- **Other possible clinical settings**: Smoldering Myeloma, Insufficient Response, High Risk CR, Plasma Cell Leukemia, Renal Impairment, Relapse/ Progression

Induction

Response obtained with Novel Induction Regimens



- *Adapted from: How I treat MM in younger patients by Stewart K, Richardson P , San Miguel JF . Blood 2009; 114: 5436-43*

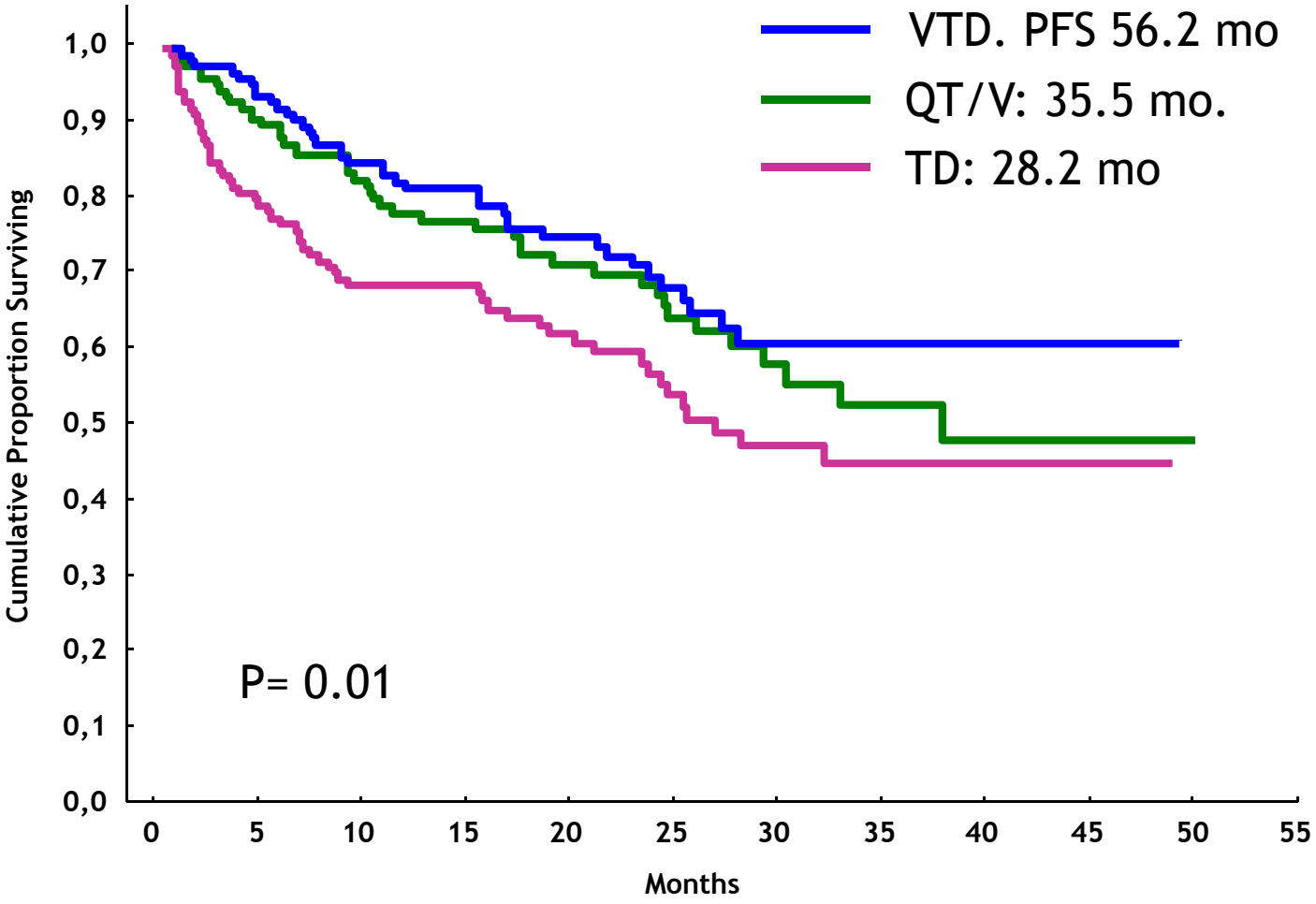
GIMEMA MM0305 study Phase III: VTD vs TD

	Induction	First ASCT	2nd ASCT	Consolidation	Best Response	PFS
Regimen			**CR, %**			**3-year**
VTD n=241	19	38	42	49	58	68%
TD n=239	5	23	30	34	41	56%
P	0.0001	0.0004	0.01	0.0001	0.001	0.005

VTD vs TD arm: any grade 3 or 4 adverse event 56% vs. 33%, <0·0001

Cavo M et al. Lancet 2010;376: 2043-4

PETHEMA/GEMmenos2005 Phase III study:
PFS according to treatment arm

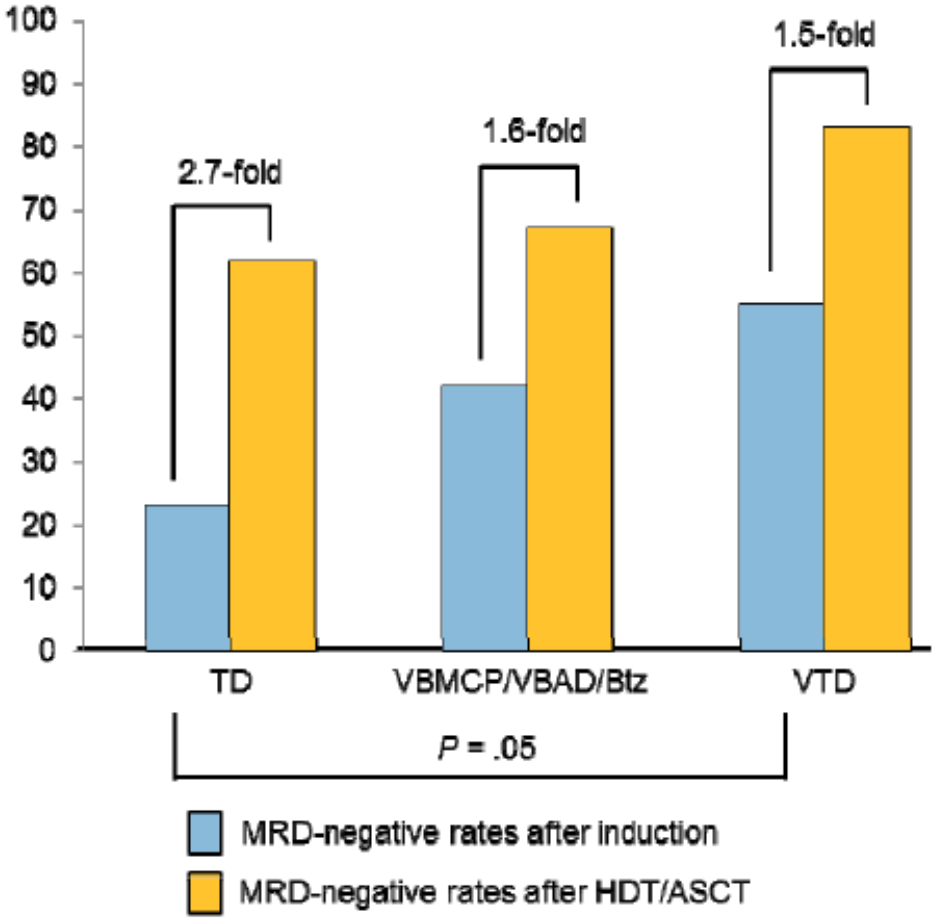


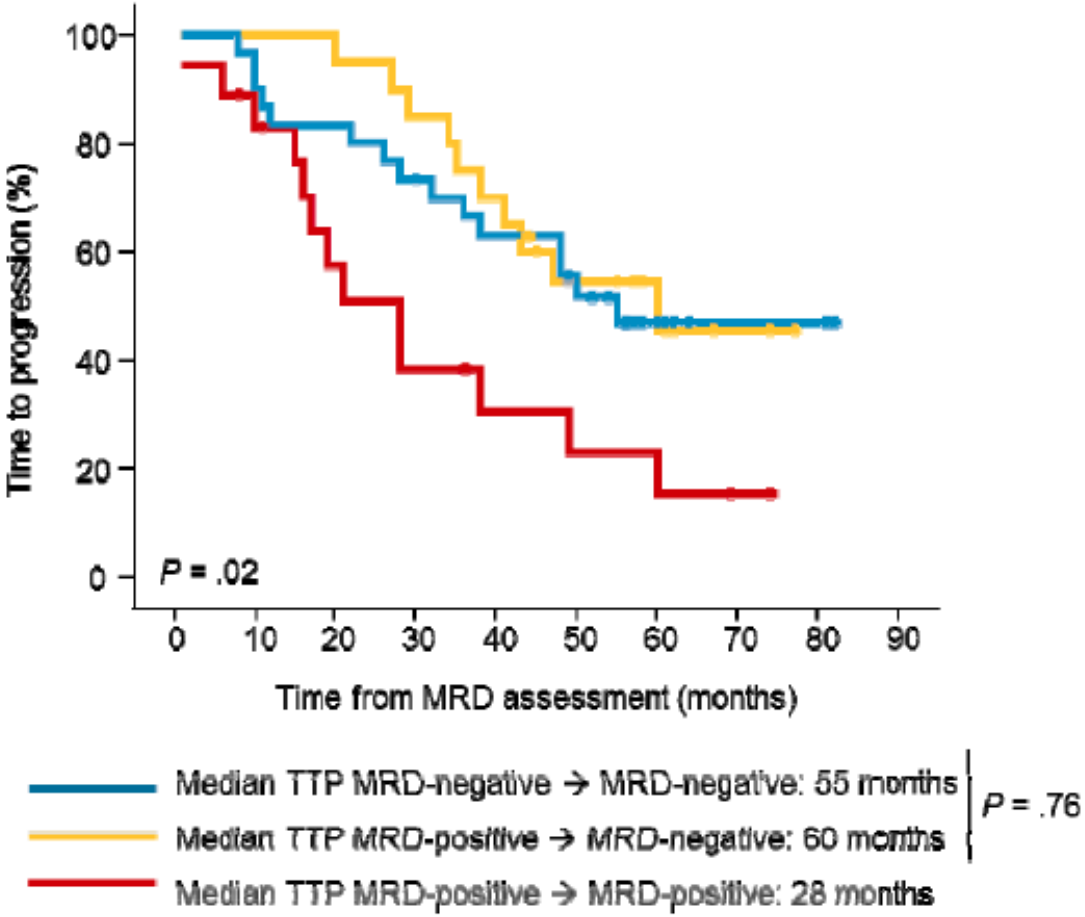
patients with high-risk cytogenetics had a significantly shorter OS and PFS irrespective of the treatment arm

Rosiñol L et al. Blood. 2012 Aug 23;120(8):1589-1596. Epub 2012 Jul 12.

PETHEMA/GEMmenos2005 Phase III study:

MRD kinetics before and after HDT/ASCT among patients in CR

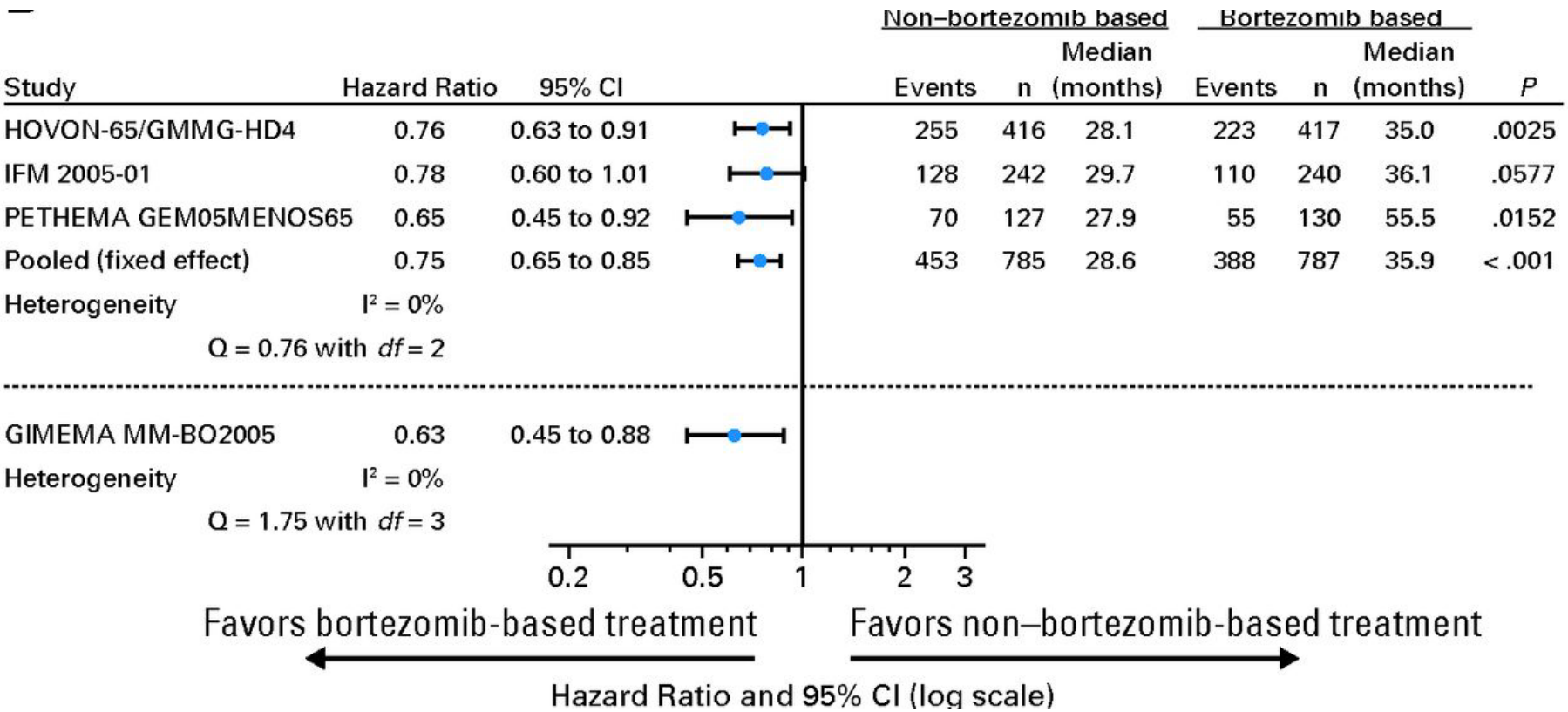




Paiva et al. 2014. Submitted

Bortezomib-Based Versus Nonbortezomib-Based Induction Treatment Before ASCT in Patients With Previously Untreated MM: A Meta-Analysis of Phase III Randomized, Controlled Trials

1572 patietes from the IFM 2005-01 (BD *v* VAD induction), HOVON-65/GMMG-HD4 (BAD e *v* VAD), and PETHEMA GEM05MENOS65 (BTD *v* TD)



bortezomib-based versus nonbortezomib-based induction:
PFS: 35.9 m. vs. 28.6 m. ($P < .001$); 3-y OS: 79.7% vs. 74.7% ($P = .04$). PN grade ≥ 3: 6% *v* 1%.

Sonneveld P et al. JCO 2013;31:3279-3287

Phase II: Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma

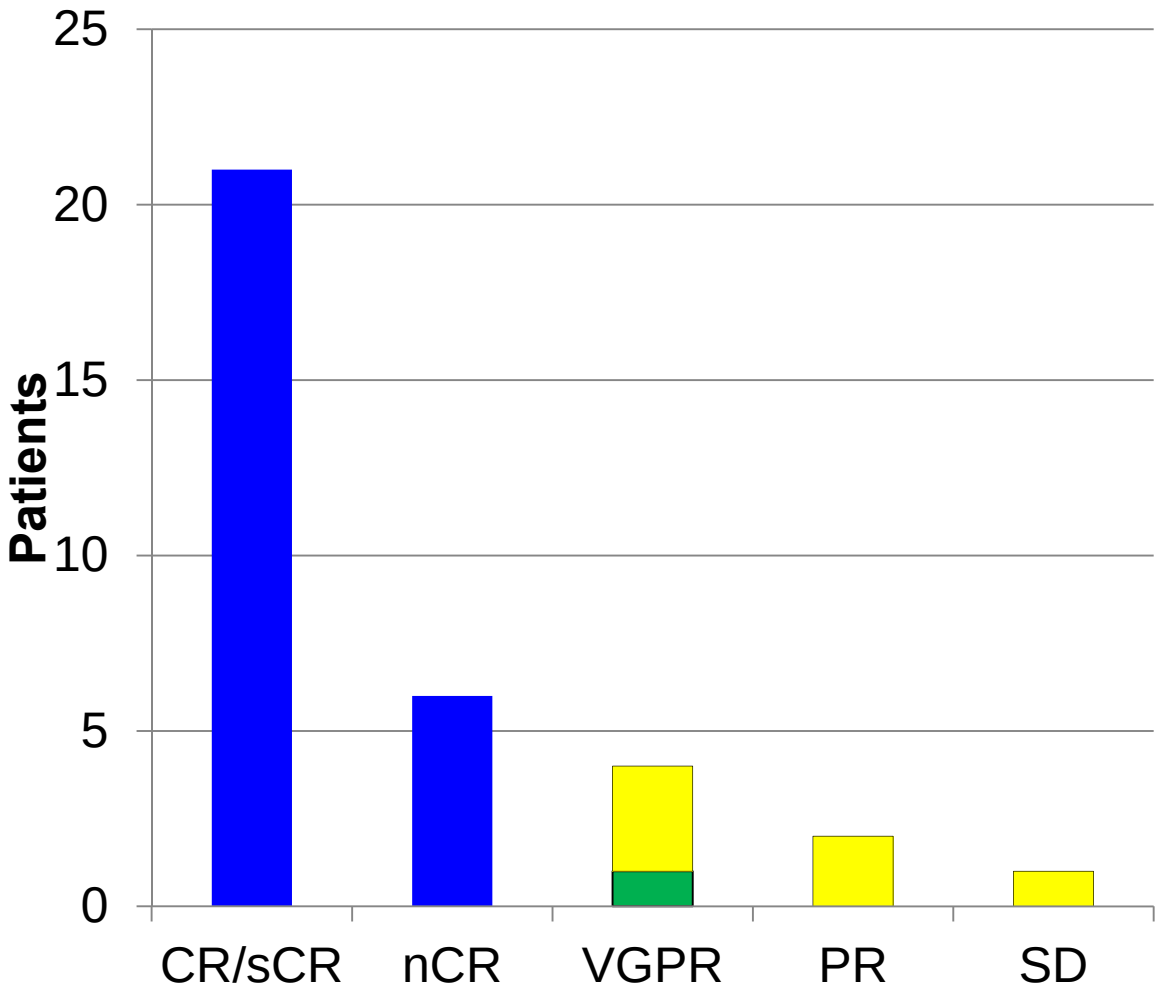
Time to CR/sCR and PFS	
CR/sCR, n/N (%)	22/43 (51)
Patients reaching CR/sCR ≥ 8 cycles of CRd, n/N (%)	5/22 (23)
Median time to CR/sCR, months (range)	5 (2-18)
PFS at 12 months, % (95% CI)	97 (78-99)
PFS at 18 months, % (95% CI)	91 (68-98)

*4 patients have come off study treatment: 3 – progression and 1 - personal reasons. All other patients remain on study treatment

Korde N et al. ASH2013#538)

MRD Status after CRd therapy: MFC

Among 27 nCR/sCR* patients assessed by MFC, all 27 are MRD negative



MRD NEGATIVE

FLOW POSITIVE AFTER 8 cycles

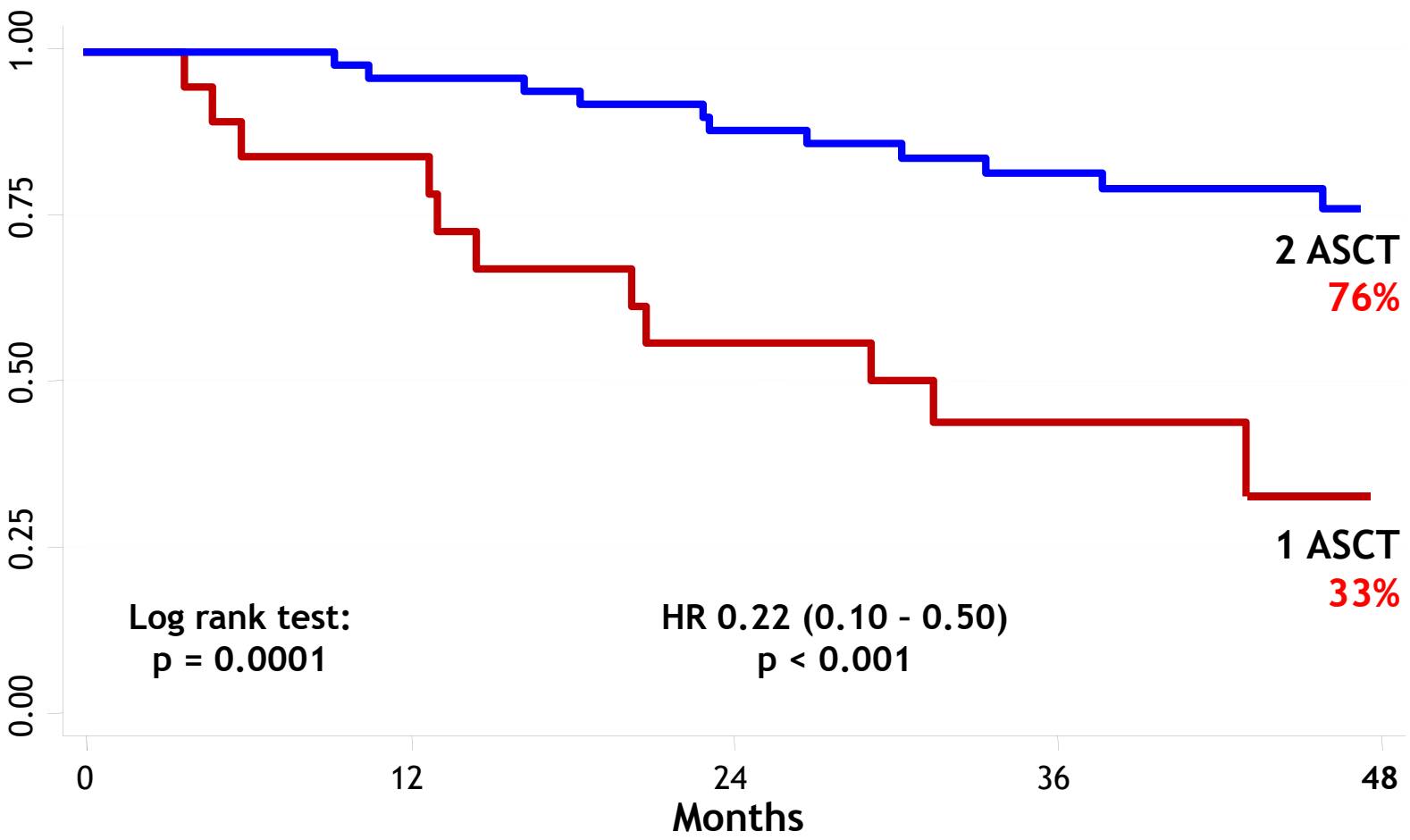
FLOW NEGATIVE AFTER 8 cycles

*2 patients (1 sCR and 1 nCR) not available for interpretation

Korde N et al. ASH2013#538)

Post-transplant consolidation
(including second transplants)

OS According to Preplanned ASCT(s) for Pts with del(17p) and/or t(4;14) and who Failed CR after B-based Induction Regimens



Cavo M et al. ASH2013#767

GIMEMA MM0305 study Phase III: VTD vs TD

Response to different treatment phases in the per-protocol population. (VTD n=160, TD n=161)
- follow-up of 30.4 months from start of consolidation -

CR rate, %	VTD	TD	P
After induction	22	6	<.0001
After First ASCT	44	30	.01
After second ASCT	49	40	.1
After consolidation	61	47	.01

During maintenance therapy with dexamethasone 10%, in the VTD-treated group and 15.5%, in the TD-treated group achieved negative immunofixation

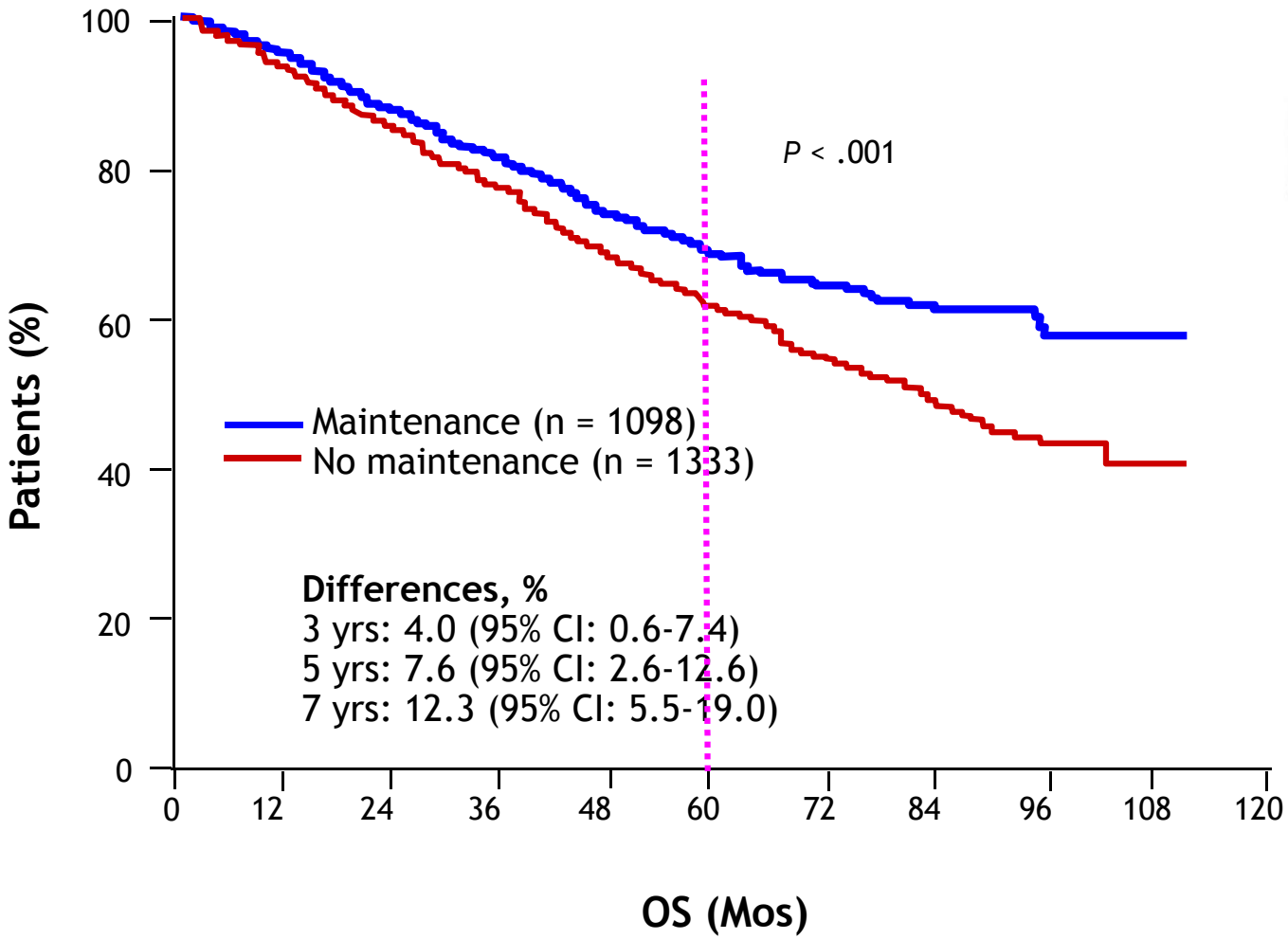
- *In the VTD arm*, PFS curves were independient of t(4;14) and/or del(17p). 3y PFS: 59% range
- *Molecular Response: VTD +29%, TD +17%*
- *3-y PFS (Landmark at start consolidation therapy): VTD 60%, TD 48% (HR 0.69, p= .04)*
- *all-grade AEs during consolidation therapy: 16.2% vs. 4.9%, (P = .001), including grade 2 and 3 PN (8.1% vs.2.4%), and all-grade thrombocytopenia (5.5% vs. 0%, P = .002)*

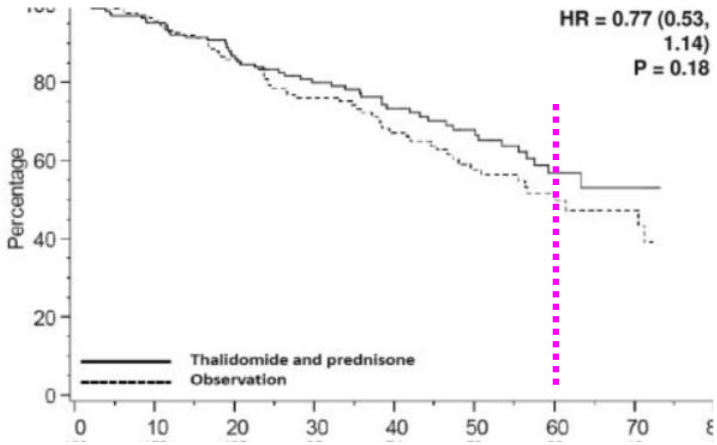
Cavo M et al. Blood 2012

Maintenance Therapy

Thalidomide or Lenalidomide ± Bortezomib?

Meta-analysis of Myeloma IX plus Other Studies: Late OS Benefit With Thalidomide





4-year OS: **68% with thal-prd**
60% with observation

Stewart et al. Blood 2013

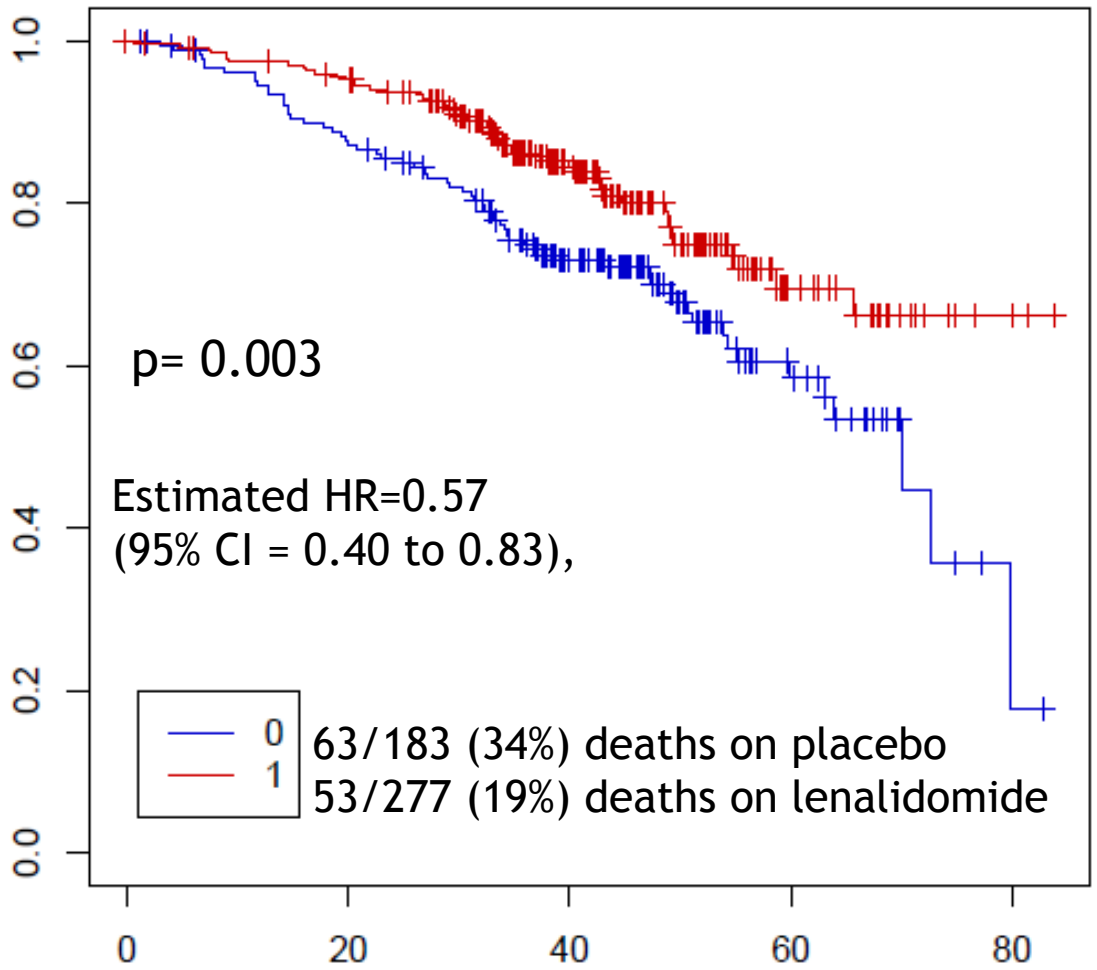
Morgan GJ, et al. Blood. 2012;119:7-15

Phase III lenalidomide maintenance trials after Auto-SCT

Reference	Trial, n	Previous therapy	Maintenance	PFS/ PFS2	Follow-up & Survival	Tolerance , additional data
McCarthy PL, 2012 2013	CALGB 00104, n= 460	Thal- or Len-induction regimens: 74% Single ASCT 100%	A: Len, 5-15 mg/dx21d until PD B: Placebo	A: 3y PFS 66 % *p< .001* B: 3y PFS 39%	34 mo *p= .03* 48 mo:. *p= .008*	- 3 fold increased SPMs with lenalidomide - better prognosis for lenalidomide in induction
Attal M, 2012 2013	IFM 2005/02 n= 614	- VAD (52%) and VD (44%). Pre-ASCT cons.: DCEP (≈25%). Tandem ASCT 21%. Cons: Len 25mg/x21 two cycles	A: Len, 10-15 mg/dx21d until PD* B: Placebo *Maintenance stopped at 24 months	A: PFS 41 mo *p< .001* B: PFS 23 mo	30 mo. *p= .2* 45 mo. *p= .7* 67 mo: *p= .8*	- Reduced survival after 1st progression (29 m vs 48 m). - 2.4 fold increased risk of SPMs with lenalidomide maintenance
Palumbo 2014	402	MPR 4 cycles & tandem ASCT vs MPR 10 cycles	2x2 randomized l A: lenalidomide (10 mg/dx21d until PD B: Observation	A: 42.7 mo *p< .0001* B: 17.5 mo	follow-up: 48 months 4y OS: 80% vs 62%, *p*= .01	- Similar OS from relapse between maintenance vs observation
Palumbo A, 2013	389	Rd 4 cycles plus ASCT vs Rd 4 cycles plus CRD six cycles	2x2 randomized A: Len 25mg/dx21 plus pred 50mg e.o.d. until PD B: Len 25 mg/dx21 until PD	A: 2y PFS 73% *p= .03* B: 2Y PFS 56%	follow-up: 14 mo. A vs B: no differences in OS	DRAEs similar in the RP and R arms (infections 3% vs. 3%)

Len: Lenalidomide, Thal: thalidomide, PD: progression disease, Rd: Revlimid (lenalidomide) and attenuated dexametasone, CRD: cyclophosphamide dexamethasone and lenalidomide; DRAEs: Drug-related adverse events, Relapse/Progresión, ASCT: autologous stem cell transplant

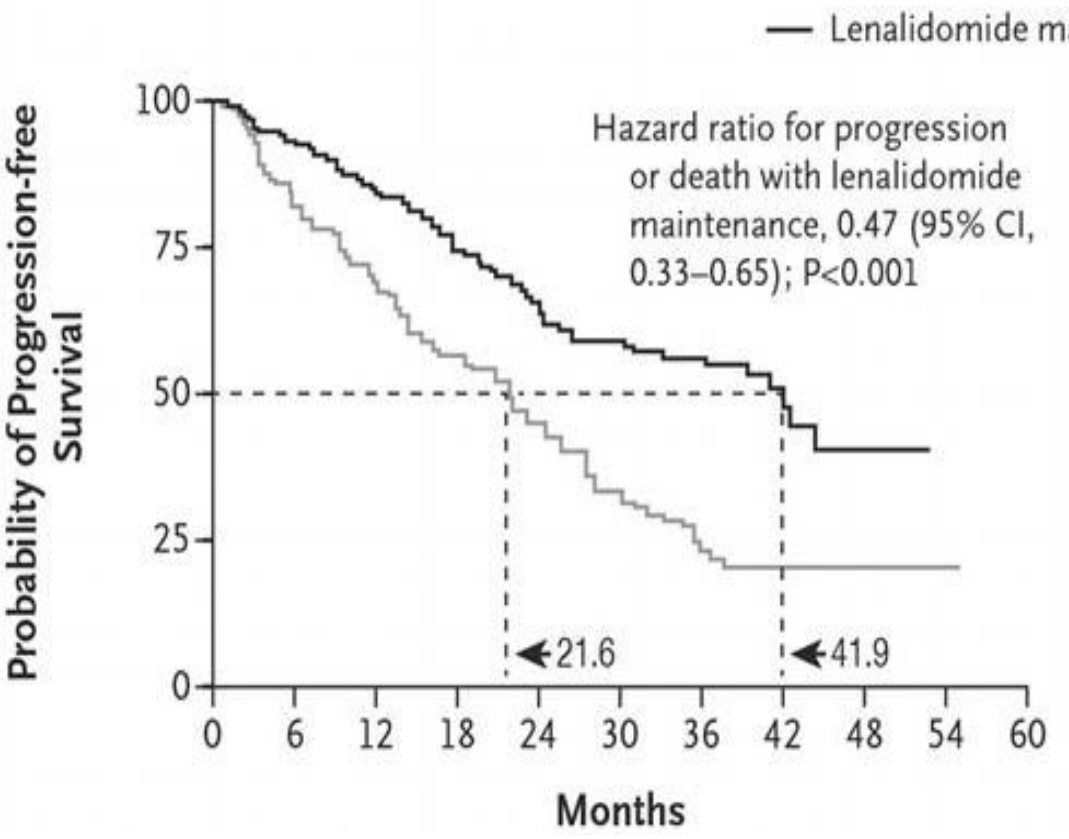
CALGB 100104: Updated OS, 12 mo. crossover

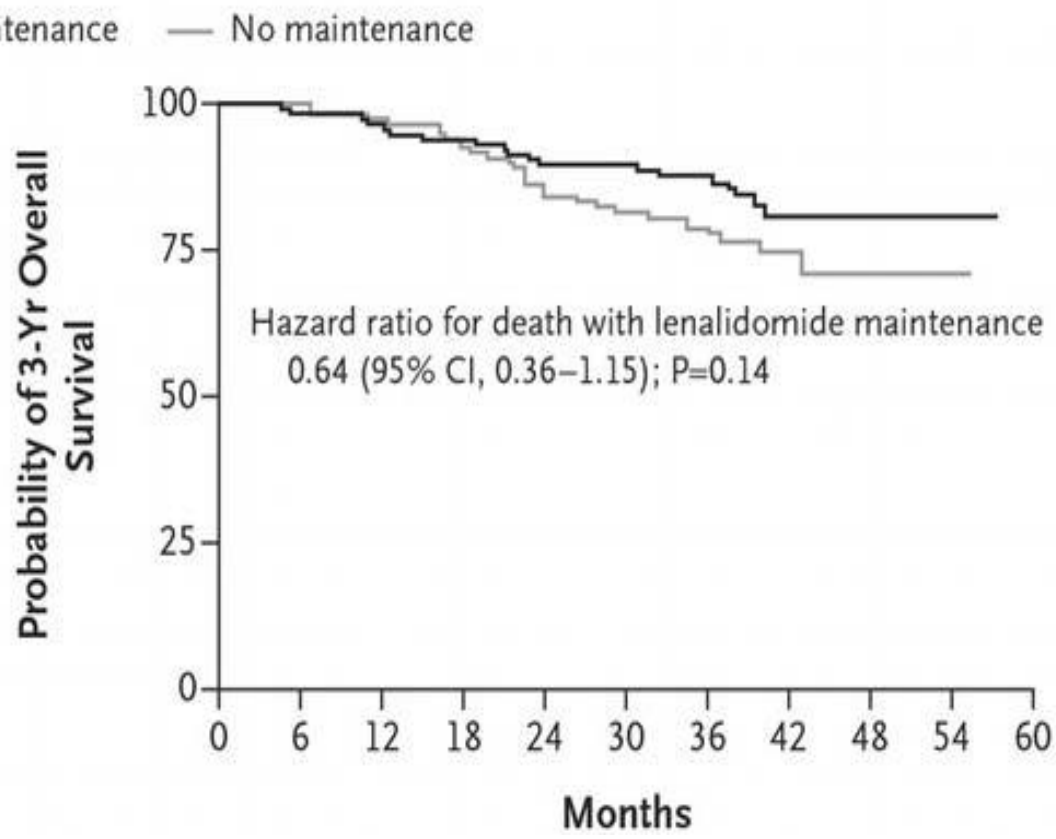


Analysis including placebo patients crossing over within 12 months of randomization on lenalidomide arm with a median follow-up of ~48 months.

McCarthy PL et al. CALGB 100104 IMW 2013 follow up to January 7, 2013

MPR vs MEL200 ± Lenalidomide Maintenance
Len Maintenance and Survival

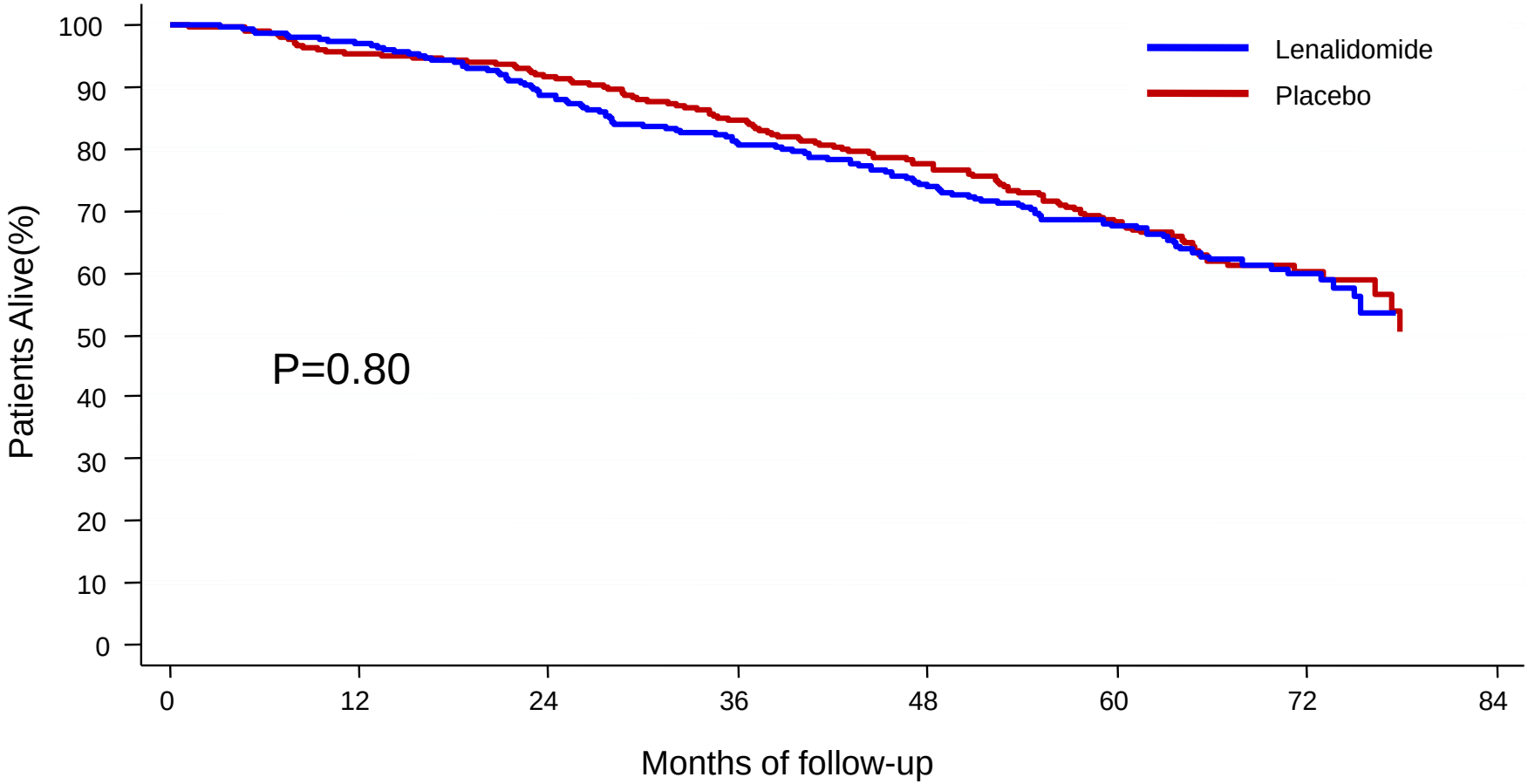




Palumbo et al. NEJM 2014;371:895-905

IFM 2005-02 : OS from randomization (Nov 2013)

(Follow-up 67 mo. Duration of maintenance: 24 mo.)

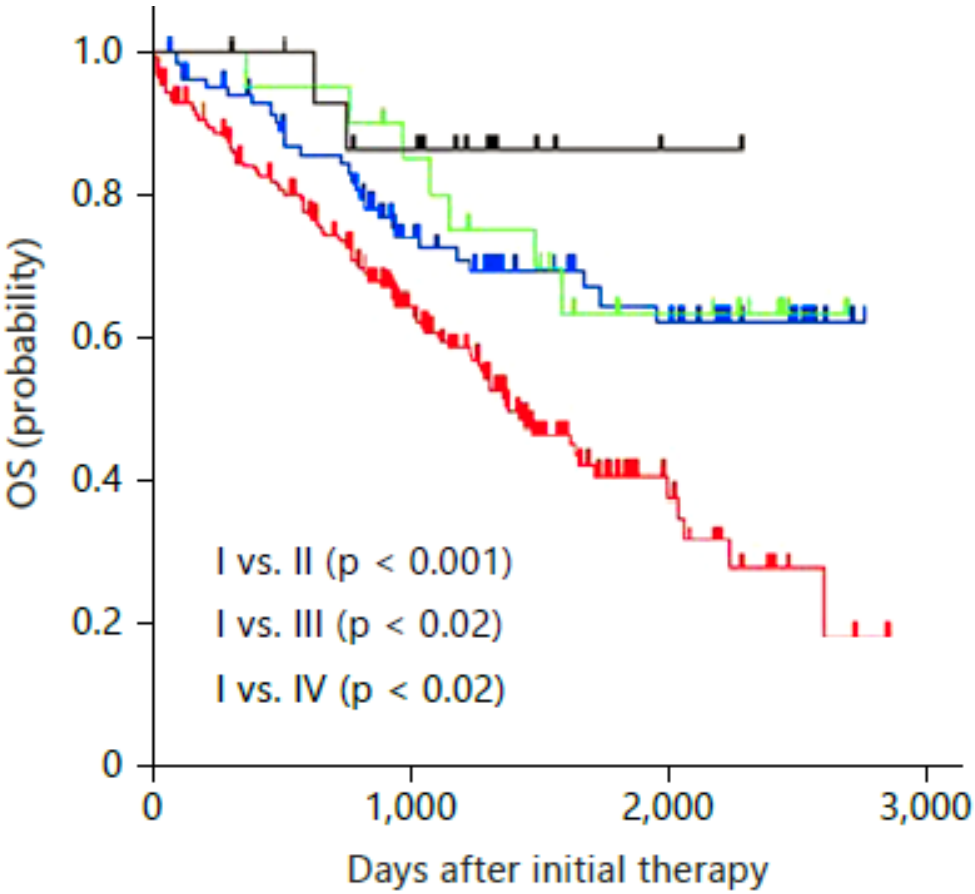


N at risk								
Lenalidomide	307	294	264	236	215	165	64	2
Placebo	307	287	276	250	227	160	52	3

Attal M et al. ASH2013#406

Elderly Patients

Survival of Multiple Myeloma Patients Aged 65–70 Years in the Era of Novel Agents and ASCT



I Chemotherapy (n = 192)
II Novel agents (n = 88)
III Chemotherapy + auto-SCT (n = 21)
IV Novel agents + auto-SCT (n = 17)

Ozaki S. Acta Haematol 2014;132:211–21

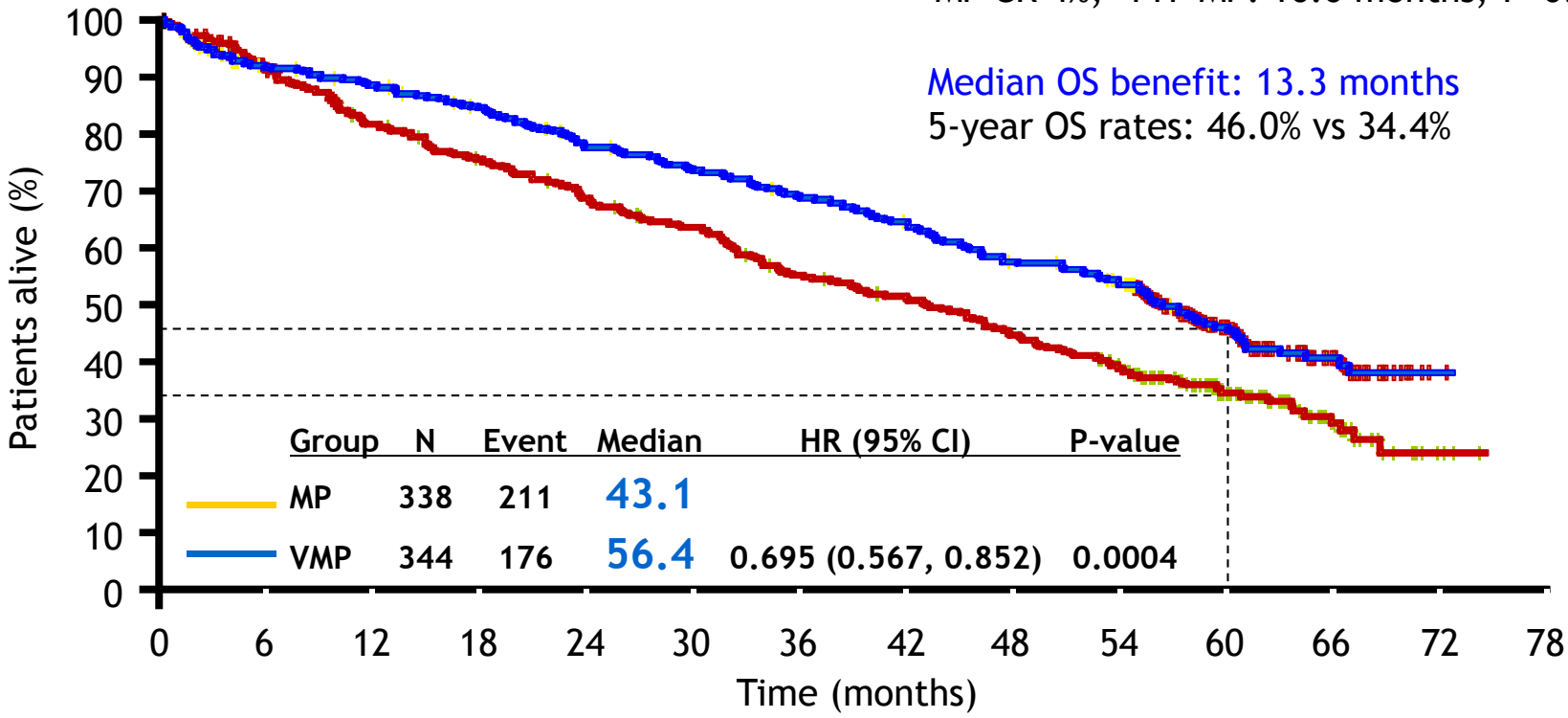
VISTA: median follow-up of 60.1 months
OS (ITT): 31% reduced risk of death with VMP

VMP CR 30%, TTP : 24.0 months

MP CR 4%, TTP MP: 16.6 months, P<0.000001

Median OS benefit: 13.3 months

5-year OS rates: 46.0% vs 34.4%



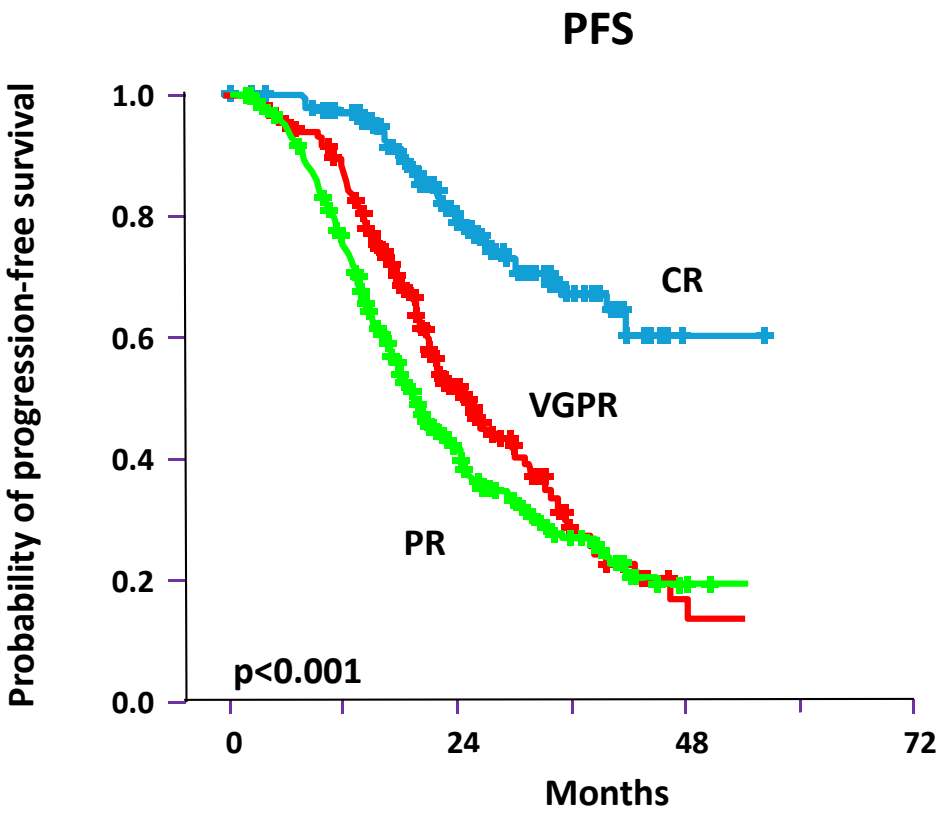
Number of patients at risk:

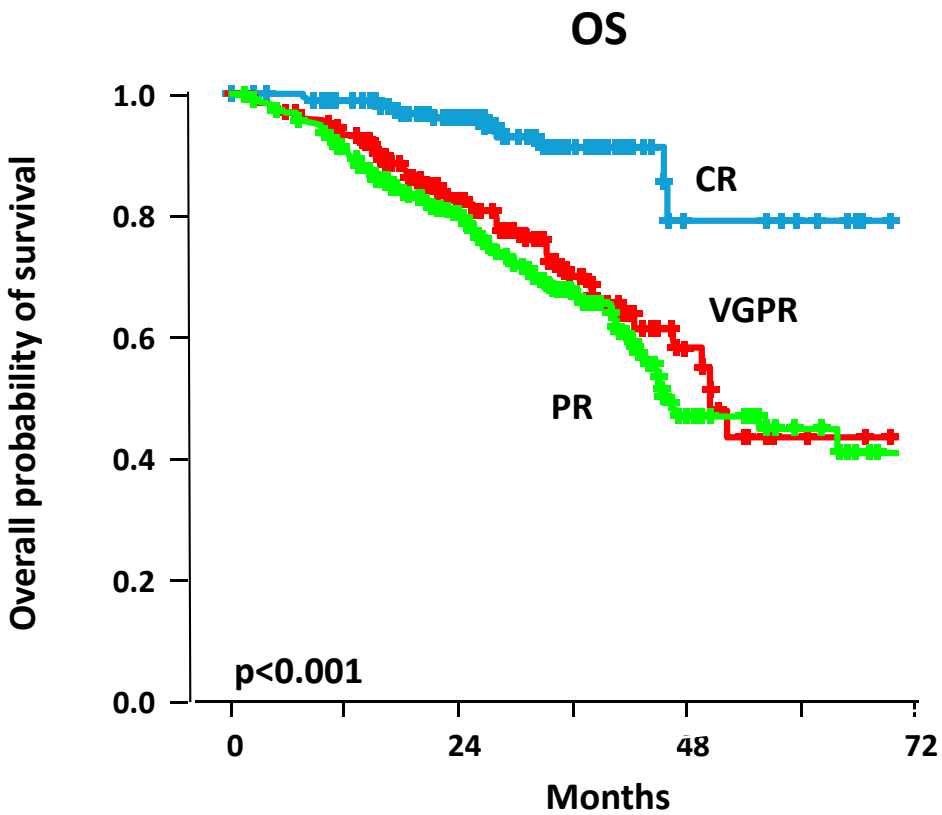
338	301	262	240	216	196	168	153	133	112	61	24	3
344	300	288	270	246	232	216	199	176	158	78	34	1

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

CR correlates with long-term PFS and OS in elderly patients treated with novel agents

- Retrospective analysis: 3 randomized European trials of GIMEMA and HOVON groups (n=1175). First-line treatment: MP (n=332), MPT (n=332), VMP (n=257), VMPT-VT (n=254)





- **Significant benefit also seen when analysis is restricted to patients >75 years old**

Gay F *et al*. Blood;117:3025-31.

Attenuated Induction and Maintenance for elderly MM patients:

All recent clinical trials include reduced-intensity induction regimens

ONCE-WEEKLY ADMINISTRATION OF BORTEZOMIB AS A STRATEGY TO IMPROVE TOLERABILITY

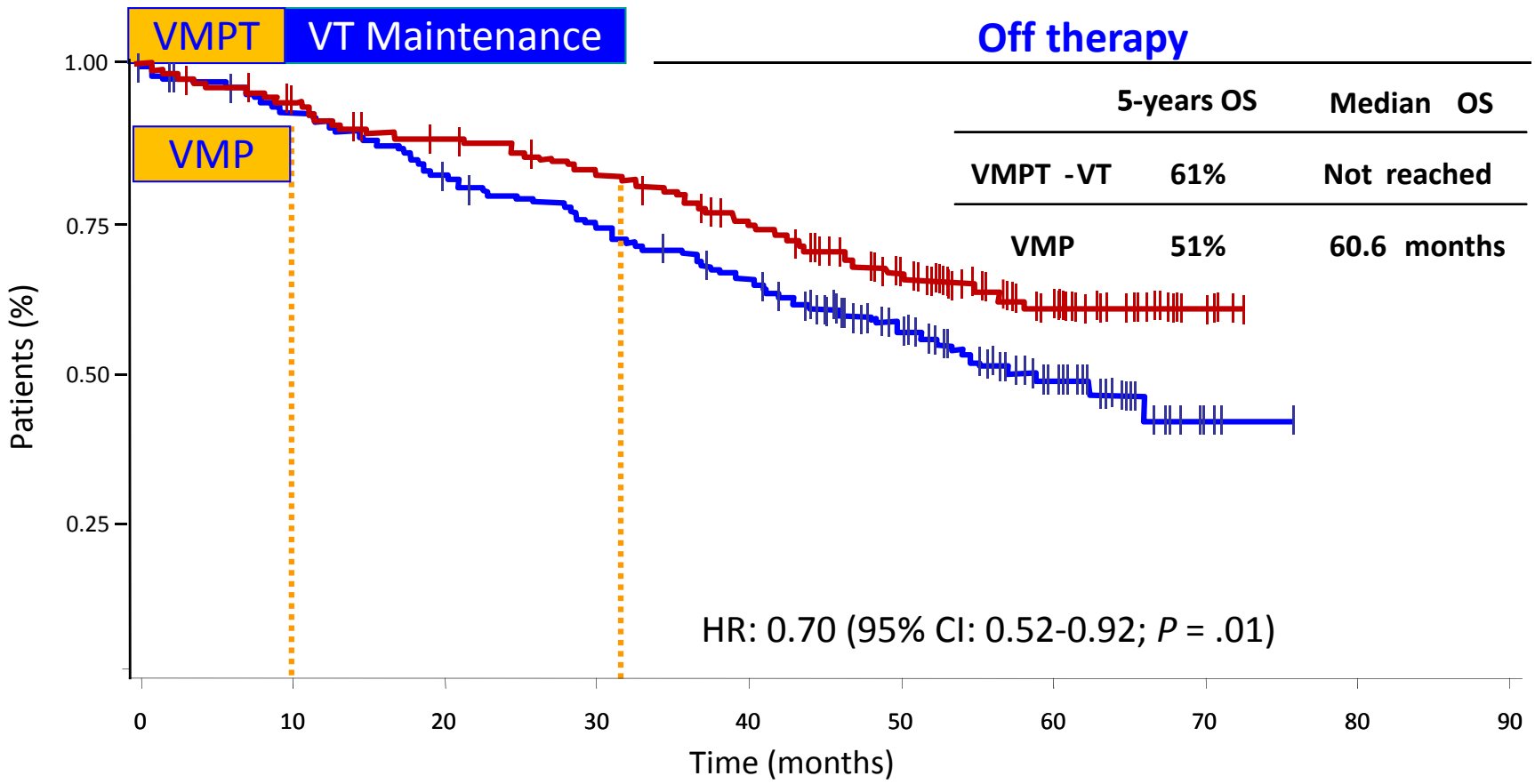
Study	Grade ¾ GI toxicity	Grade 3/4 peripheral neuropathy	Discontinuation due to AE	Planned bortezomib dose	% of the planned delivered total bortezomib dose
VISTA: VMP[1-3, 6] Bortezomib twice-weekly	20%	14%	34%	67.6 mg/m^2	57%
GIMEMA[4, 6] Bortezomib once-weekly		5%	17%	46.8 mg/m^2	86%
PETHEMA/GEM[5, 6] Bortezomib once-weekly	7%	7%	12%†	36.4 mg/m^2	90%

†Discontinuations due to SAEs

1. San Miguel et al. NEJM 2008;359:906. 2. San Miguel et al. NEJM 2008;359:906; Supplementary Appendix. 3. Mateos et al. J Clin Oncol 2010; 28: 2259-66. 4. Palumbo et al. J Clin Oncol 2010;28:5101-9. 5. Mateos et al. Lancet Oncol 2010;11:934-41. 6 Mateos MV. Haematologica 2014 [Epub]

GIMEMA: VMP vs. VMPT-VT (>65 years MM)

Median Follow-up: 54 monts. OS: 30% Reduced Risk of Death

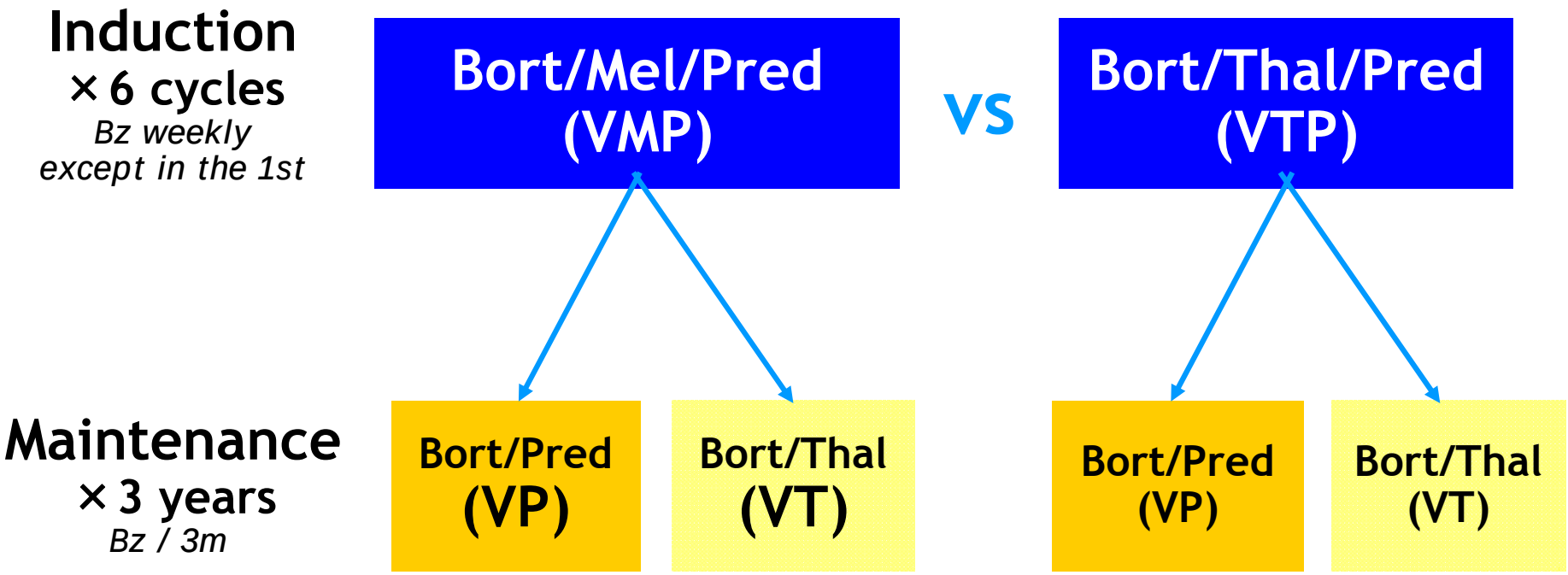


	5-years OS	Median OS
VMPT -VT	61%	Not reached
VMP	51%	60.6 months

5y PFS: VMPT-VT 29% VT 13% (P<0.0001)

Palumbo A. ASH2012#200 & J Clin Oncol. 2014;32:634-40

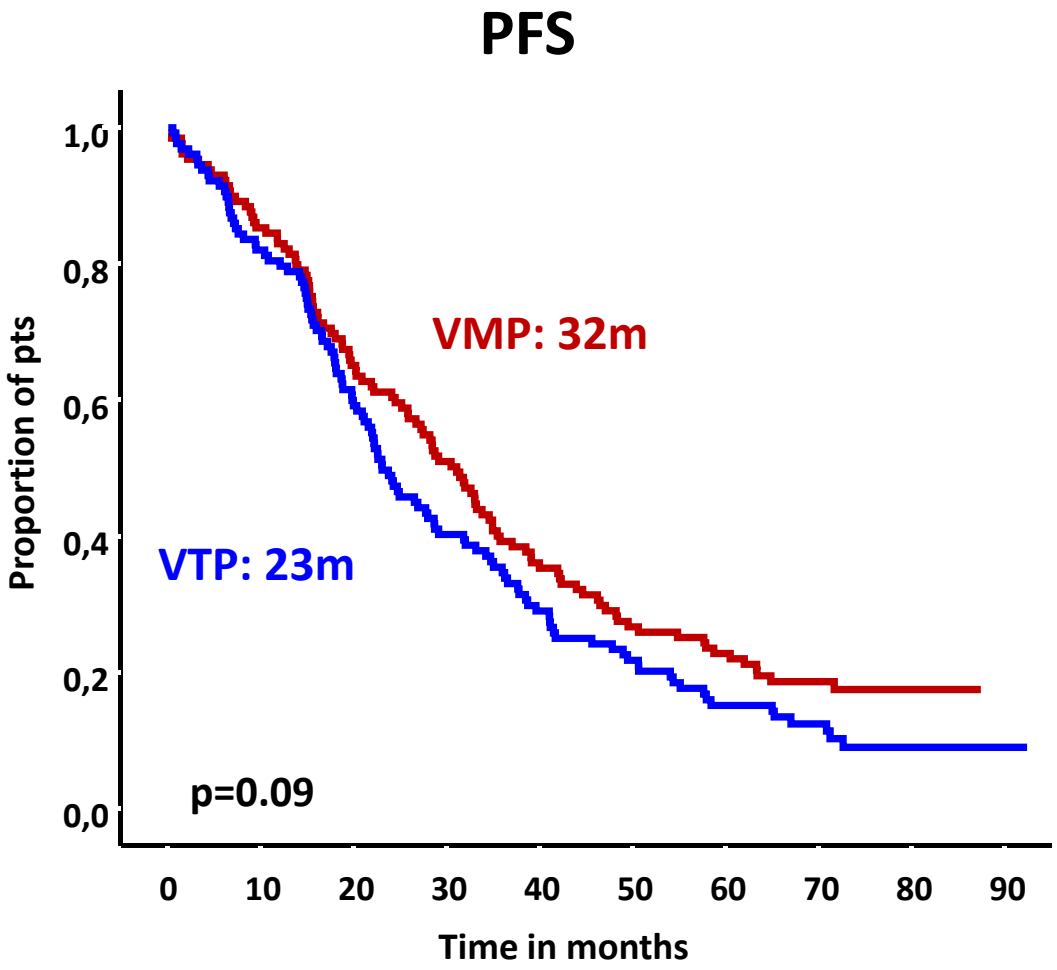
Bortezomib: Weekly Induction Followed by Maintenance in Newly Diagnosed Older MM Patients PETHEMA/GEM 05 >65y Study

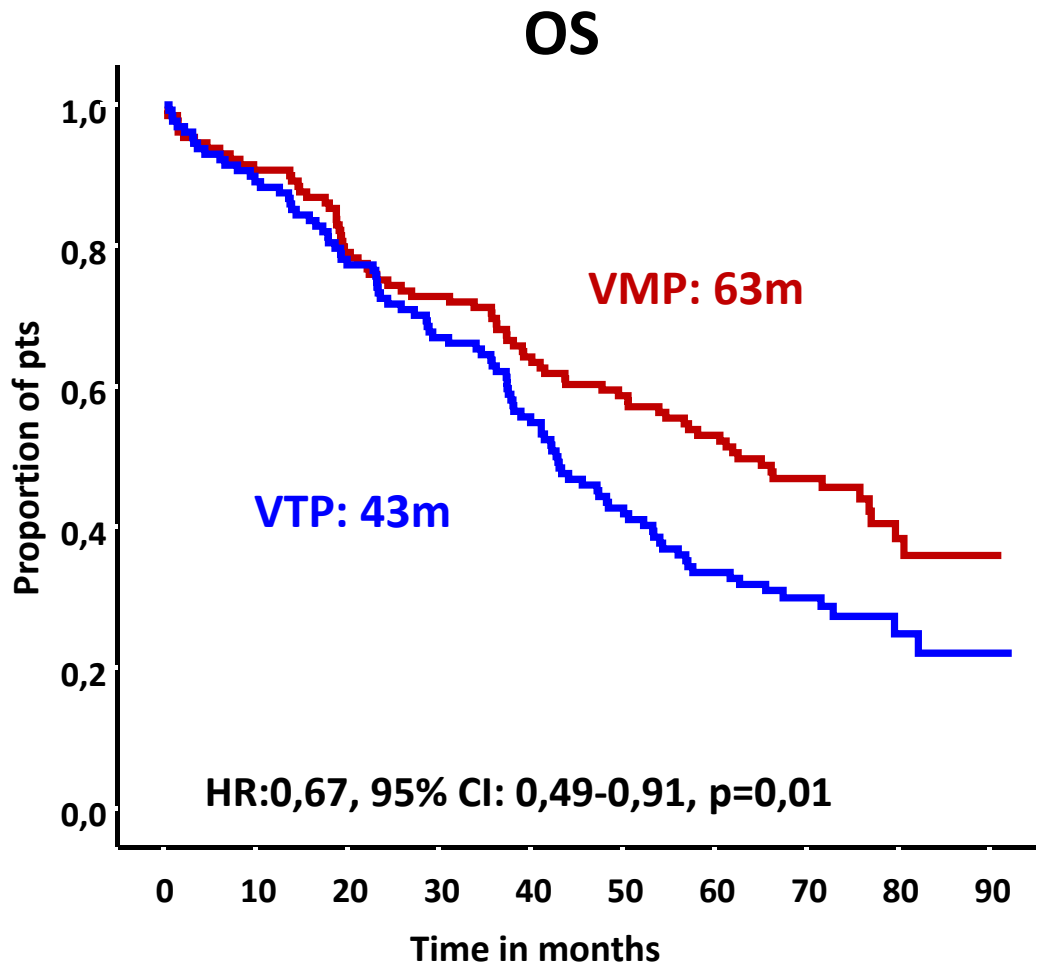


Mateos MV et al. *Lancet Oncol 2010*

Outcome of the whole series of patients according to the induction (n:260)

Median f/u: 72 m (6yrs)



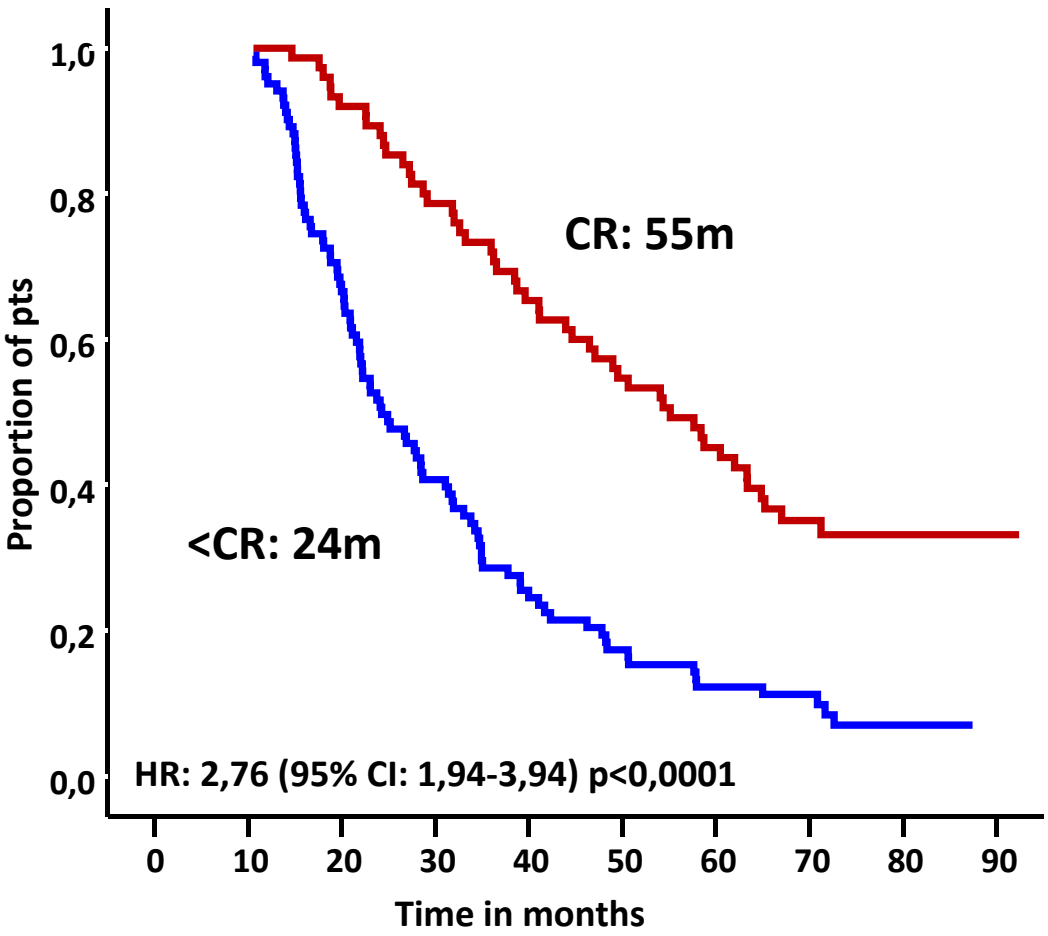


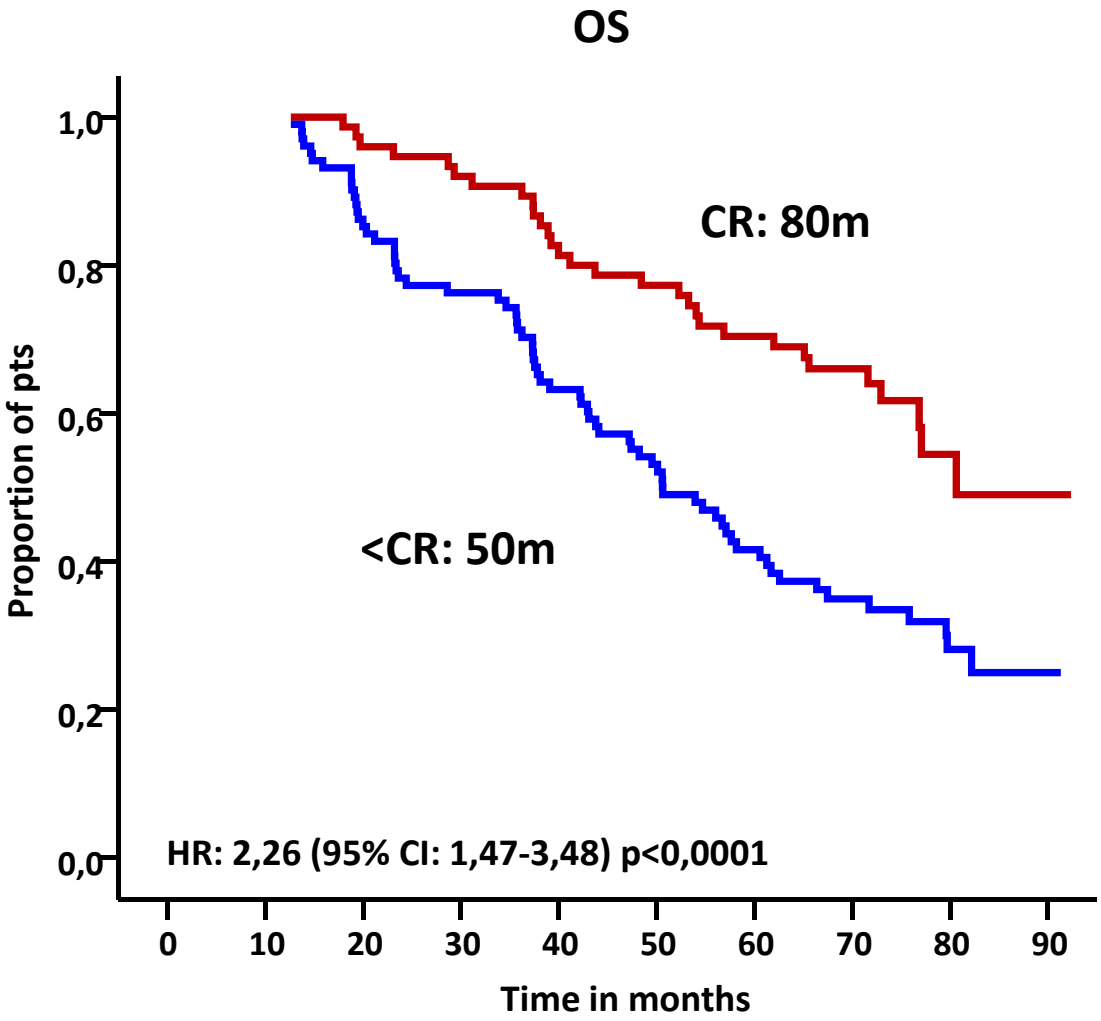
VT or VP as maintenance *did not influence the outcome of both induction groups*

Mateos MV. Blood 2014

Impact of response in the whole series of patients (n:260)

Median f/u: 72 m (6yrs)





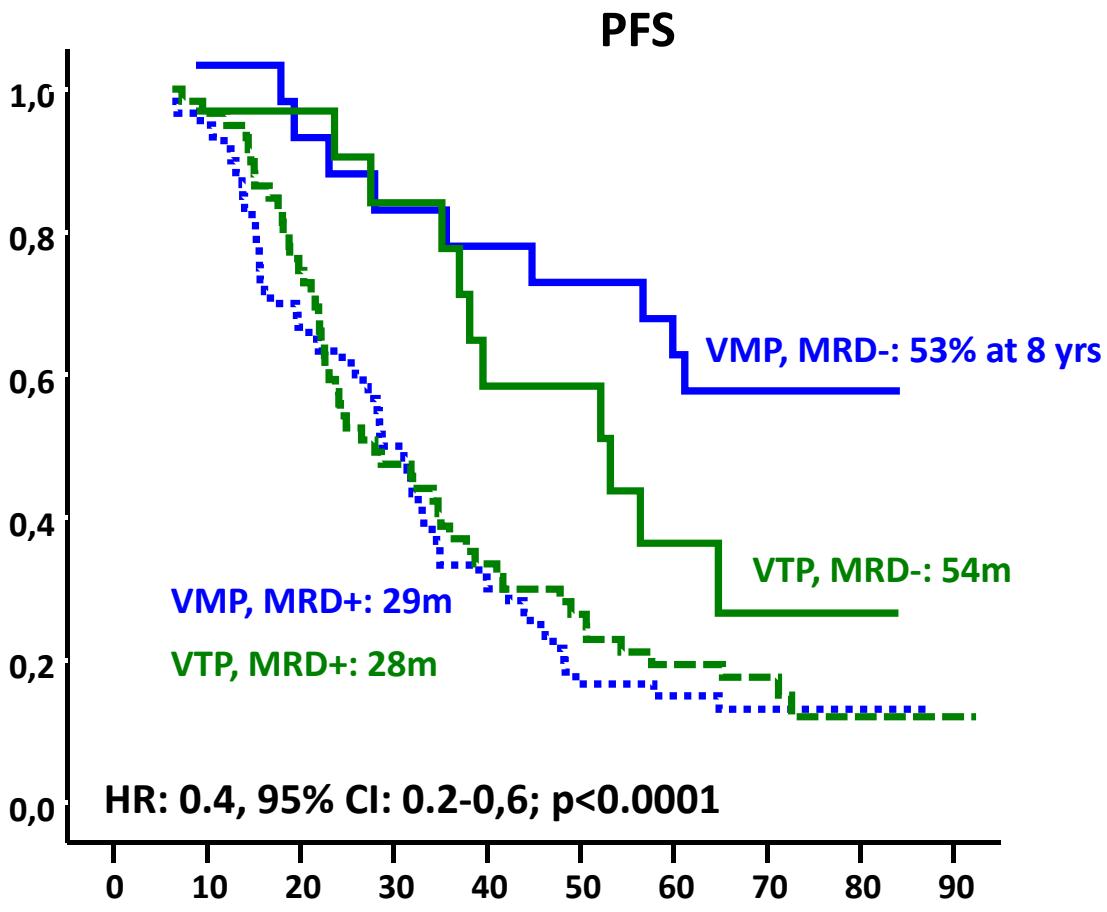
The benefit of CR was more evident for VMP than VTP arm

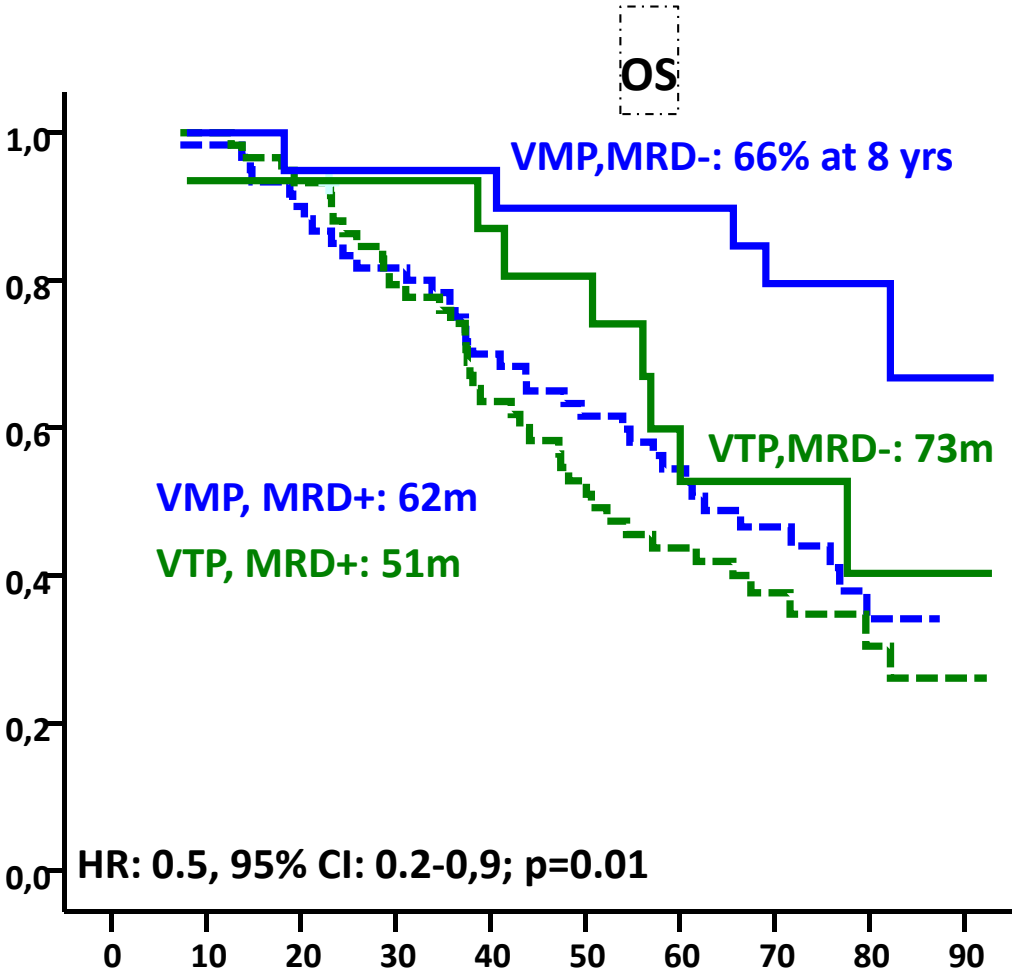
Mateos MV. Blood 2014

Does VMP induce more profound responses than VTP?

Median follow-up: 72 m (6 yrs)

CR rate: VMP (20%)→ 70% were flow- CR. VTP (27%)→ 45% were flow- CR

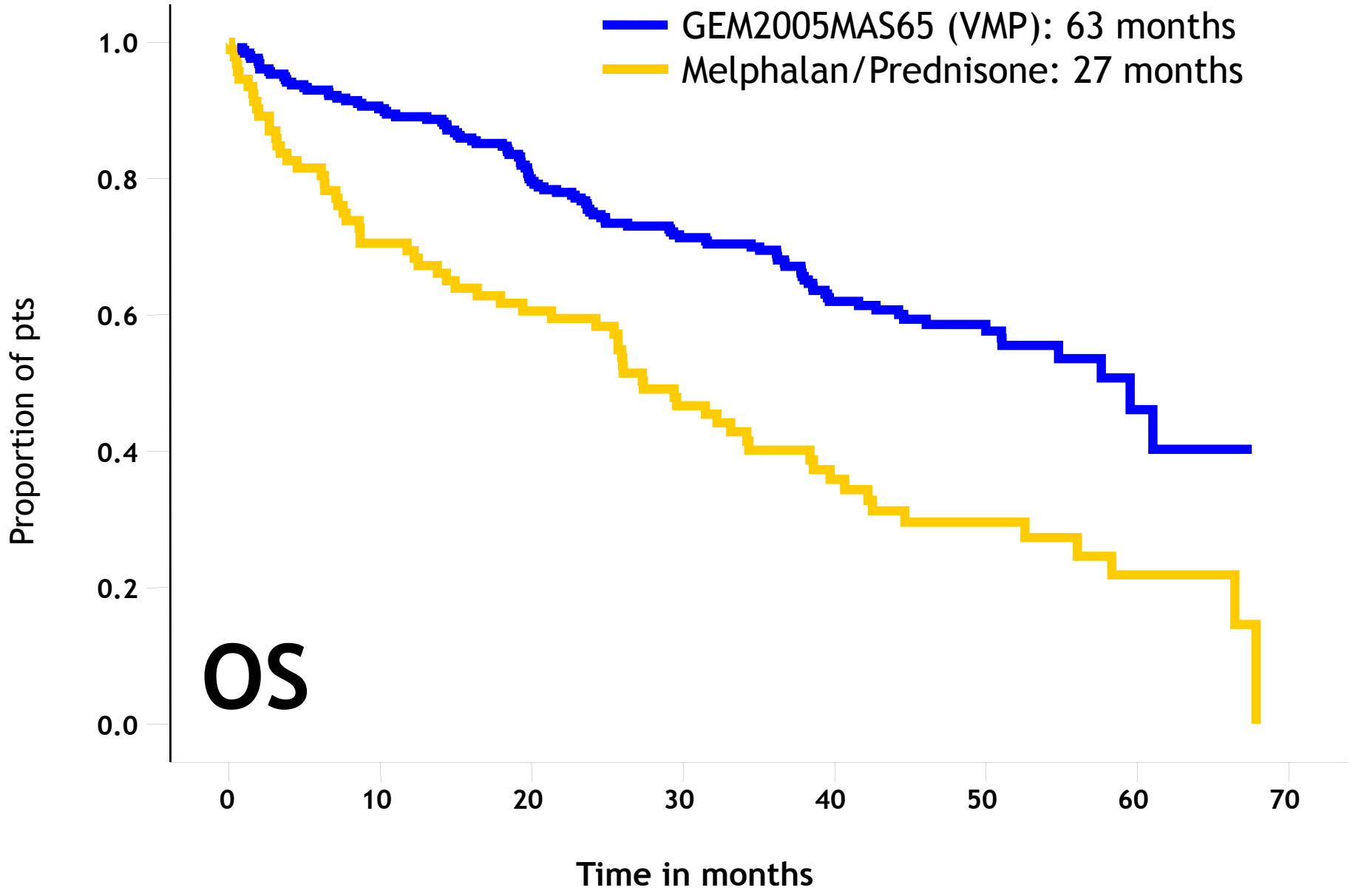




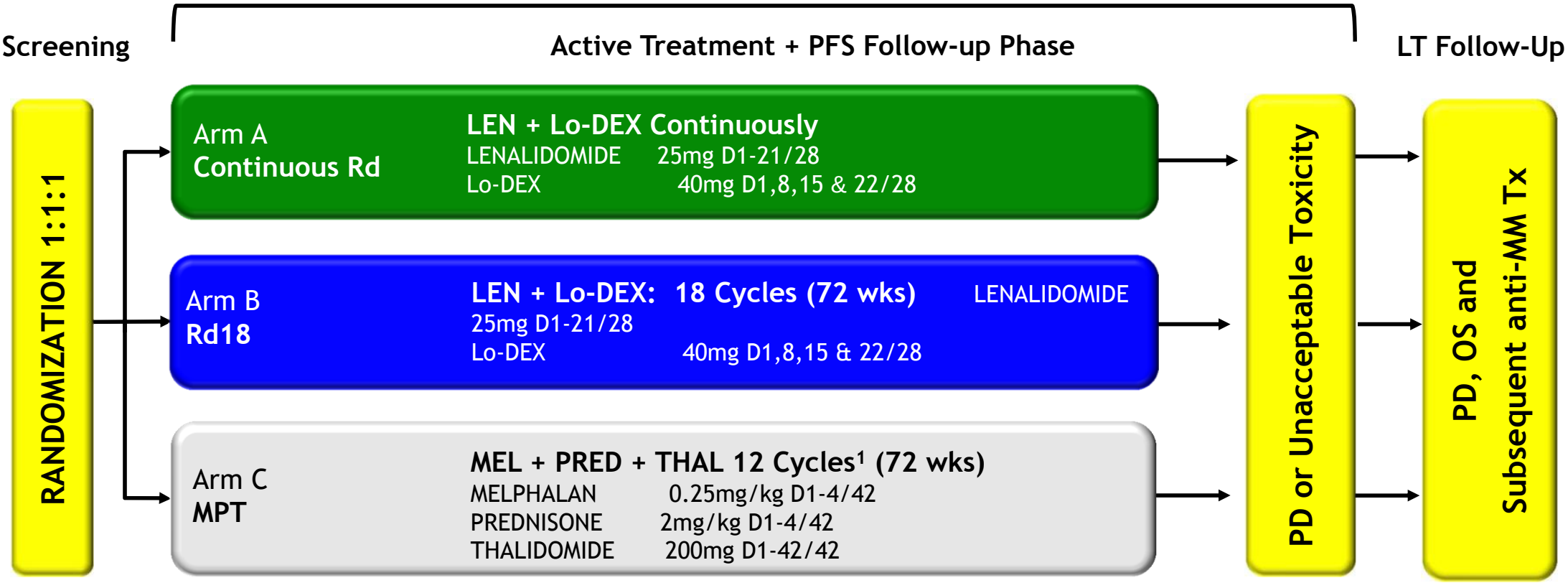
VMP induces more profound responses

Mateos MV. Blood 2014

GEM05mas65 vs. MM-PETHEMA 96



FIRST Trial: Study Design (n= 1623)



Pts > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL[2] (100 mg D1-42/42); MEL[2] 0.2 mg/kg D1–4

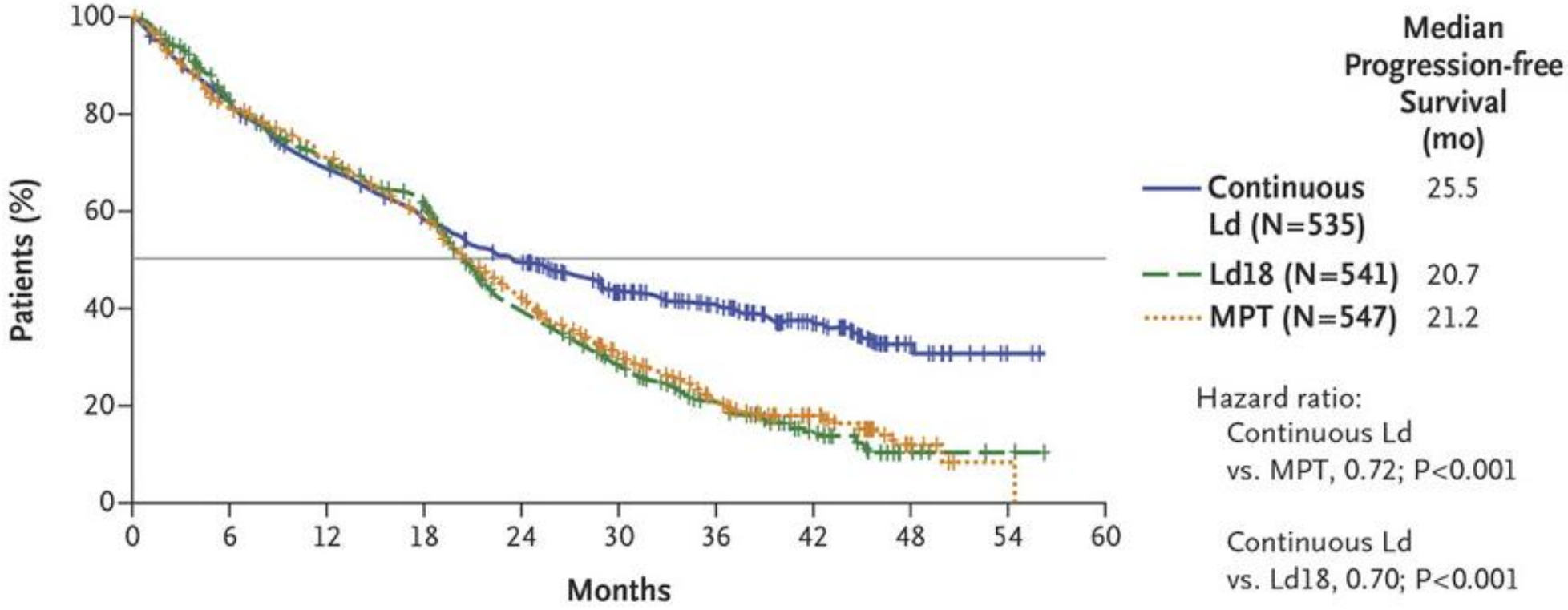
- Stratification: age, country and ISS stage

ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

[1]Facon T, et al. Lancet 2007;370:1209-18; [2]Hulin C, et al. JCO. 2009;27:3664-70.

Facon T, et al. Continuous Lenalidomide and Low-dose Dexamethasone Demonstrates a Significant PFS and OS Advantage in Transplant Ineligible NDMM Patients – The FIRST Trial: MM-020/IFM 0701. *Plenary presentation at: American Society of Hematology*. 2013; December 7-10; New Orleans, LA.

FIRST Trial: Final Progression-free Survival

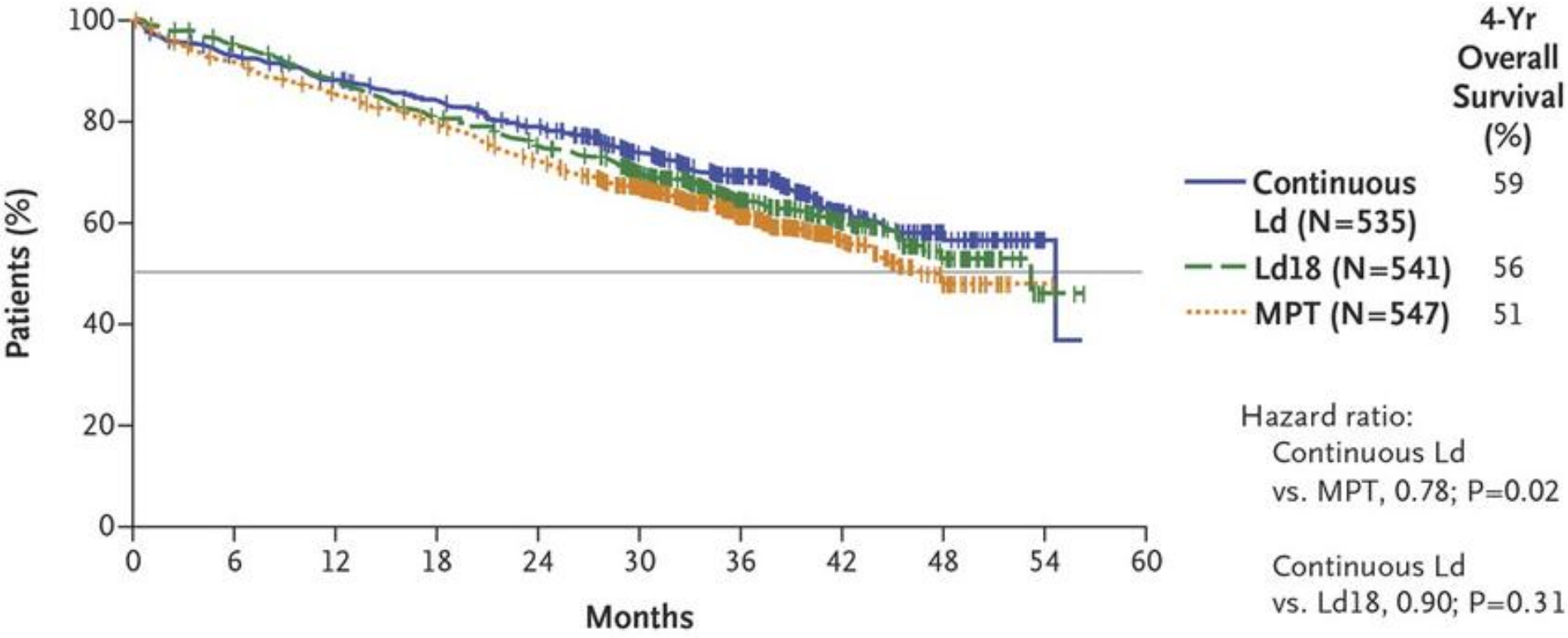


No. at Risk

Continuous Ld	535	400	319	265	218	168	105	55	19	2	0
Ld18	541	391	319	265	167	108	56	30	7	2	0
MPT	547	380	304	244	170	116	58	28	6	1	0

Facon T et al. N Engl J Med 2014; 371:906-917

FIRST Trial: Overall Survival

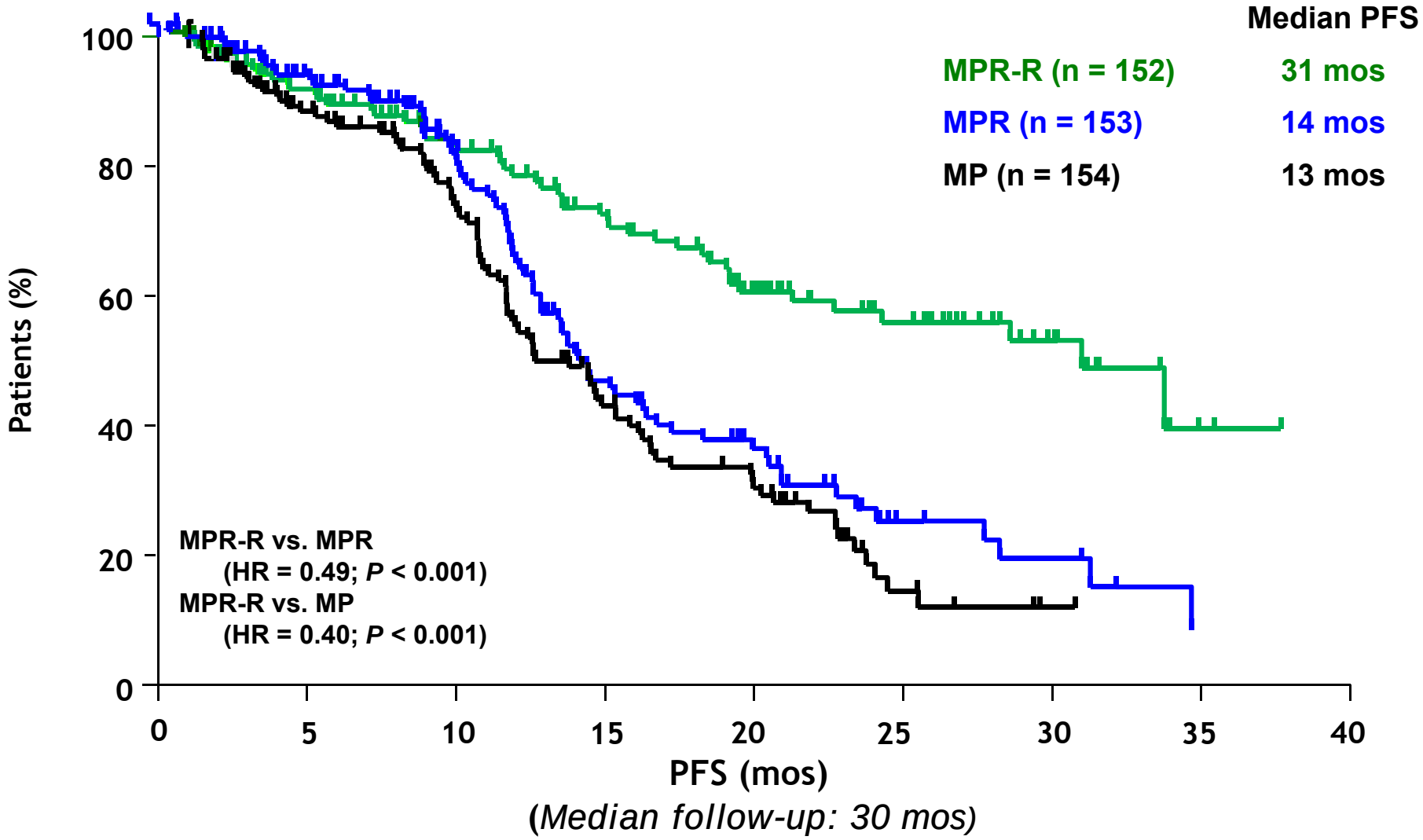


No. at Risk											
Continuous Ld	535	488	457	433	403	338	224	121	43	5	0
Ld18	541	505	465	425	393	324	209	124	44	6	0
MPT	547	484	448	418	375	312	205	106	30	3	0

Facon T et al. N Engl J Med 2014; 371:906-917

MM-015: Progression-Free Survival

(as published in NEJM)[1]

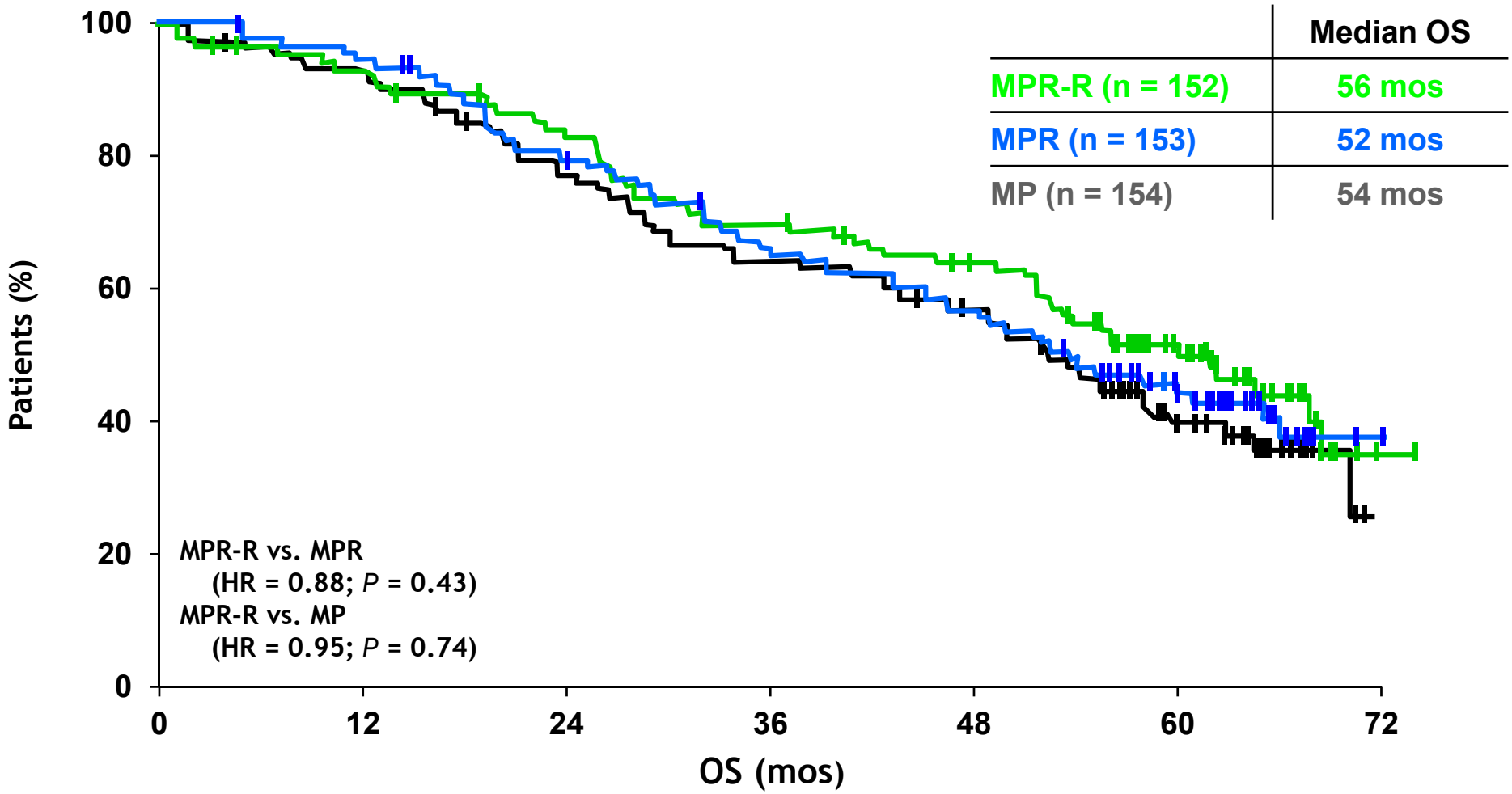


HR, hazard ratio; mos, months; MP, melphalan, prednisone, and placebo followed by placebo maintenance; MPR, melphalan, prednisone, and lenalidomide followed by placebo maintenance; MPR-R, melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance.

Dimopoulos MA et al. PFS2 in Elderly Patients With Newly Diagnosed Multiple Myeloma: Results From the MM-015 Study. Oral presentation at the 55th Annual Meeting of the American Society of Hematology (ASH). 2013; December 7-10; New Orleans, LA, USA

MM-015: Updated Overall Survival

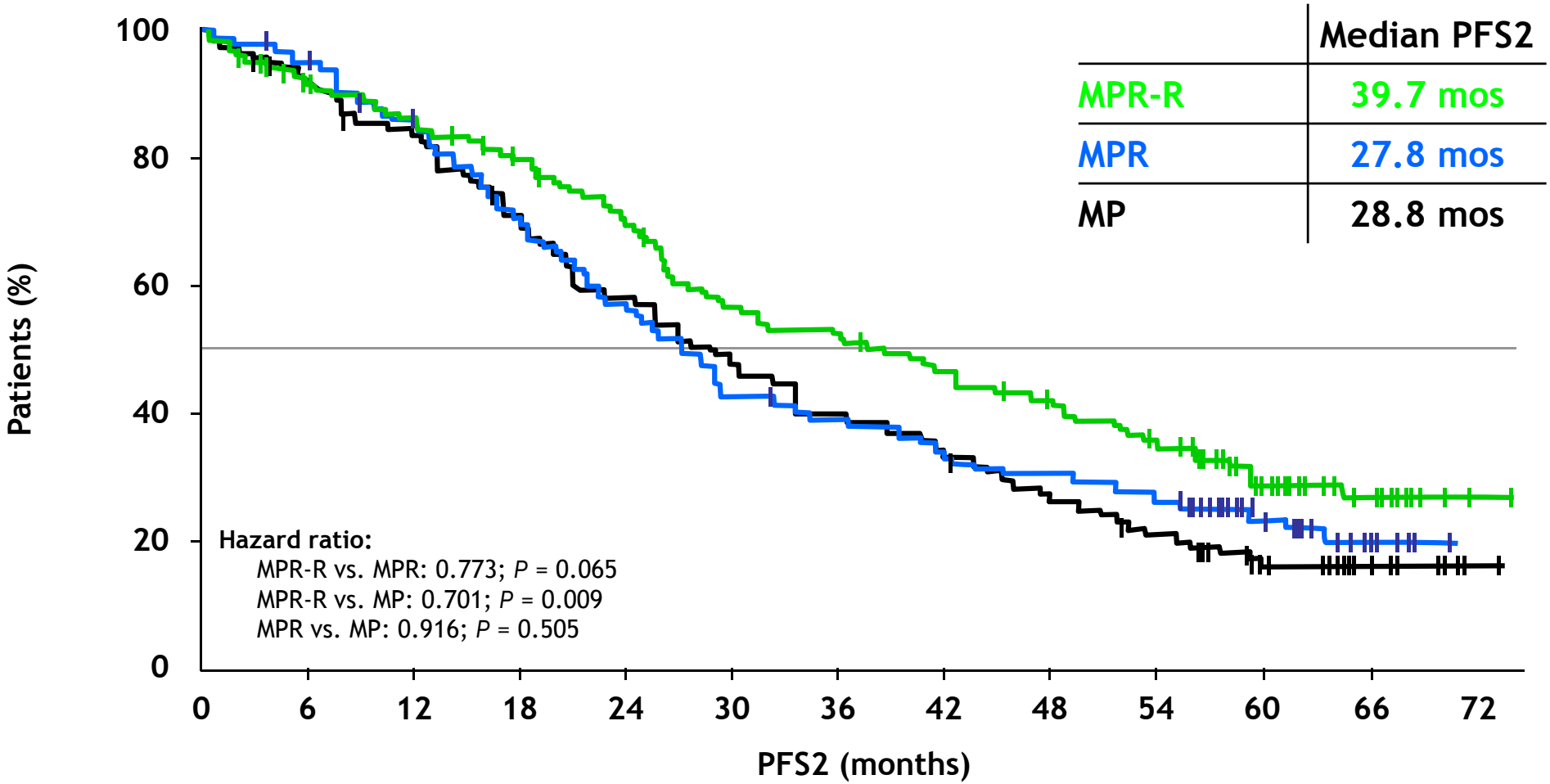
245 deaths (53% of ITT)



(April 2013 – median follow-up 62 mos)

Dimopoulos MA et al. PFS2 in Elderly Patients With Newly Diagnosed Multiple Myeloma: Results From the MM-015 Study. Oral presentation at the 55th Annual Meeting of the American Society of Hematology (ASH). 2013; December 7-10; New Orleans, LA, USA

MM-015: PFS2 by Treatment Group



Dimopoulos MA et al. PFS2 in Elderly Patients With Newly Diagnosed Multiple Myeloma: Results From the MM-015 Study. Oral presentation at the 55th Annual Meeting of the American Society of Hematology (ASH). 2013; December 7-10; New Orleans, LA, USA

MM-015 Trial: Effect of Lenalidomide-based Therapy on Health-related Quality of Life

- Patients receiving lenalidomide maintenance had the most pronounced improvements: Global Health Status/Quality of Life [$P<0.05$], Physical Functioning [$P<0.01$], and Side Effects of Treatment [$P<0.05$] out of six pre-selected health-related quality of life domains (Global QoL, Physical Functioning, Fatigue, and Pain from QLQ-C30, and Disease Symptoms, and Side Effects of Treatment from QLQ-MY20)

- Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance improves health-related quality of life in patients with newly diagnosed multiple myeloma.

Dimopoulous MA et al. Haematologica 2013 May;98(5):784-8

RRMM

Bortezomib and Lenalidomide

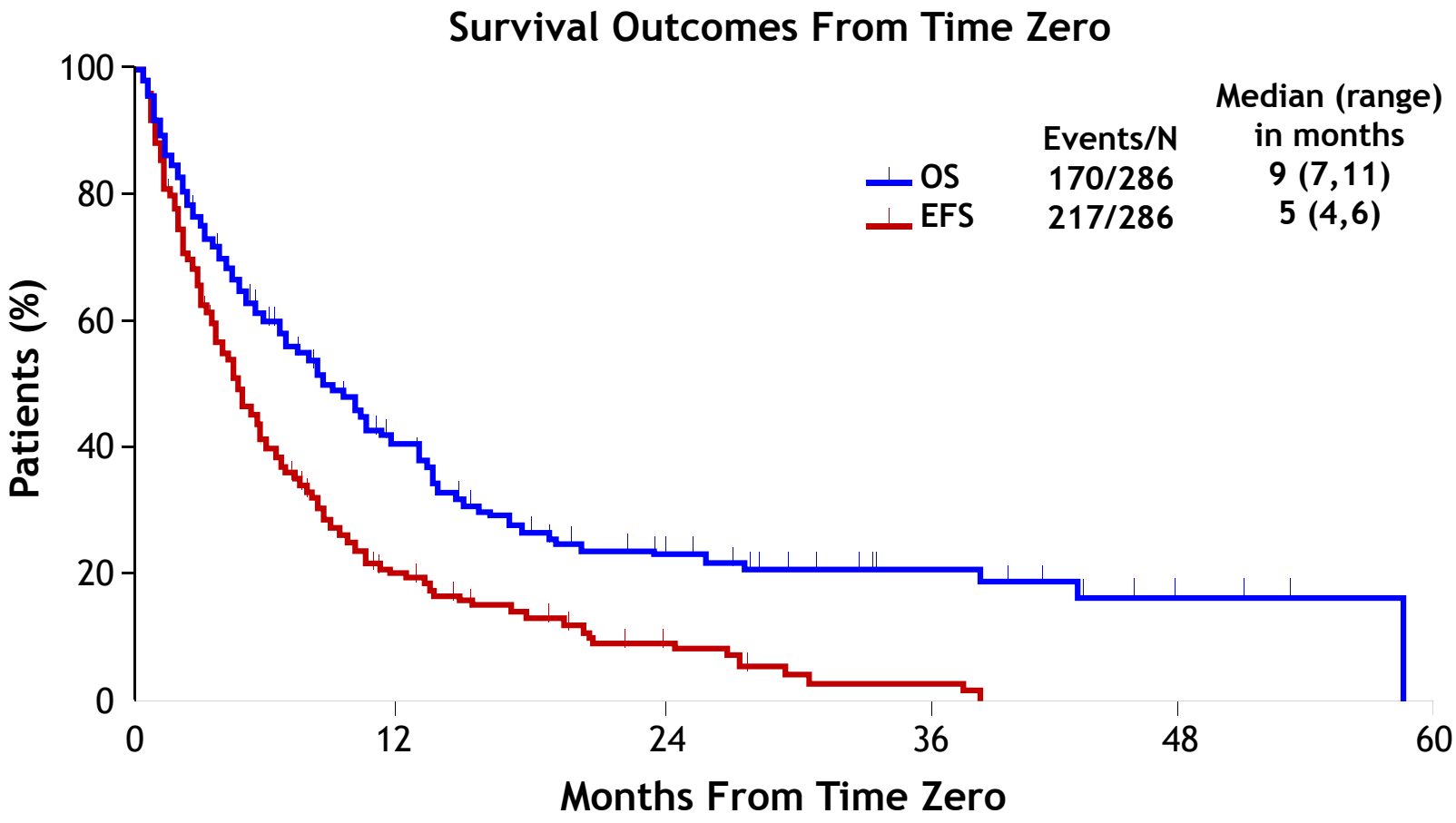
Consolidated Data in RRMM

Regimen	Trial	ORR, %	CR/nCR, %	> VGPR, %	DOR, months	TTP or PFS, months	Median OS, months
Len + Dex	MM-009[1]	61	24	NE	16	11	35[5]
Len + Dex	MM-010[2]	60	25	NE	17	11	35
Bortezomib	APEX[3]	38	13	NE	8	6	29.8
B/Dox	MMY 3001[4]	44	13	27	10	9	NE

1. Weber DM, et al. N Engl J Med. 2007;357:2133-42. 2. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
3. Richardson PG, et al. N Engl J Med. 2005;352:2487-98 and Blood 2007. 4. Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-901.

After IMiDs and Bortezomib

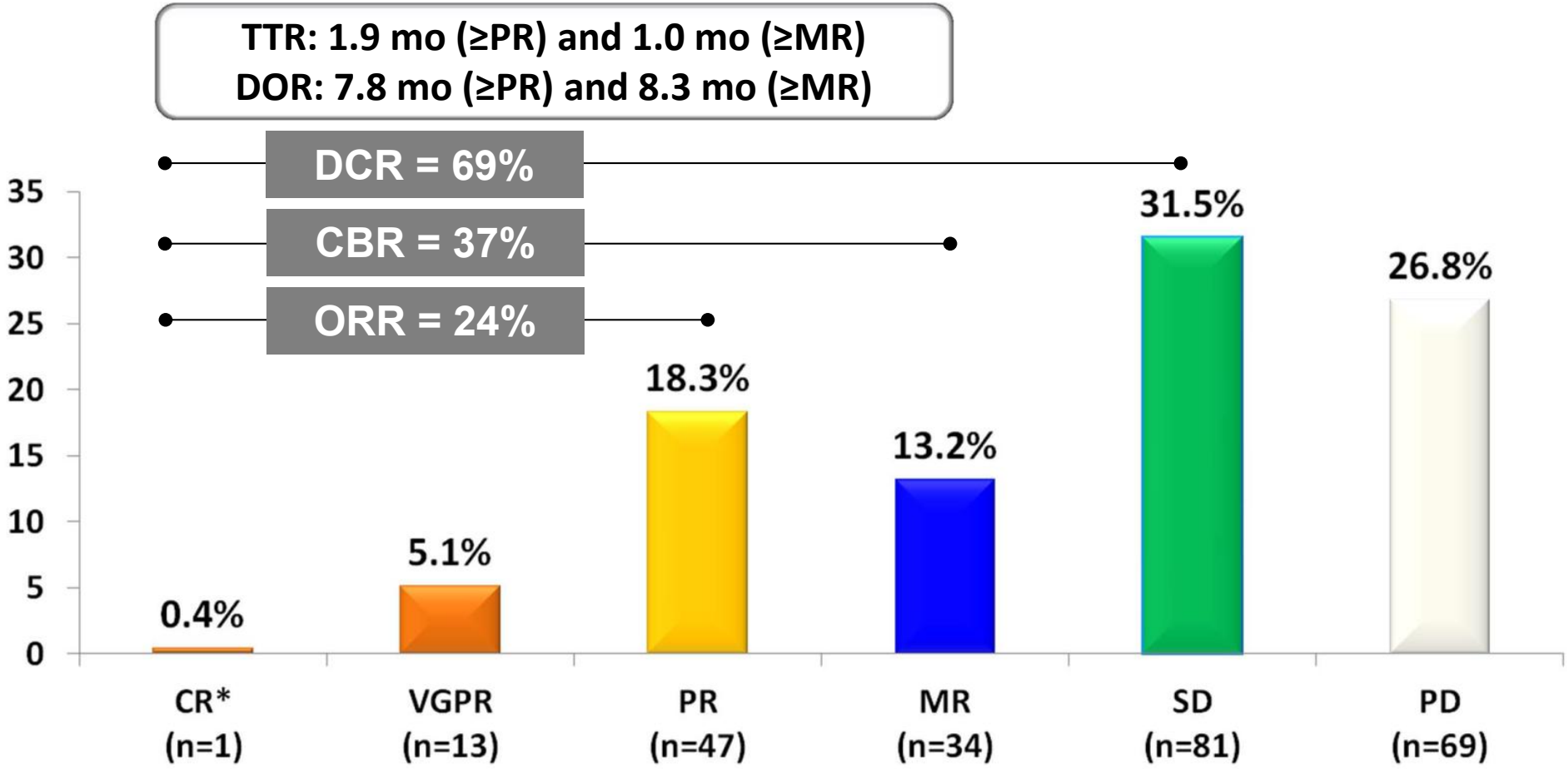
MMRR patients refractory to bortezomib and refractory, intolerant or ineligible (in the opinion of the treating physician) to receive treatment with an IMiD



Kumar SK. *Leukemia*. 2012; 26:149-57.

Carfilzomib: Single-Agent Anti-tumor Activity

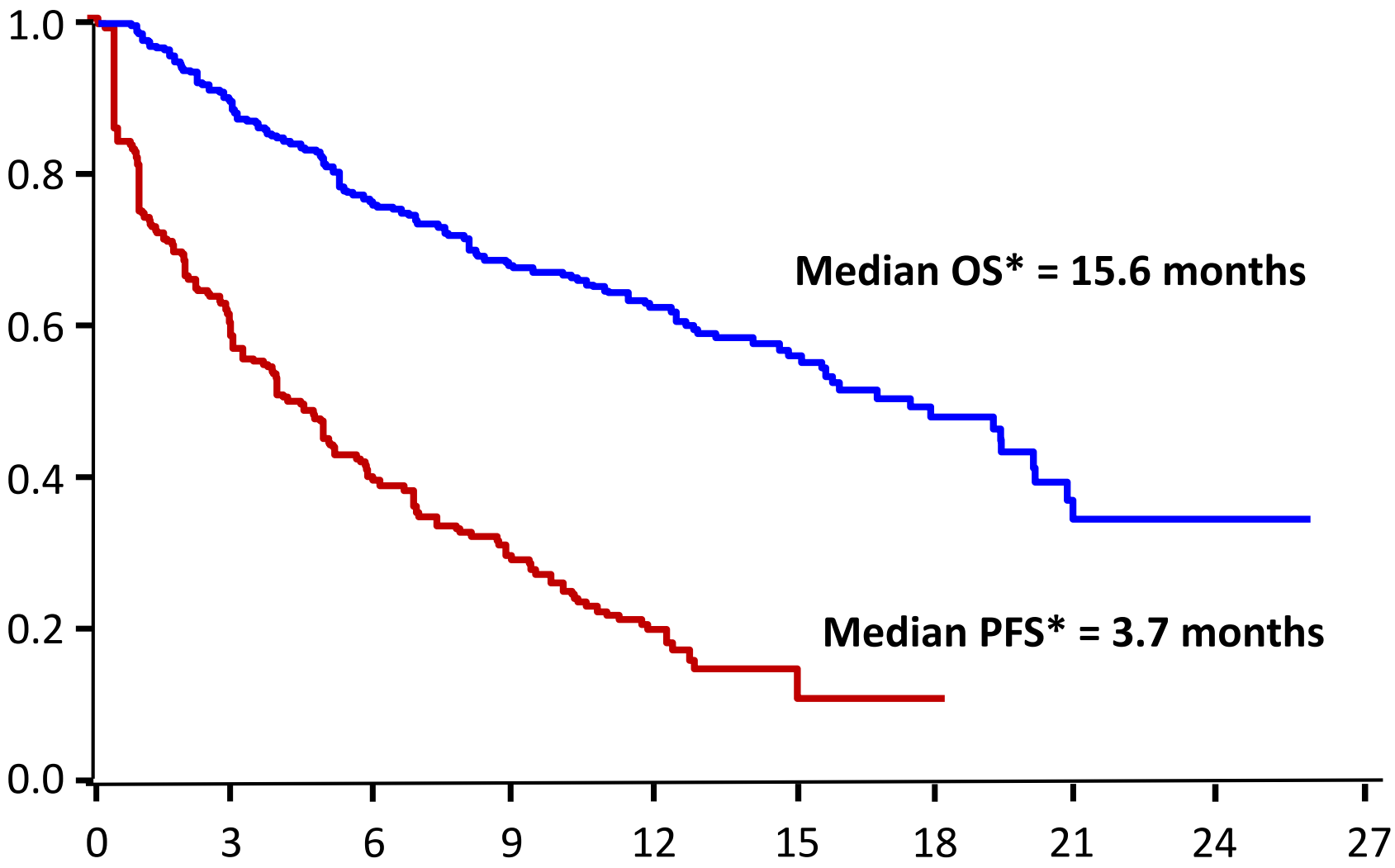
response-evaluable population (N=257†)



Subset analyses of higher risk populations showed similar response rates
(e.g., unfavorable cytogenetics, baseline peripheral neuropathy)

Siegel D, et al. *Blood*. 2012; 120:2817-25; Siegel D, et al. ASCO 2011. Abstract 8027 (poster presentation); Wang M, et al. ASH 2011. Abstract

Carfilzomib: PFS and OS in response-evaluable population (n=257)

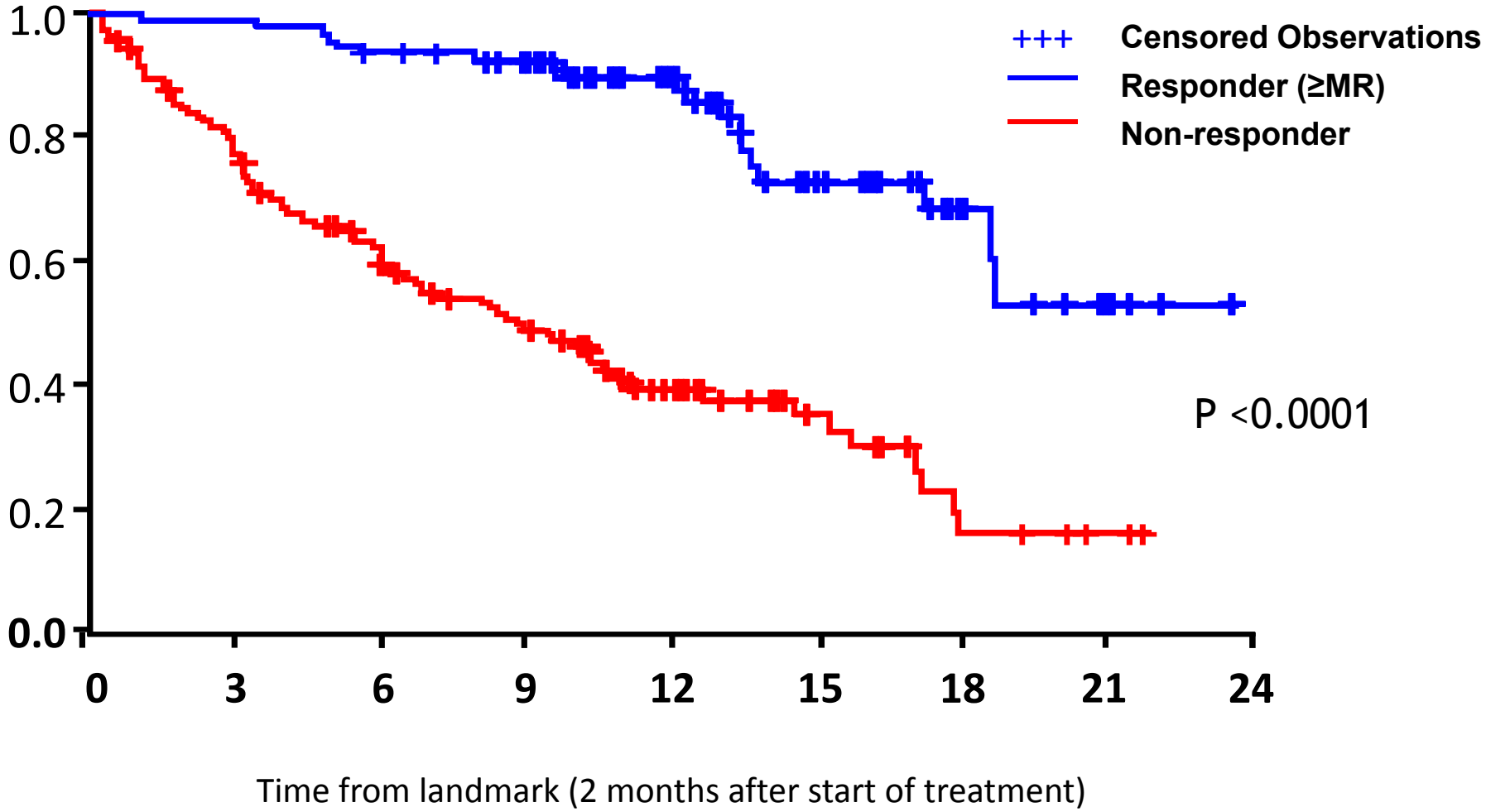


Siegel D, et al. *Blood*. 2012; 120:2817-25

Carfilzomib: Single-Agent Anti-tumor Activity

response-evaluable population (N=257†)

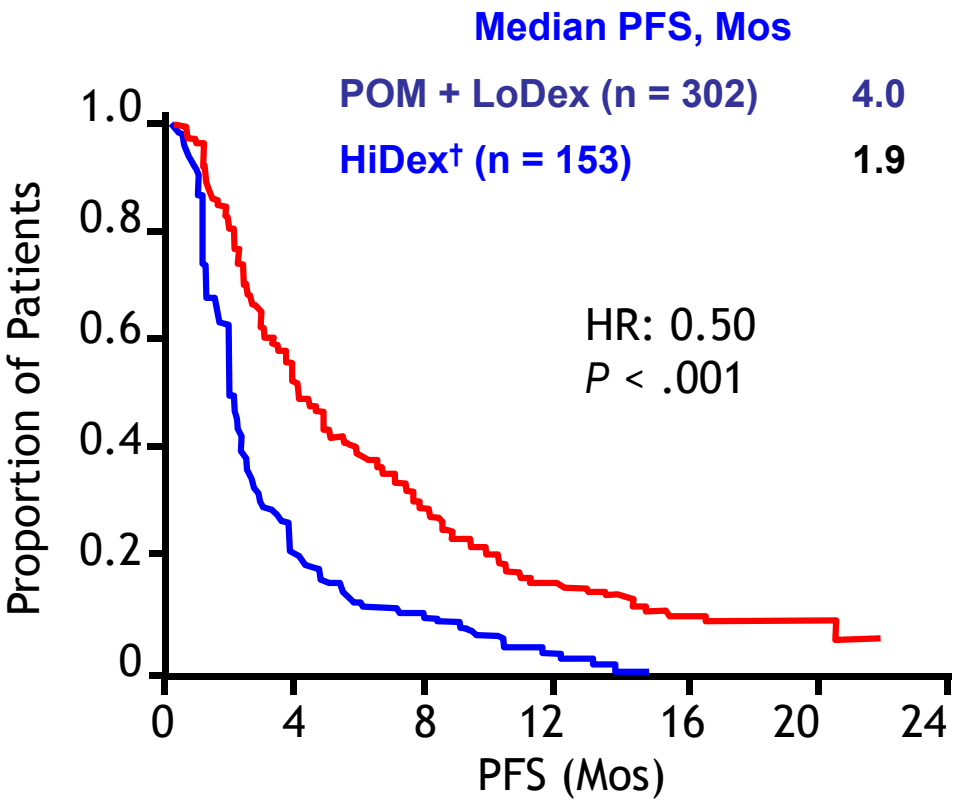
Landmark Analysis of OS: Responders vs Non-Responders

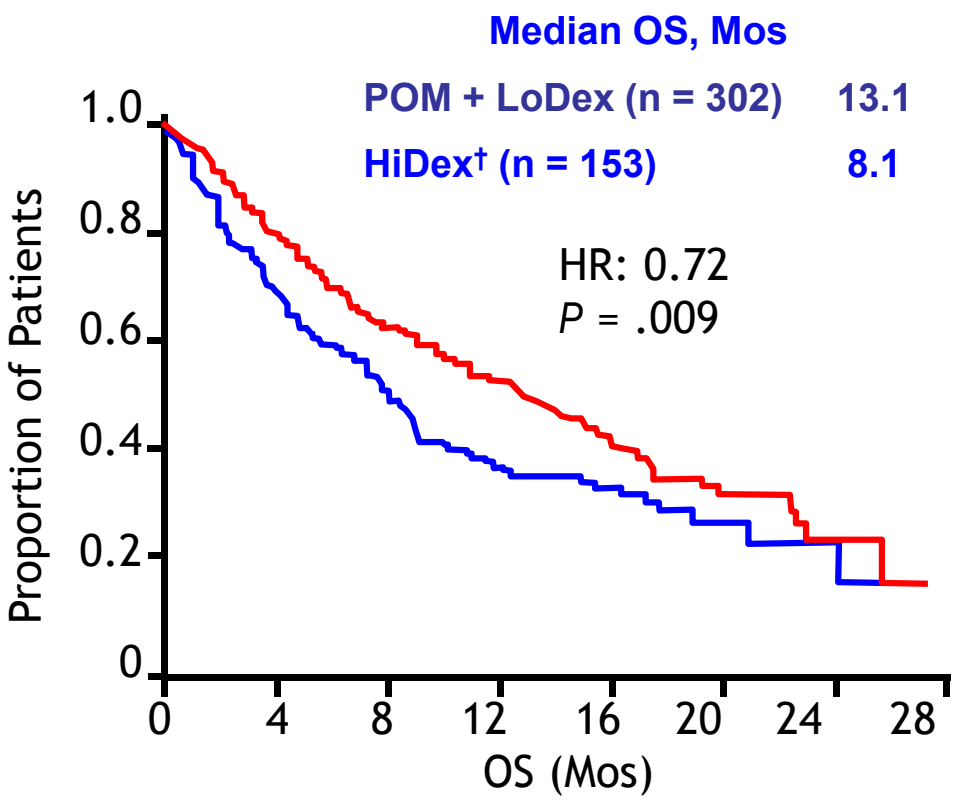


*Interpretation of time to event endpoints are limited in exploratory analyses

Siegel D, et al. *Blood*. 2012; 120:2817-25 [supplementary materials]; ODAC Briefing Document. June 20, 2012.

MM-003 Final Analysis: Pomalidomide/ LoDex vs HiDex: PFS and OS



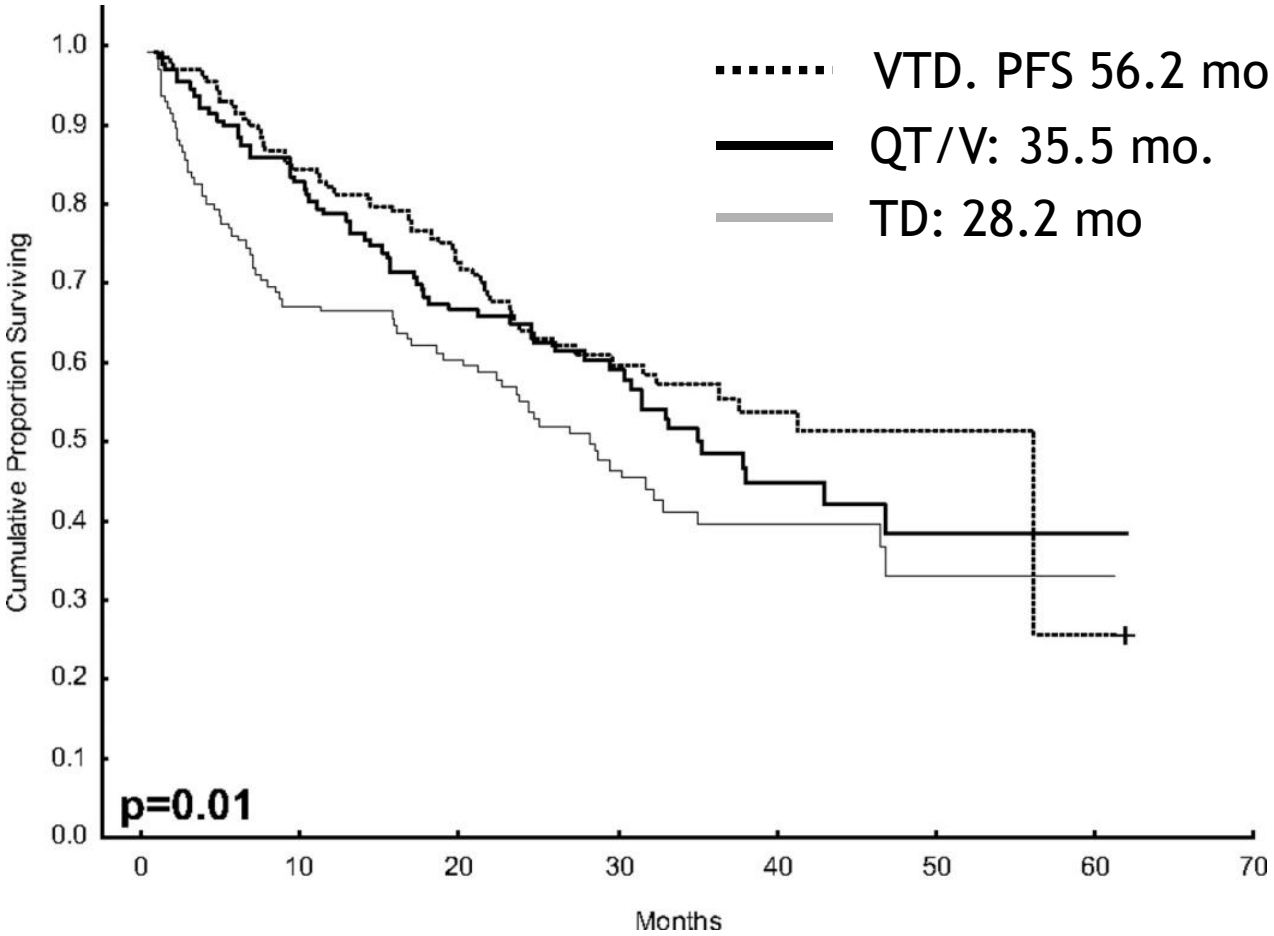


*Primary endpoint.

†85 pts (56%) on the HiDex arm received subsequent POM.

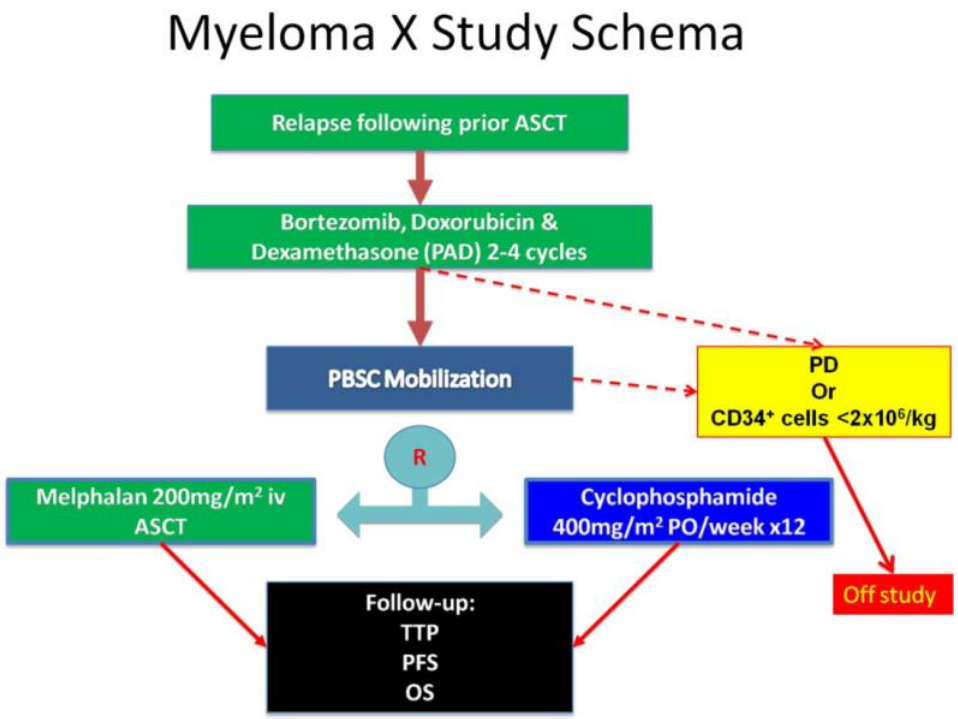
Dimopoulos MA, et al. ASH 2013#408

¿What is the best salvage therapy for most patients treated in first line with current treatment strategies?



Rosiñol L et al. Blood. 2012;120:1589-1596

A Second ASCT Induces Superior Durability of Response Following Bortezomib-Containing Re-Induction Therapy for Relapsed MM: Final Results from The BSBMT/UKMF Myeloma X Intensive Trial



Inclusion Criteria

•Patients with MM previously treated with an ASCT requiring therapy for **first PD**.

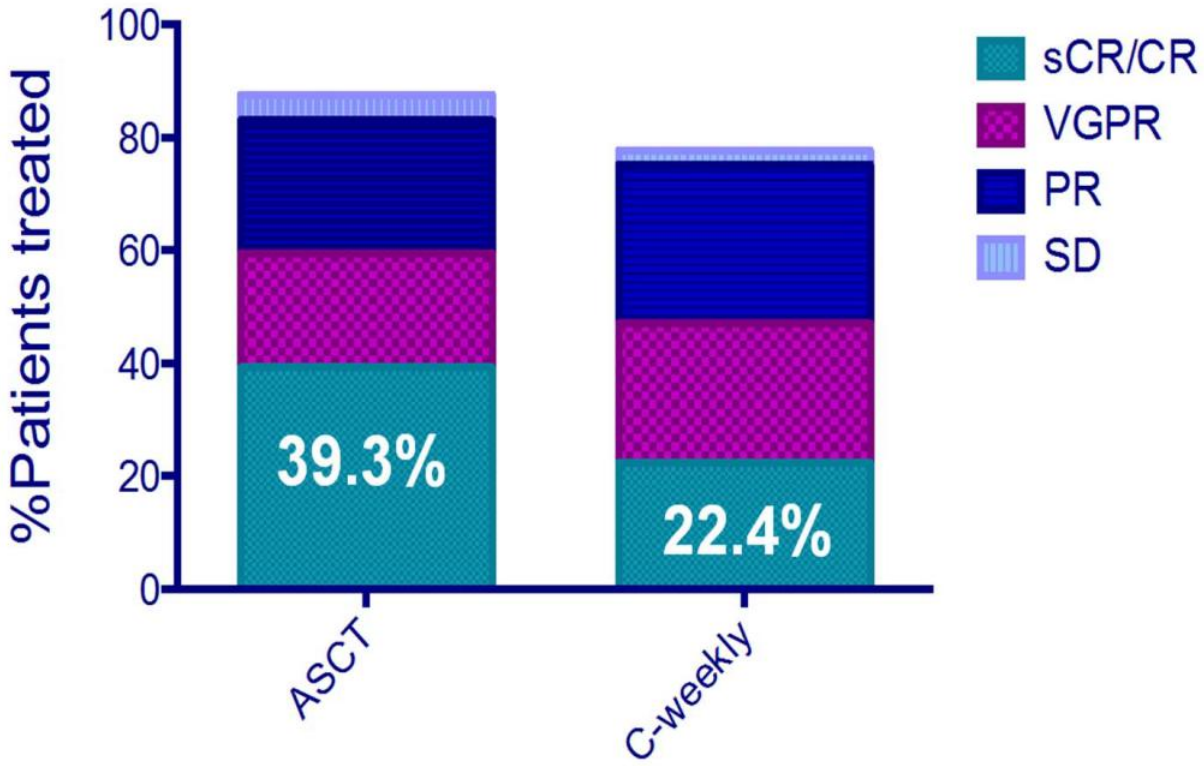
• **Patients with PD ≥18 months from time of 1st ASCT**

PAD Administration

- 52.9% completed 4 cycles
- 58.2% experienced treatment delay (primarily due to cytopenias)
- 50.5% required a dose modification
- G-CSF used to support PAD cycles in 48 (16.2%) patients

Cook G et al. ASH2013#765 & EBMT 2014#O133

A Second ASCT Induces Superior Durability of Response Following Bortezomib-Containing Re-Induction Therapy …….



- Median TTP (ITT) for ASCT is **19 mo.** vs **11mo.** for C-weekly (HR 0.36); p<0.0001)

Cook G et al. ASH2013#765 & EBMT 2014#O133