Maintenance Therapy MM

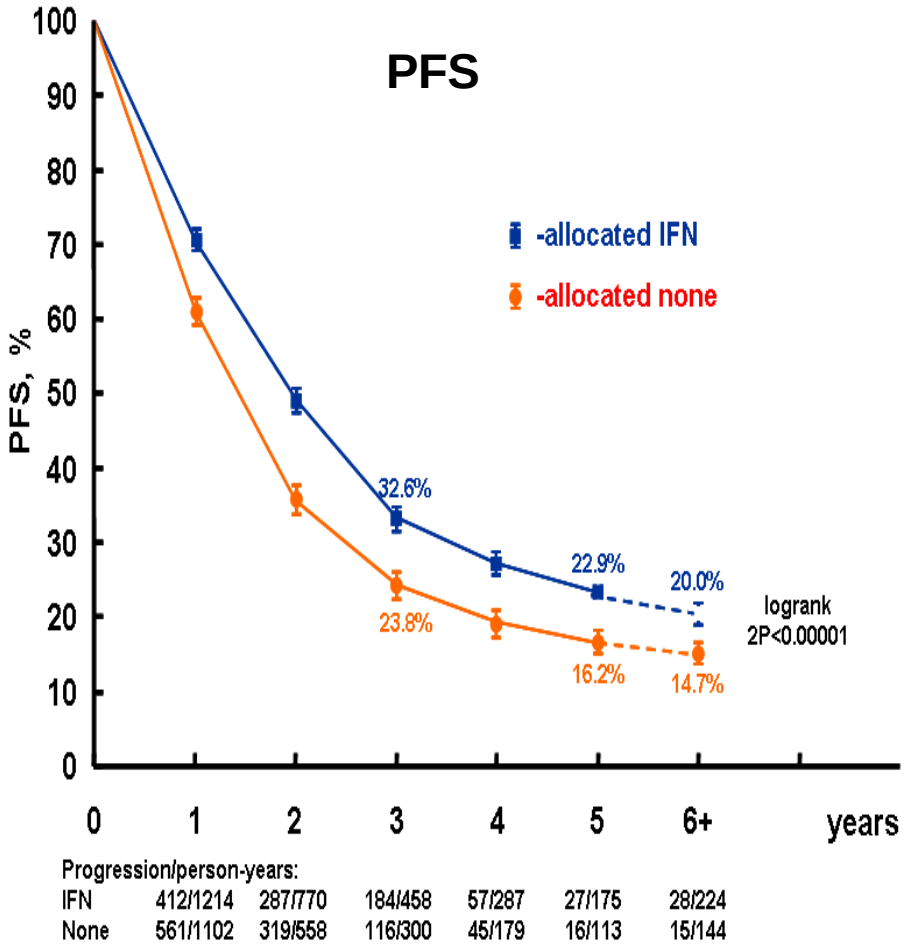
What are the appropriate study endpoints?

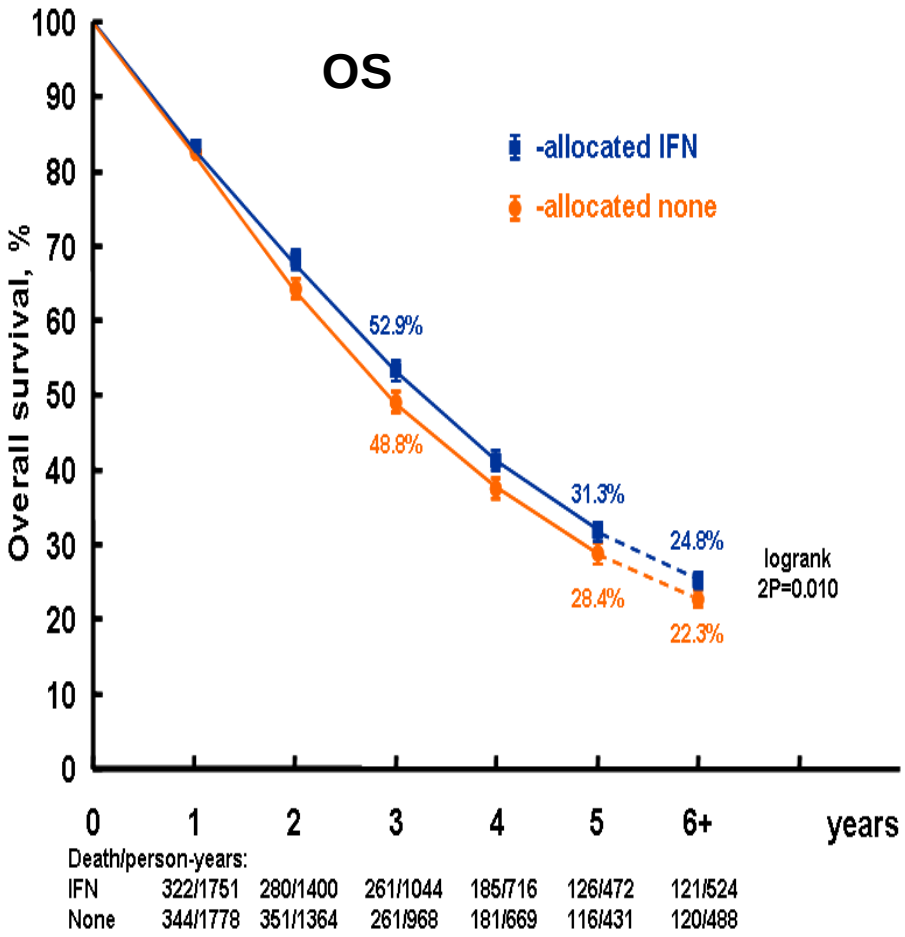
- PFS is certainly appropriate as a surrogate in RRMM to hasten market approval; Td vs D, Vd vs D, Rd vs D, DVD vs Vd
- Patients with multiply relapsed disease that have longer plateaus clearly translate to improved OS the endpoint of greatest interest.
- For newly diagnosed patients OS needs to be demonstrated MPV vs MP, MPT vs MP

Questions to Evaluate Maint. Trials

- In maintenance studies does PFS predict improved OS?
- Have these QOL studies been done?
- What fraction of patients on no maint get diarrhea, skin rashes DVT
- In patients that progress was the maintenance agent available to placebo patients-this is a key for study design
- Were induction arms identical in maint trial

Interferon *Meta-analysis of >750 Patients--12 Trials*





BJH 2001, 113, 1020-1034.

Thalidomide Maintenance after Conventional Chemotherapy (CC)

- **No Trial comparing Thal vs no maintenance after the same Induction Therapy.**
- **The only Maintenance experience with Thal is provided by the 7 MP vs MPT trials:**
  - **5 used Thal maintenance after MPT:**
    OS benefit of the MPT arm: 1/5.
  - **2 did not use Thal maintenance after MPT:**
    OS benefit of the MPT arm: 2/2.
  - **Thal is not required to improve OS after MPT**

Maintenance therapy in non-ASCT Pts

		Maintenance versus no maintenance		
	N	**CR + VGPR, %**	**Med PFS, months**	**Med OS, months**
GIMEMA[6] MPT vs MP	255	36 vs 12	22 vs 14	45 v 48
HOVON 49[7] MPT vs MP	344	23 vs 8	33 vs 21	40 v 31
Nordic[8] MPT vs MP	363	6 vs 3*	15 vs 14	29 vs 32

**** CR rate only.***

6. Palumbo A, Blood 2008;112:3107-14. 7. Wijermans. JCO 2010;28(19):3160-6. 8. Waage Blood. 2010;116(9):1405-12.

Maintenance after ASCT with thali

	N	Initial dose, mg	Maintenance versus no maintenance	
			FU, mo	EFS or PFS
Barlogie[1]	668			
Abn Cyto				
Attal[2]	597			
Spencer[3]	243			
Morgan[4]		100	38	~21 vs 15 m†
Stewart[5]	332	200 (+pred)	48	28 vs 17 m
Lokhorst[6]	536	50 (vs IFN)	52	34 vs 25 m
Krishnan[7]	366	200 (+dex)	36	3-yr 49 v 80%

83% received salvage thalidomide→

62% received salvage thalidomide→

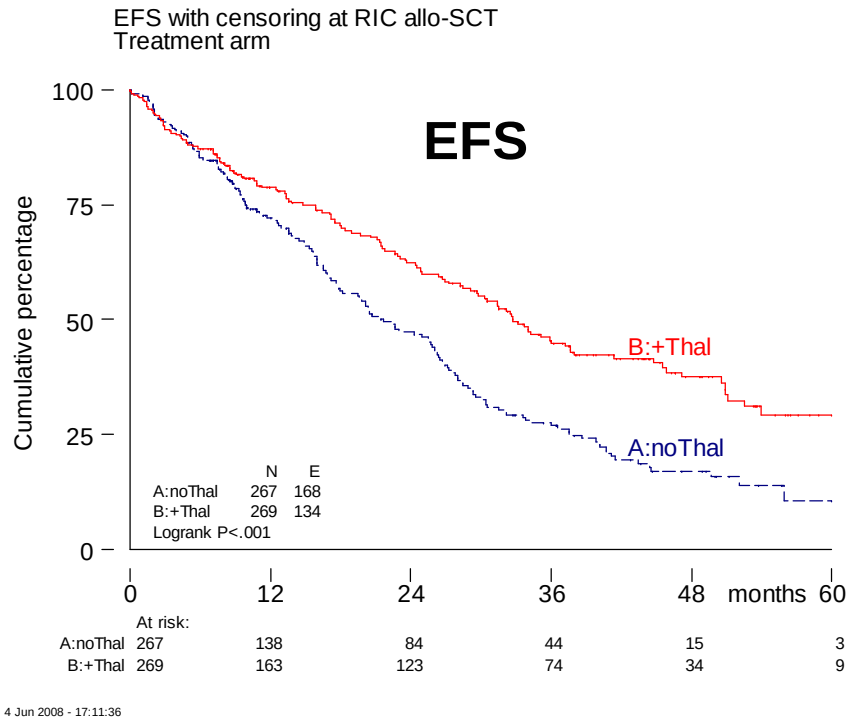
54% received salvage thalidomide→

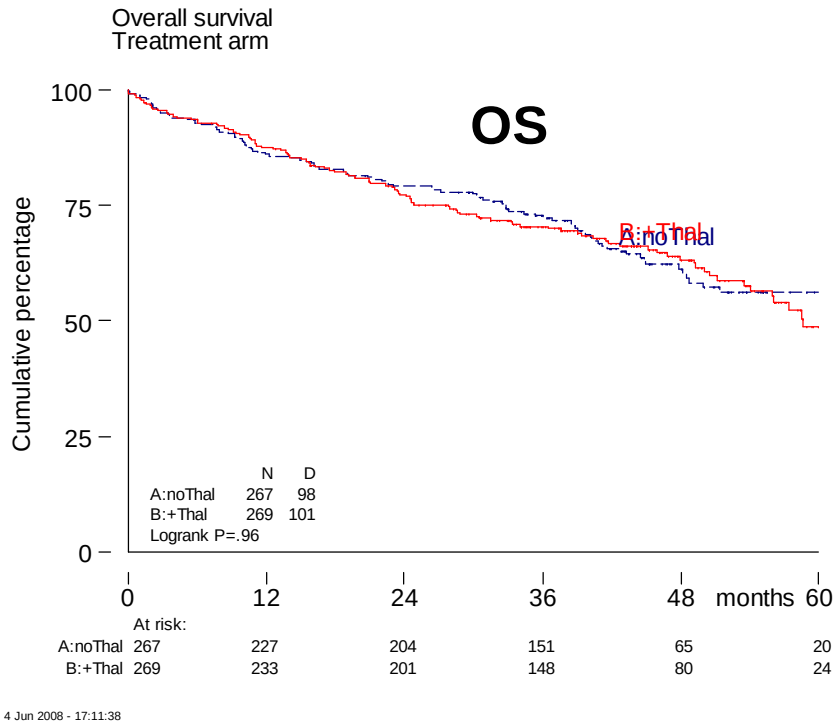
* *CR rate only.* † *Pooled ASCT and nonASCT patients*

1. Barlogie B, N Engl J Med. 2006;354:1021-30, updated Blood. 2008;112(8):3115-21. 2. Attal M, Blood. 2006;108:3289-94. 3. Spencer A, J Clin Oncol; 2009;27:1788-93. 4. Morgan GJ, ASH. 2010;abs 623. 5. Stewart ASH 2010, Abs 39; 6. Lokhorst Blood (2010); 115:1113-1120 7. Krishnan. ASH 2010;#41-

HOVON 50
Best response on protocol

	VAD+IFN	TAD+Thal	p
≥ PR	**79 %**	**88%**	0.005
≥ VGPR	**54 %**	**66%**	0.005
≥ CR	**23 %**	**31%**	0.04



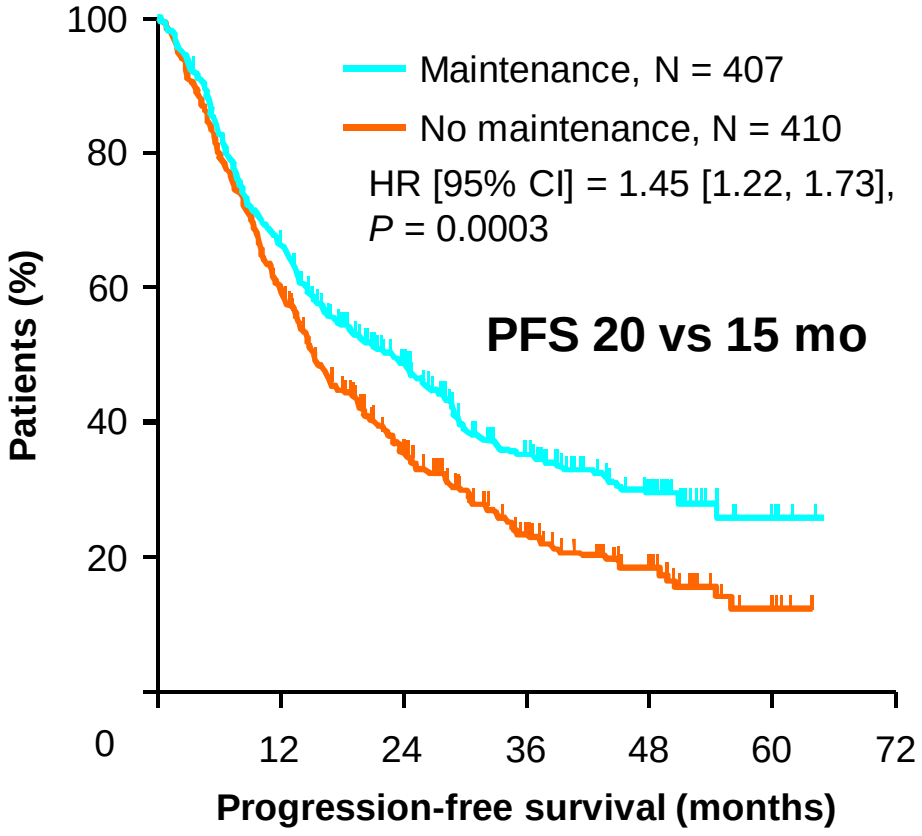


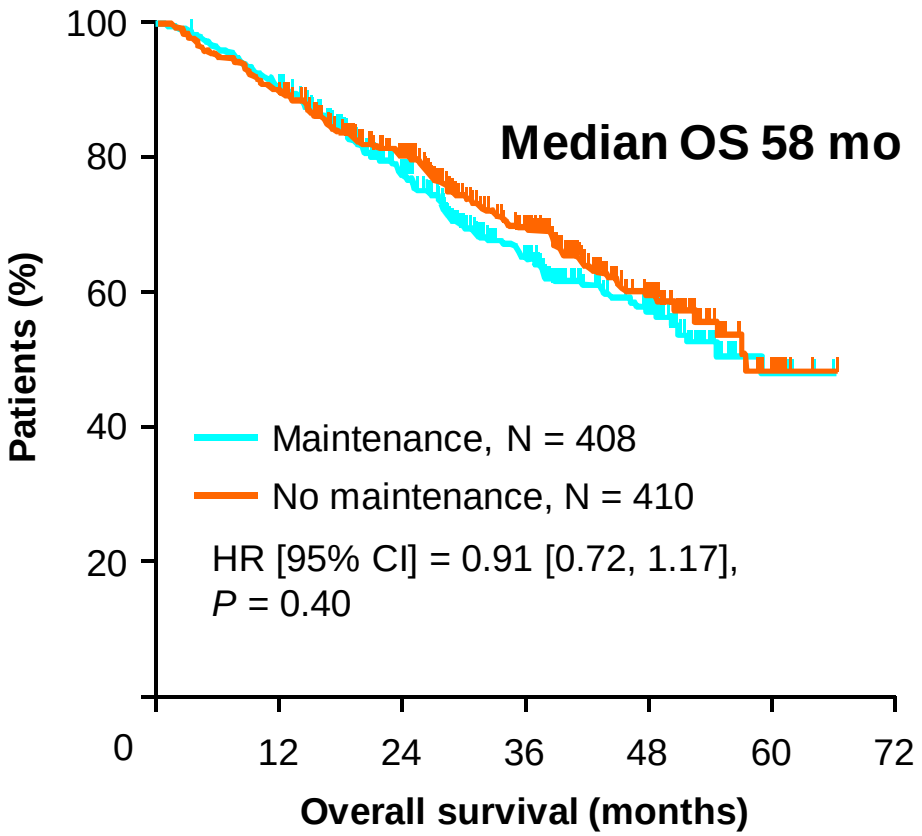
Lokhorst Blood (2010); 115:1113-1120

Median fu is 52 months

PFS and OS according to maintenance randomization

Median follow-up from maintenance randomization was 38 months (range 12–66 months)





Thalidomide maintenance improves PFS with no OS advantage

Morgan Lancet MRC IX

Maintenance with Lenalidomide

	Initial TT	N	Time of Rando	Lenalidomide versus Placebo	
				Median PFS after Rando	OS after Rando
Attal et al.[1]	SCT	614	3 m post SCT	41 m vs 23 m***	4-year OS 73% vs 75%
McCarthy et al.[2]	SCT	460	SCT	39 m vs 21 m***	3-year OS 88% vs 80%*
Palumbo et al.[3]	MPR	305	Diagnosis	31 m vs 14 m**	3-year OS 70% vs 62%

1. Attal M, et al. NEJM 2012

2. McCarthy et al, NEJM 2012.

3. Palumbo et al, NEJM 2012

IFM 2005-02: Grade 3–4 AEs (unblinding)

AE	Placebo	Lenalidomide
Anemia	2%	3%
Thrombocytopenia	7%	14%
Neutropenia	18%	51%
Febrile Neutropenia	1%	1%
Infections	5%	13%
DVT/PE	2%	6%
Skin disorders	4%	7%
Fatigue	2%	5%
Peripheral Neuropathy	1%	1%

Attal et al N Engl J Med 2012

Number of patients with at least one SPM (10/2011)

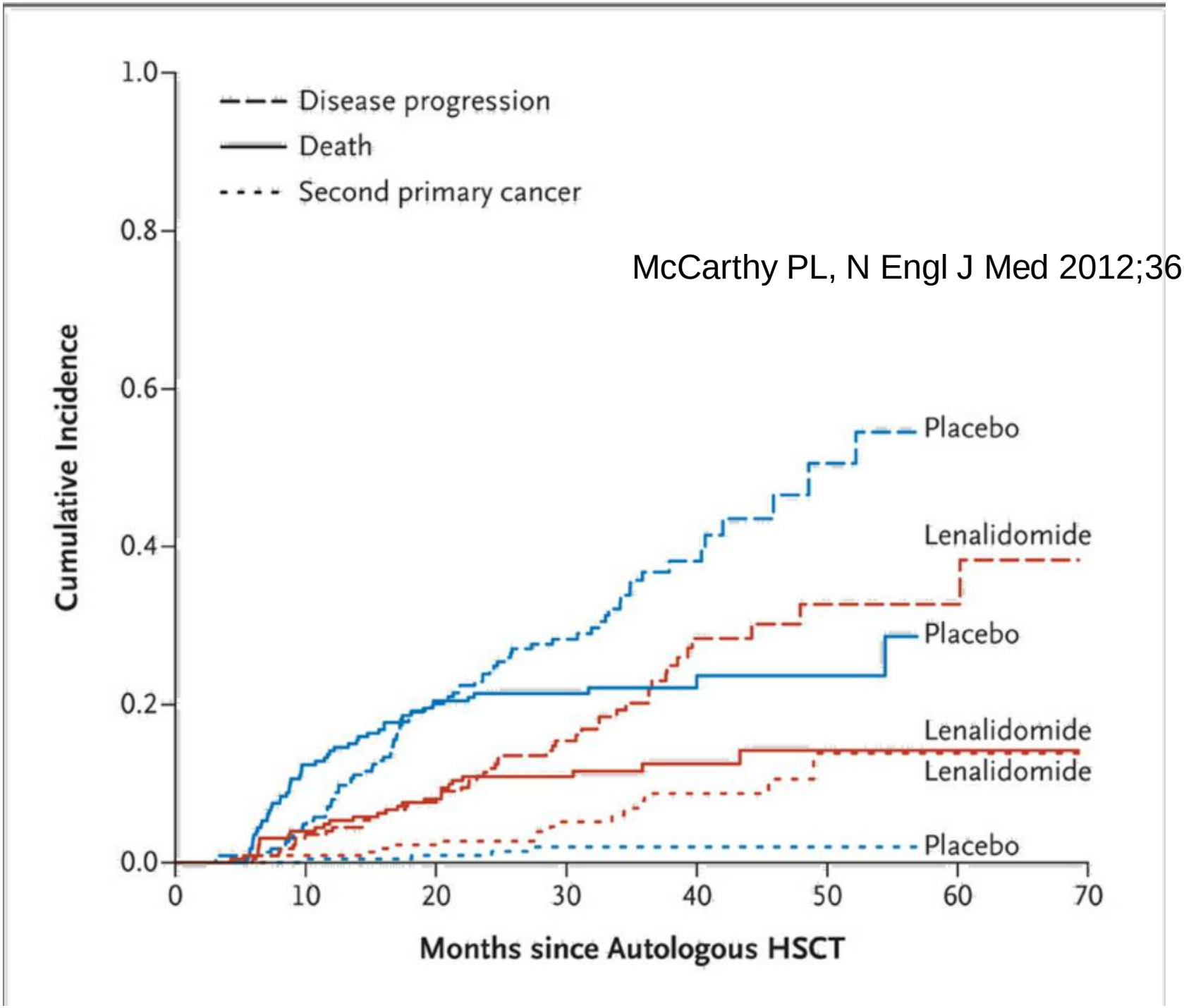
	Lenalidomide (N= 306)	Placebo (N= 302)	Total (N= 608)
Hematologic malignancies (%)	13 (4.2)	5 (1.7)	18 (3.0)
AML/MDS	5	4	
ALL	3	0	
Hodgkin lymphoma / Non-HL	4 / 1	0 / 1	
Solid tumours (%)	10 (3.3)	4 (1.3)	14 (2.3)
Esophageal / Colon	4	0	
Breast	2	0	
Lung / Sinus	1	1	
Kidney / Prostate	3	2	
Melanoma	0	1	
Non-Melanoma skin cancers (%)	5 (1.6)	3 (1.0)	8 (1.3)
Total (%)	26* (8.5)	11** (3.6)	37 (6.1)

Attal et al N Engl J Med 2012

Lenalidomide toxicity

	Grade 3 Non Hematologic AE		Grade 4 Non Hematologic AE		
	N	%	N	%	
Max Non-Hematologic Len	**73**	***32***	**8**	***3***	**<0.001**
Placebo	**37**	***16***	**6**	***3***	

McCarthy PL, N Engl J Med 2012;366:1770-81.



McCarthy PL, N Engl J Med 2012;366:1770-81.

Maintenance with Bortezomib

	Initial therapy	Maintenance		
		Maintenance regimen	PFS	OS
Mateos et al.[1]	VMP vs VTP	VT	32 m	2-year: 86%
		VP	24 m	2-year: 81%
Palumbo et al.[2]	VMPT	VT	3-year: 60%	3-year: 89%
	VMP	0	3-year: 42%*	3-year: 89%
Sonneveld et al.[3]	PAD + SCT	V	3-year: 48%	3-year: 78%
	VAD + SCT	T	3-year: 42%*	3-year: 71%*

1. Mateos mv, lancet oncol 2010 2. Palumbo a, J Clin Onco 2010 3. Sonneveld p, ASH 2010

Induction Therapy Myeloma

Doublet? Triplet? Quadruplet?

- In myeloma progression is usually biochemical not clinical
- Does patient survival or QOL change whether therapy is initiated when M protein is 1.3 rather than 0.8 ?
- If survival is not the end point improved QOL is of interest to our patient population.

Which is the Better Strategy? Comparing doublet & Triplet combinations

Doublet Induction

↓

Relapse regimens Including the missing third agent

But NOT relapse regimens minus The third agent

versus

Triplet Induction

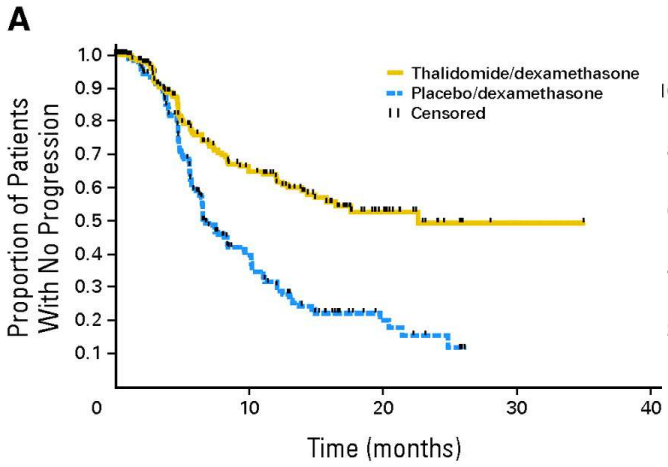
↓

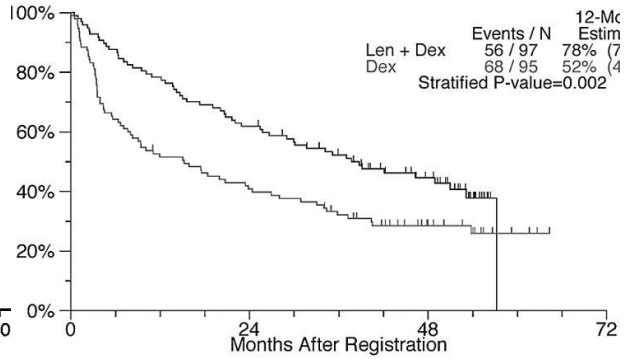
Relapse regimens New agents

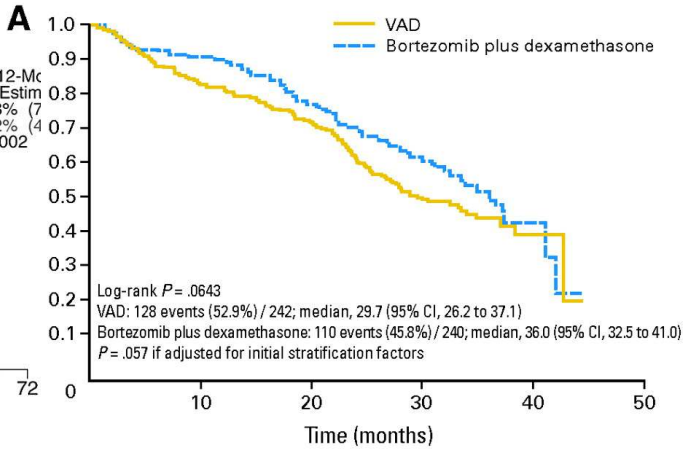
- In new diagnosis the control arm must have access to investigational agent at prog.
- In Vista of 338 randomized to MP; 130 received subsequent bortezomib **remainder did not(62%)** (JCO 28:2259-66)

Doublet-Regimens

Thal-Dex (TD) | **Len-Dex (RD)** | **Bortez-Dex (VD)**

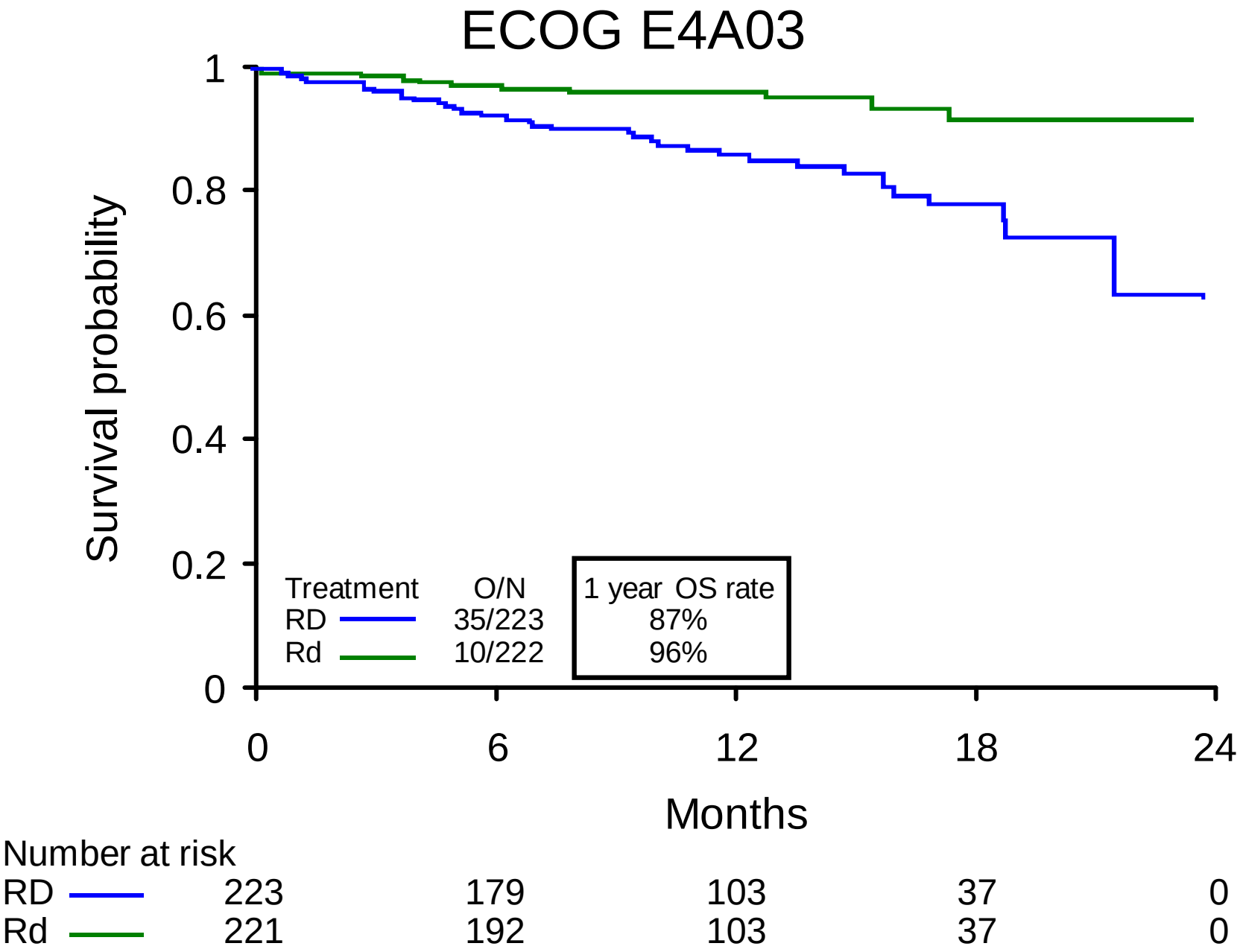






PFS better than Dex/VAD

Rajkumar, S. V. et al. J Clin Oncol 2008; 26:2171-2177
Zonder J A et al. Blood 2010;116:5838-5841
Harousseau J et al. JCO 2010;28:4621-4629



Rajkumar SV, et al. Lancet Oncology 2009

Can 3 or more drug regimens provide additional benefit?

Doublets

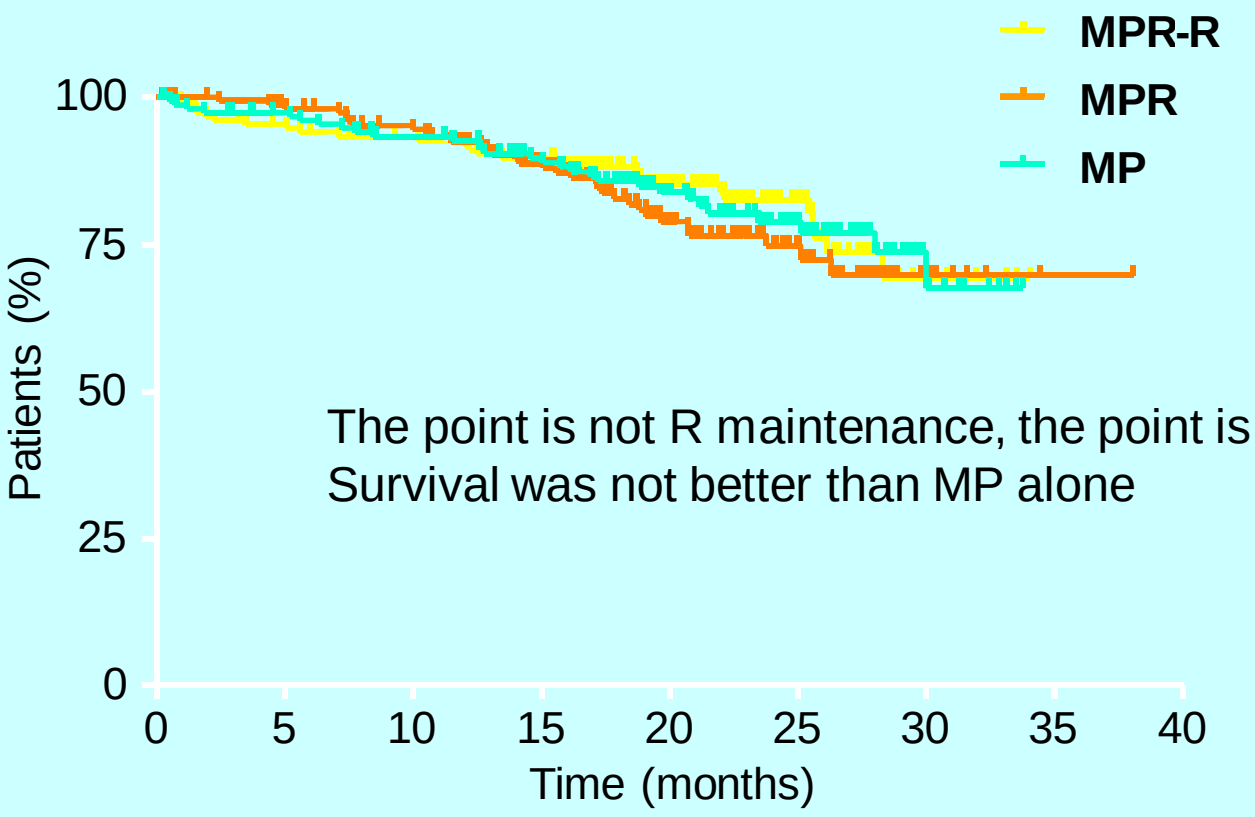
- TD
- RD
- VD

Triplets

- VTD
- VRD
- VCD

MP-plus Regimens: MPR

Overall Survival



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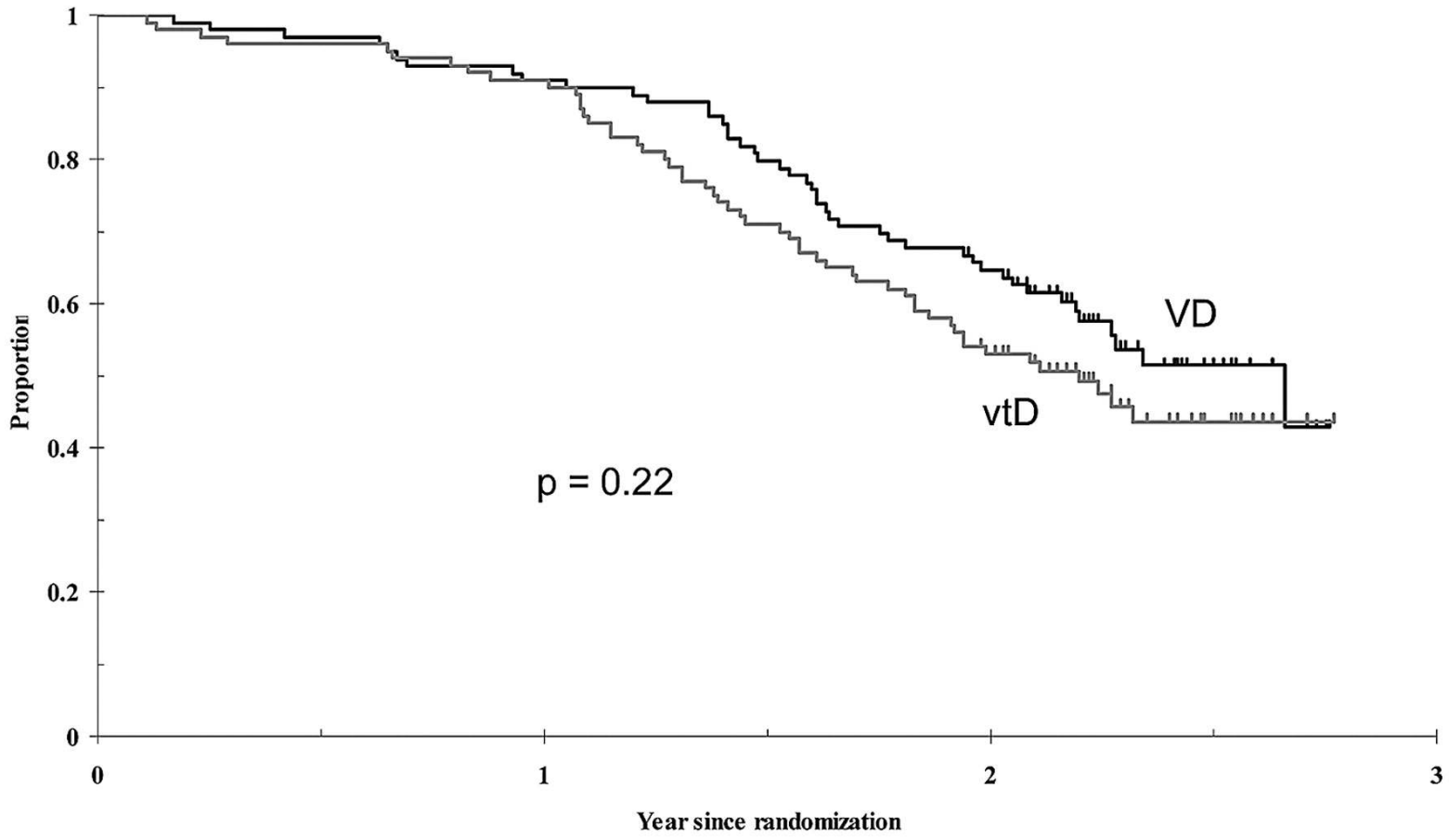
1

Palumbo A. ASH 2010; N Engl J Med 2012

VTD versus VD
Progression-free survival.

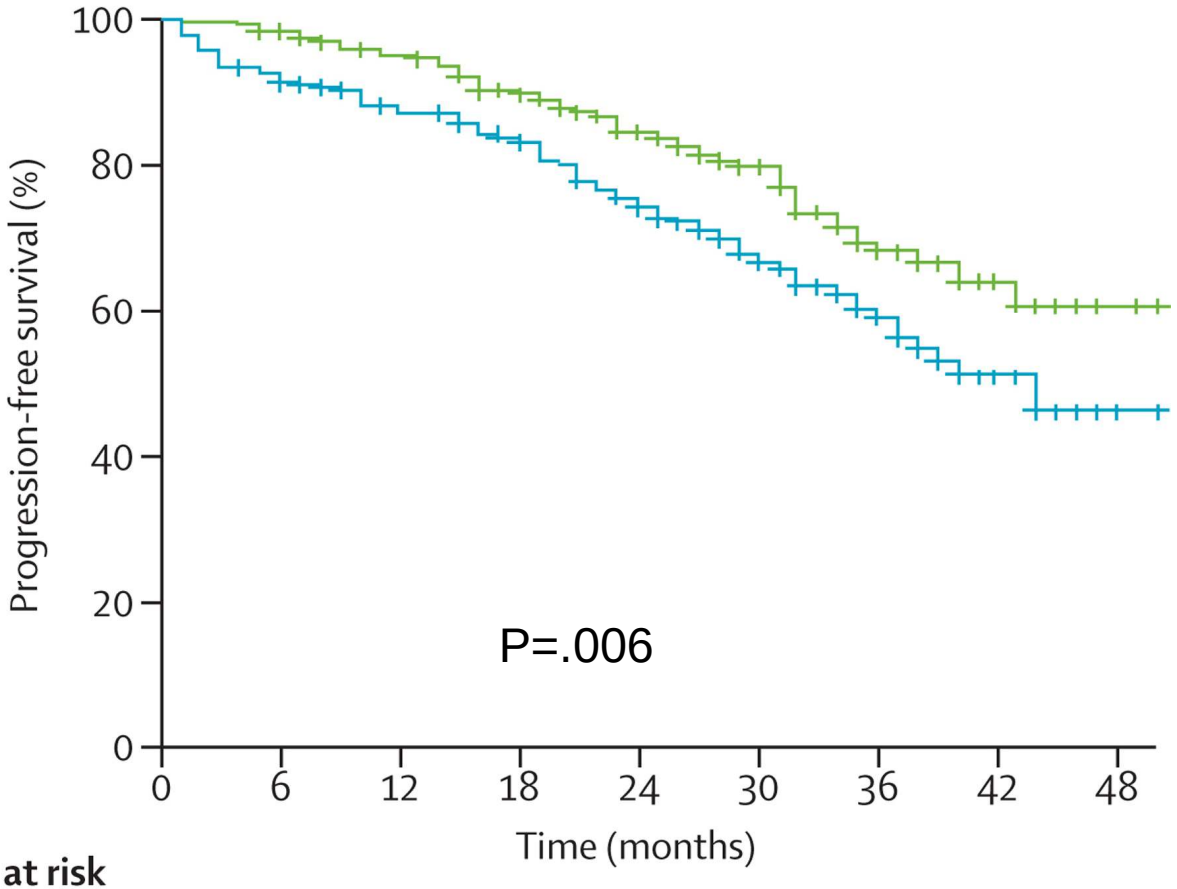
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



# at Risk	99	96	90	79	63	15	VD
	100	96	91	71	52	10	vtD

Moreau P et al. Blood 2011;118:5752-5758

VTD vs TD
Progression free survival

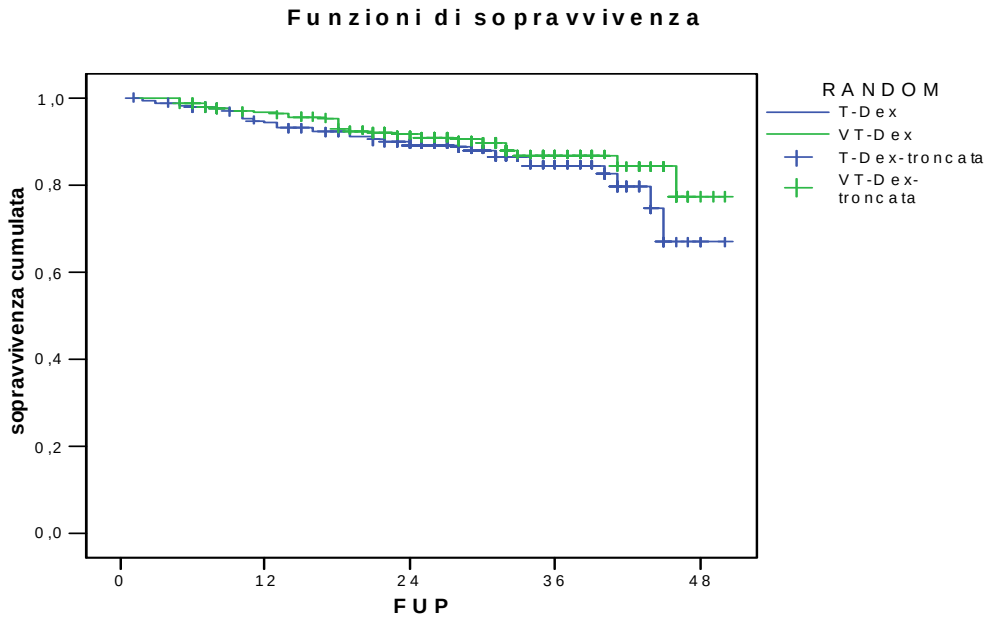


Number at risk

VTD	236	230	212	195	159	111	55	21	2
TD	238	218	200	185	158	99	51	13	2

Cavo et al. Lancet 376, Issue 9758,, Pg 2075–85

- The estimated 3-year rate of overall survival was 86% in the VTD group and 84% in the TD group (p=0·30).



Cavo et al. Lancet 376, Issue 9758,, Pg 2075–85

Options in Transplant Ineligible Patients

Non-melphalan based

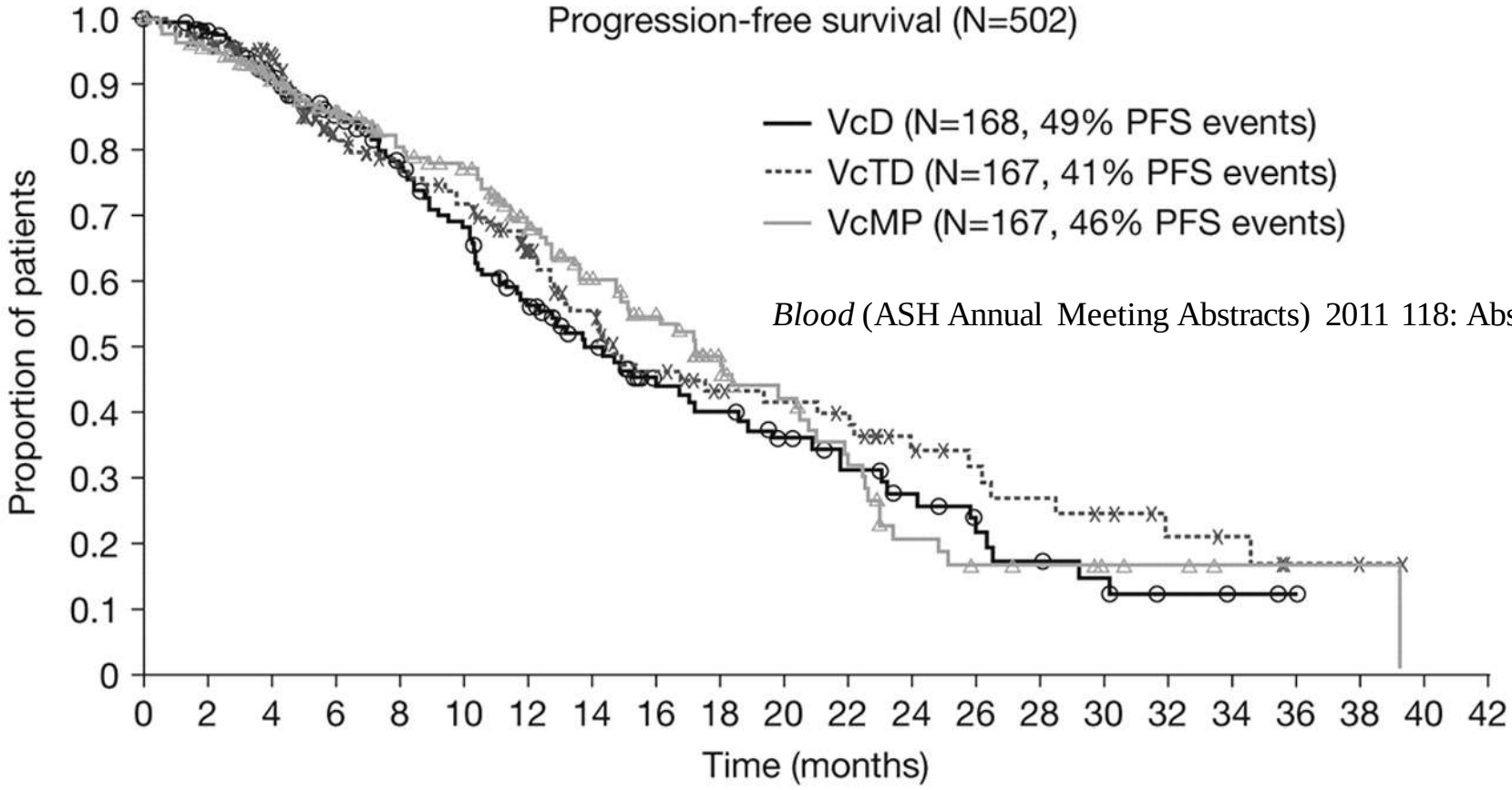
- Rd
- VCd
- VRd

Melphalan based

- MPT
- VMP

Study	Regimen	TTP PFS/EFS	Overall Survival (months)	3 year OS (%)
Facon (Lancet 2007)	MPT	28	52	~65%
San Miguel (JCO 2010)	VMP	24	NR*	69%
Rajkumar (Lancet Oncol 2010)	Rd	25	NR*	75% (Rd age ≥65)

UPFRONT

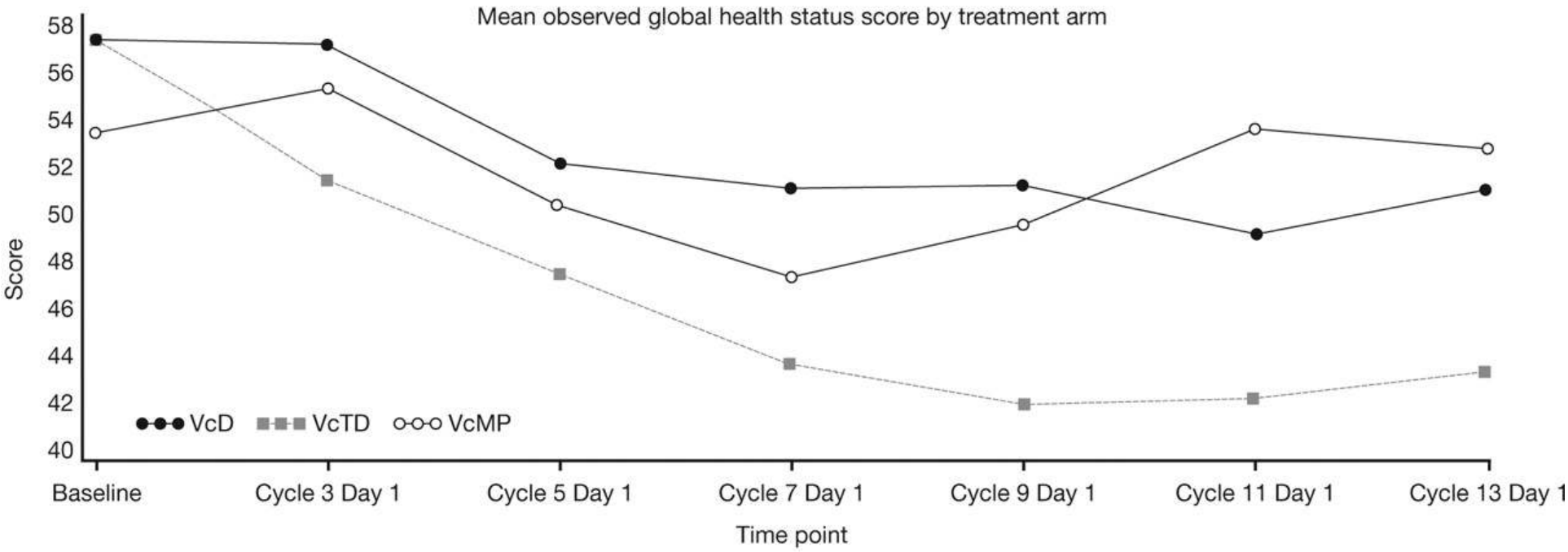


Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 1864

Patients remaining, n

VcD:	168	147	125	102	87	75	59	46	34	30	24	20	15	11	8	6	3	2	1
VcTD:	167	137	123	90	79	73	55	43	33	27	25	23	16	13	11	9	6	5	2	1
VcMP:	167	147	128	109	94	86	70	55	46	32	26	18	10	7	6	4	3	1	

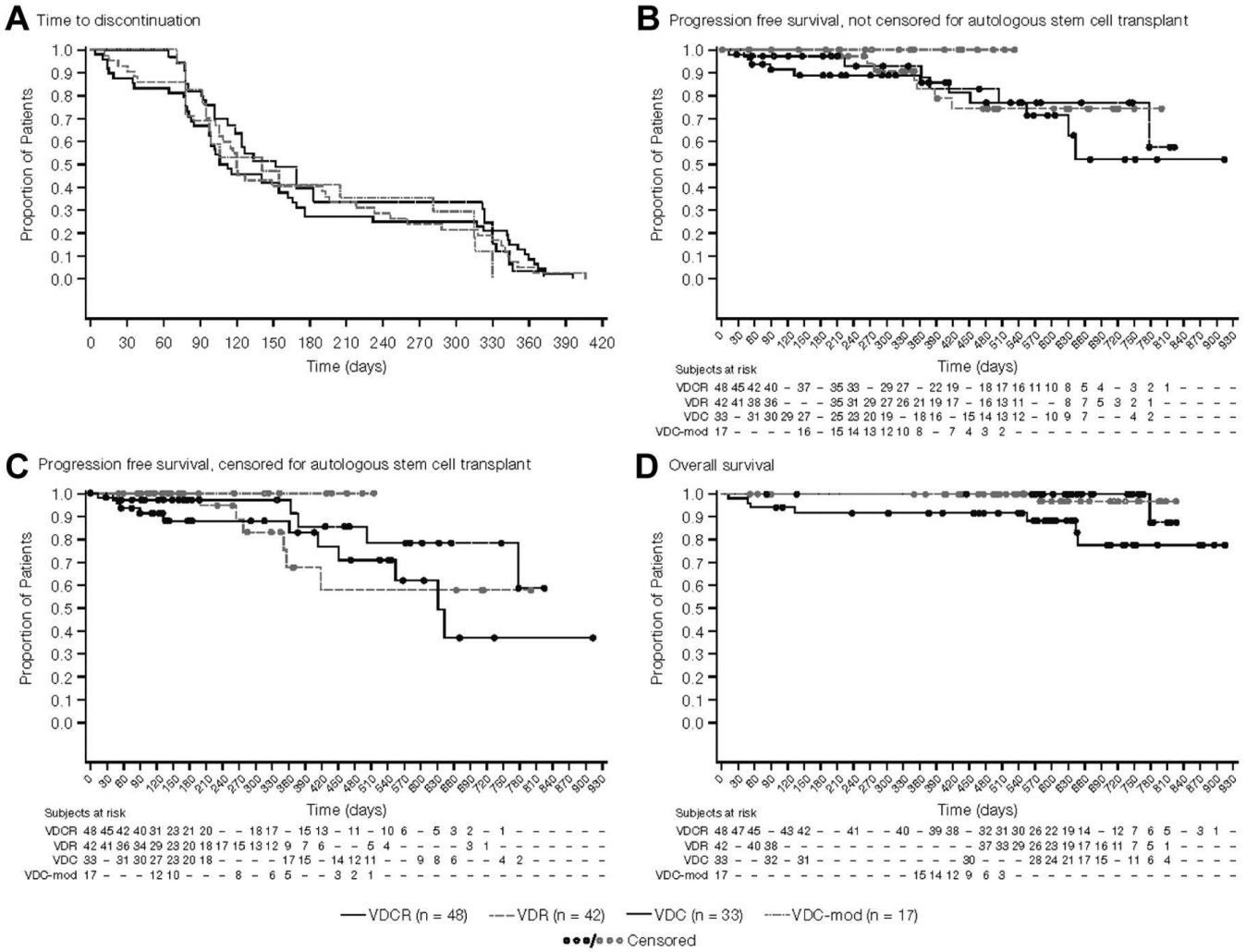
UPFRONT



Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 1864

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

EVOLUTION

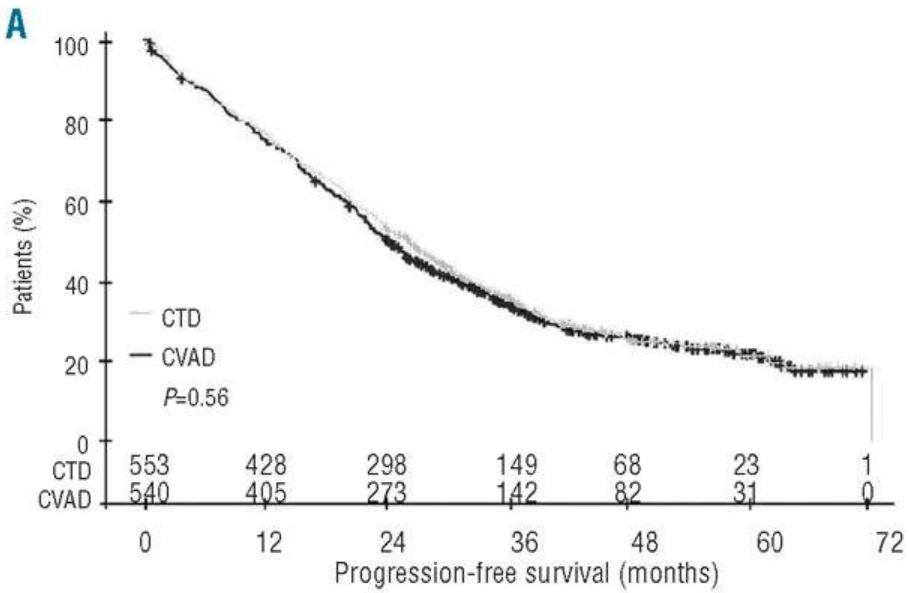


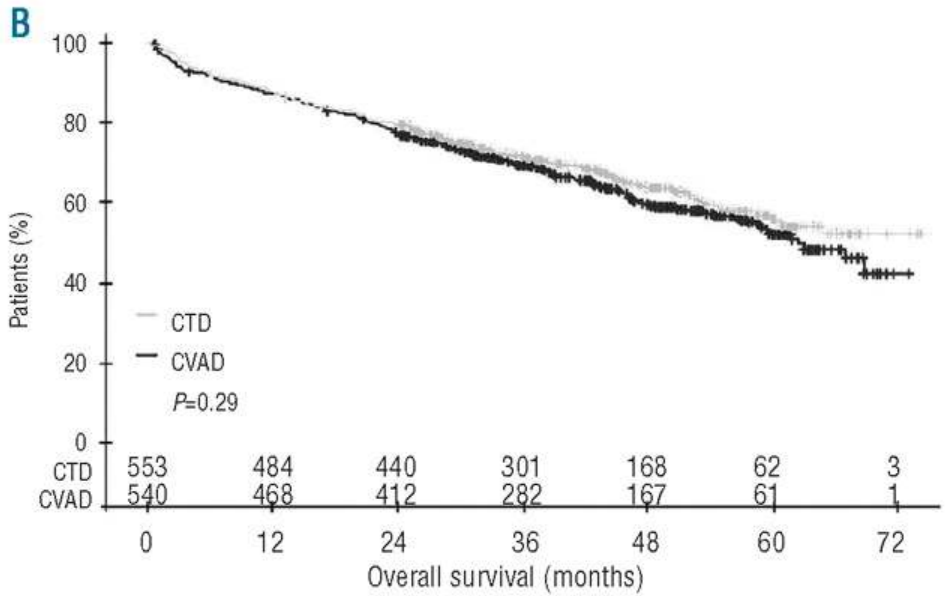
Kumar S et al. Blood 2012;119:4375-4382

Four vs triplet

No substantial advantage was noted with VDCR over the 3-drug combinations.

Impact of induction therapy on survival: (A) progression-free survival and (B) overall survival (P values from unadjusted log rank tests; per-protocol population). MRC IX
Effective salvage negates PFS & OS benefit even if thal not used up front





Morgan G J et al. Haematologica 2012;97:442-450

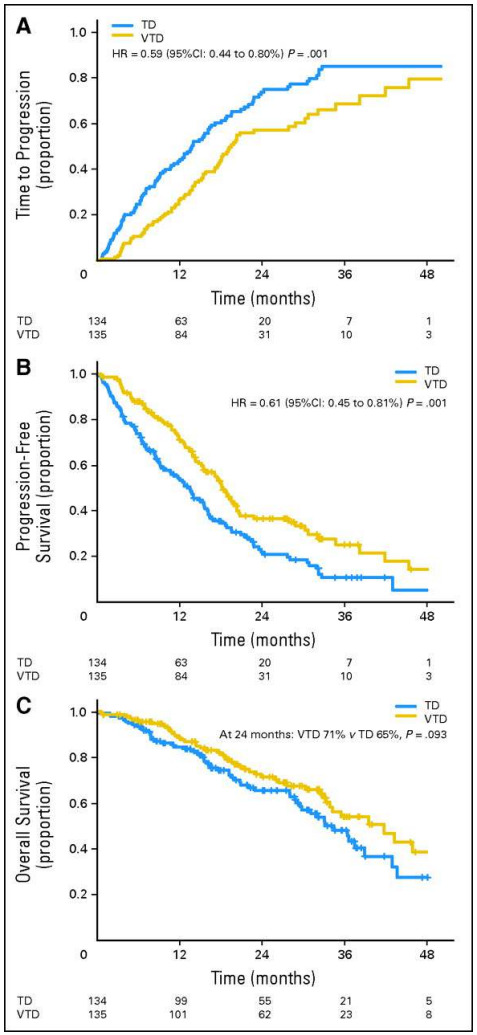
Note numbers in each arm
OS not better in subsets <CR;
Or based on High risk standard risk FISH

haematologica
the hematology journal

Comparison of the triple (bortezomib-thalidomide-dexamethasone) and dual (thalidomide-dexamethasone) treatment groups.

Even comparing doublet &
Triplet in the relapsed setting
Superior PFS does not translate
To superior OS. Moreover gr 3
neurotoxicity in triplet was 29 vs
12% p<.001

Not living longer & with
Triplet not living better



Garderet L et al. JCO 2012;30:2475-2482

JOURNAL OF CLINICAL ONCOLOGY

New Drugs

Pomalidomide in R/R Multiple Myeloma

Study	Phase	N	Treatment	Population	Median Prior Therapies (Range)	ORR (≥ PR)
Schey[1]	1	24	**Pom:** 1, 2, 5, 10 mg (28/28-day cycle)	≥ 1 prior therapy	3 (1-6)	54%
Richardson[2]	1	38	**Pom:** 2, 3, 4, 5 mg (21/28-day cycle) **Dex:** 40 mg/week[a]	≥ 2 prior therapies including Len and Bort	6 (2-17)	25%
Richardson[2]	2	22	**Pom:** 4 mg (21/28-day cycle) ± **Dex:** 40 mg/week	≥ 2 prior therapies including Len and Bort	5 (2-13)	25%
Leleu[3]	2	84	**Pom:** 4 mg (21/28-day cycle vs 28/28-day cycle) **Dex:** 40 mg/week	≥ 2 prior therapies including Len and Bort	4 (1-8)	40%

1. Schey SA, et al. *J Clin Oncol*. 2004;22:3269-3276.
2. Richardson P, et al. *Blood*. 2010;116:377-378.[abstract 864].
3. Leleu X, et al. *Blood*. 2010;116:375.[abstract 859].

Pomalidomide in R/R Multiple Myeloma

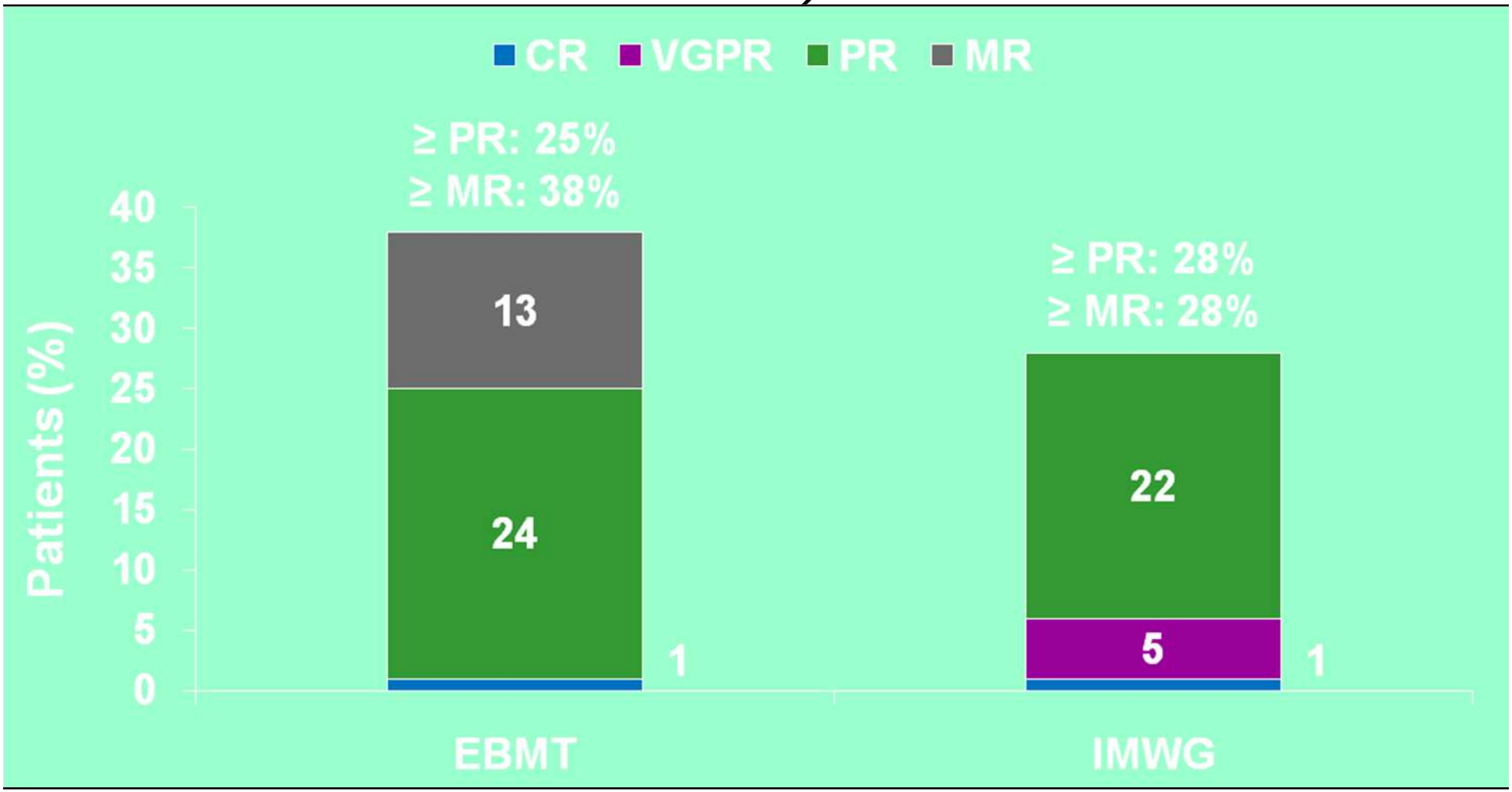
Study	Phase	N[a]	Treatment	Population	Median Prior Therapies (Range)	ORR (≥ PR)
Lacy[1]	2	60	**Pom:** 2 mg (28/28-day cycle) **Dex:** 40 mg/week	1-3 prior therapies	2 (1-3)	63%
Lacy[2]	2	34	**Pom:** 2 mg (28/28-day cycle) **Dex:** 40 mg/week	Len-refractory	4 (1-7+)	32%
Lacy[3]	2	35	**Pom:** 2 mg (28/28-day cycle) **Dex:** 40 mg/week	Len- and Bort-relapsed/refractory	6 (3-9)	26%
Lacy[4]	2	70	**Pom:** 2 mg vs 4 mg (28/28-day cycle) **Dex:** 40 mg/week	Len- and Bort-relapsed/refractory	6 (2-8+)	26%

[a] Four separate populations of a single phase 2 trial.
Bort, bortezomib; Dex, dexamethasone; Len, lenalidomide; ORR, overall response rate; Pom, pomalidomide; PR, partial response.

1. Lacy MQ, et al. *J Clin Oncol.* 2009;27:5008-5014.
2. Lacy MQ, et al. *Leukemia.* 2010;24:1934-1939.
3. Lacy M, et al. *J Clin Oncol*. 2010;28:573s.[abstract 8002].
4. Lacy M, et al. *Blood.* 2010;116:377.[abstract 863].

Pom LD Dex in R/R Myeloma

MM-002 Phase 2 Portion – Efficacy (Aggregated Data)



Pomalidomide Future Directions

Combinations	Population	N	ORR
Pomalidomide, cyclophosphamide, pred	R / R		65%
Pomalidomide, clarithromycin, dex	R / R, ≥ 3 tx		60%
Pomalidomide, bortezomib, dex	Trials underway		

Pred, prednisone; dex, dexamethasone, ORR, overall response rate; R / R, relapsed / refractory; tx, therapy.

Phase III (Europe): Pomalidomide / dex vs dex

Palumbo A, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):632. Mark TM, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):635. National Institutes of Health. Available at: www.clinicaltrials.gov. Accessed March 2011.

Carfilzomib PX-171-004

- Bortezomib naïve N= 129
- Cohort 1 20 mg/M2 N=59
- Cohort 2 20 mg/M2 cycle1 then 27 mg/M2
- PR + MR cohort 1 59.3% Cohort 2 64.2%
- Median DOR 13.1 mo; Median TTP 7.6
- Fatigue 62%; Nausea 49 %
- PN 17.1% grade 3 1 patient grade 4 none

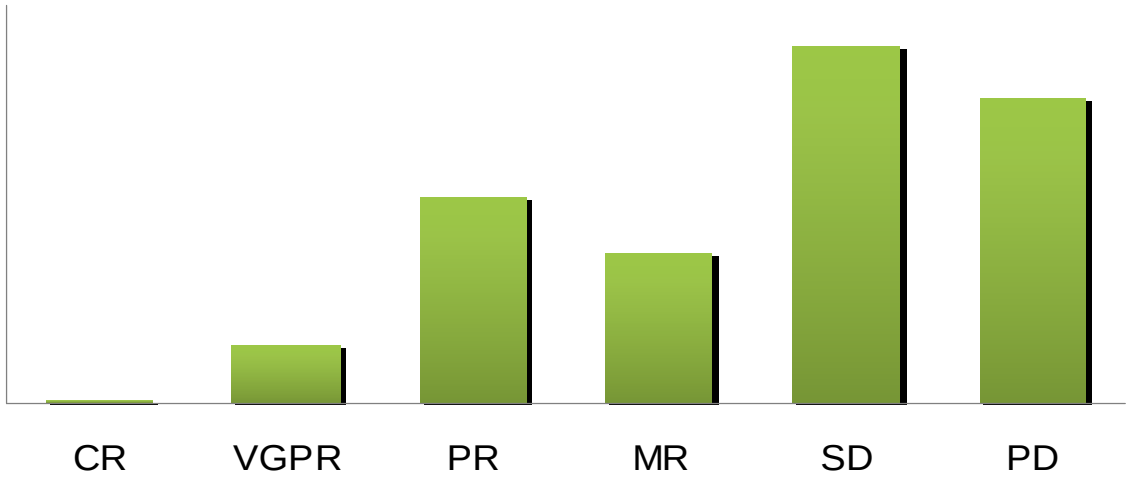
Blood 119:5661-71,2012

Carfilzomib Monotherapy in Heavily Pre-Treated MM

DCR = 69%

CBR = 37%

ORR = 24%



	Carfilzomib N = 257
Median OS	**15.4 months**
Median OS for ≥ PR	**20.7 months**
Median PFS	**3.7 months**
Median PFS for ≥ MR	**9.5 months**
Median DOR	**8 months**

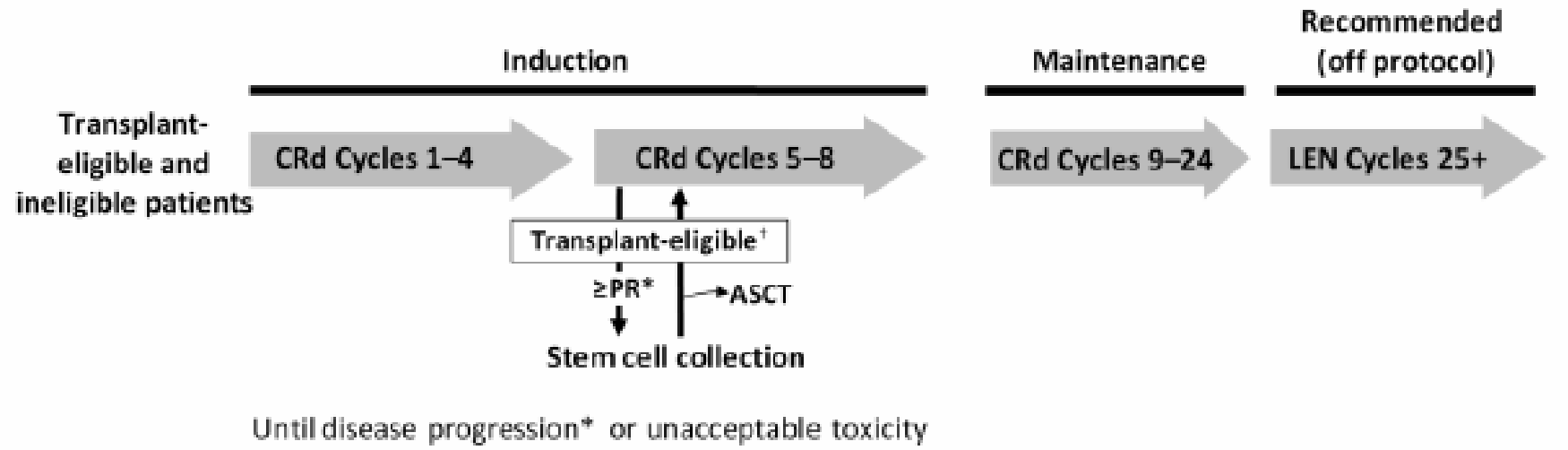
Median follow-up = 14.3 months

Unfavorable cytogenetics did not significantly impact response rates or DOR

CR, complete response; VGPR, very good partial response; PR, partial response; MR, marginal response; SD, stable disease; PD, progressive disease; DCR, disease control rate; CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival.

Siegel DS, et al. *ASCO Meeting Abstracts.* 2011;29(15 suppl):8027. Jakubowiak AJ, et al. *ASH Annual Meeting Abstracts.* 2011;118(21):1875.

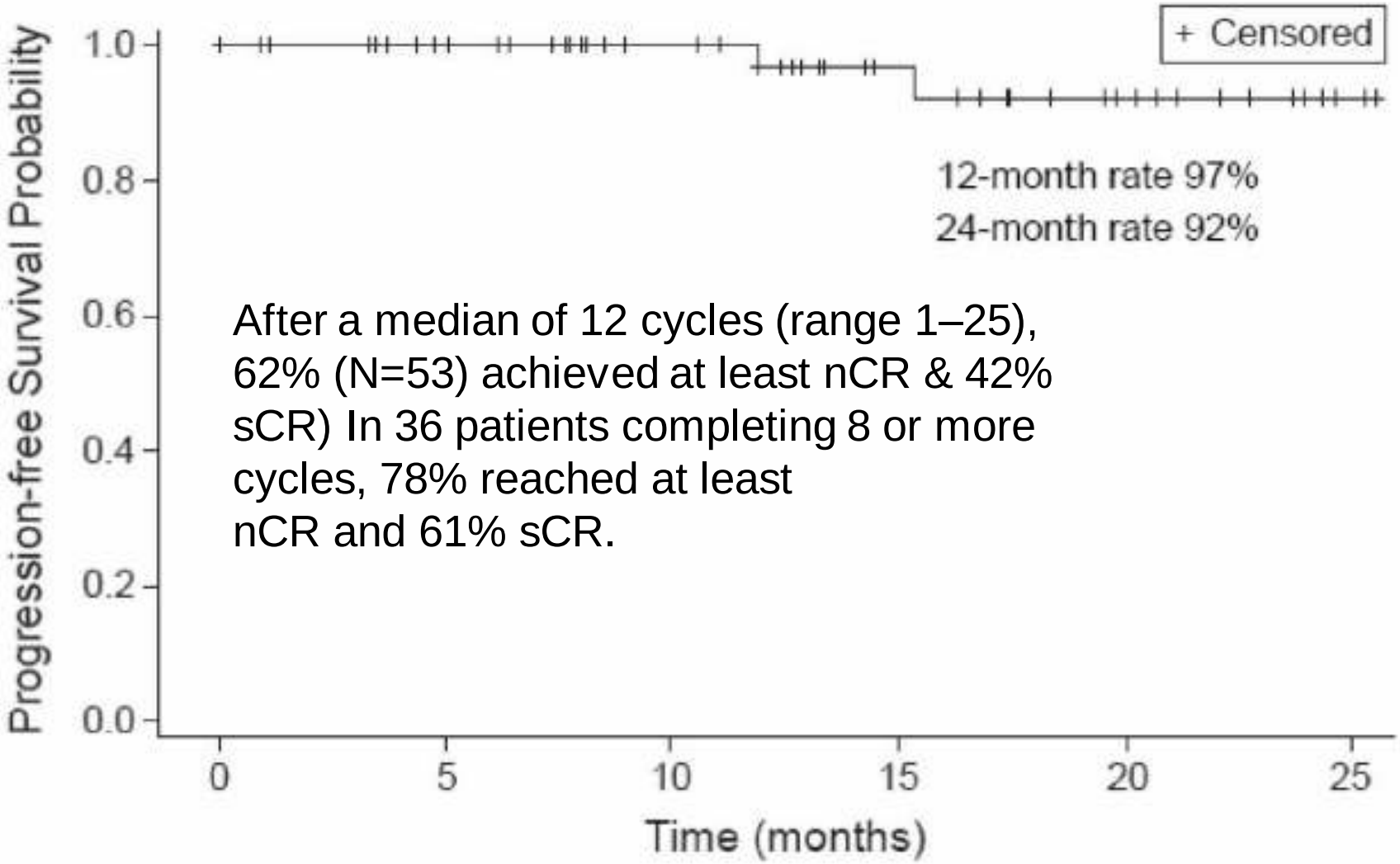
CRd new diagnosis



	Cycles 1–4	Cycles 5–8	Cycles 9–24	Cycles 25+
Carfilzomib	20/27/36 mg/m²	20/27/36 mg/m²	20/27/36 mg/m²‡	
Treatment days	1–2‡, 8–9, 15–16	1–2, 8–9, 15–16	1–2, 15–16	
Lenalidomide	25 mg	25 mg	25 mg¶	25 mg¶
Treatment days	1–21	1–21	1–21	1–21
Dexamethasone	40 mg§	20 mg	20 mg¶	
Treatment days	1, 8, 15, 22	1, 8, 15, 22	1, 8, 15, 22	

Blood. 2012 Jun 4. [Epub ahead of print]

Figure 4. Progression-free survival (N=53)



After a median of 12 cycles (range 1–25), 62% (N=53) achieved at least nCR & 42% sCR) In 36 patients completing 8 or more cycles, 78% reached at least nCR and 61% sCR.

Blood. 2012 Jun 4. [Epub ahead of print]

Carfilzomib abstract 303 Siegel

- 20/M2 12 cycles same schedule all prior bortezomib
- Neuropathy 69%
- IMiD 77%
- ≥PR 18% ≥MR 30%
- Median TTP 5.3 mos
- Patients being enrolled @27/M2

Niesvetsky Blood 2010 abstract 304

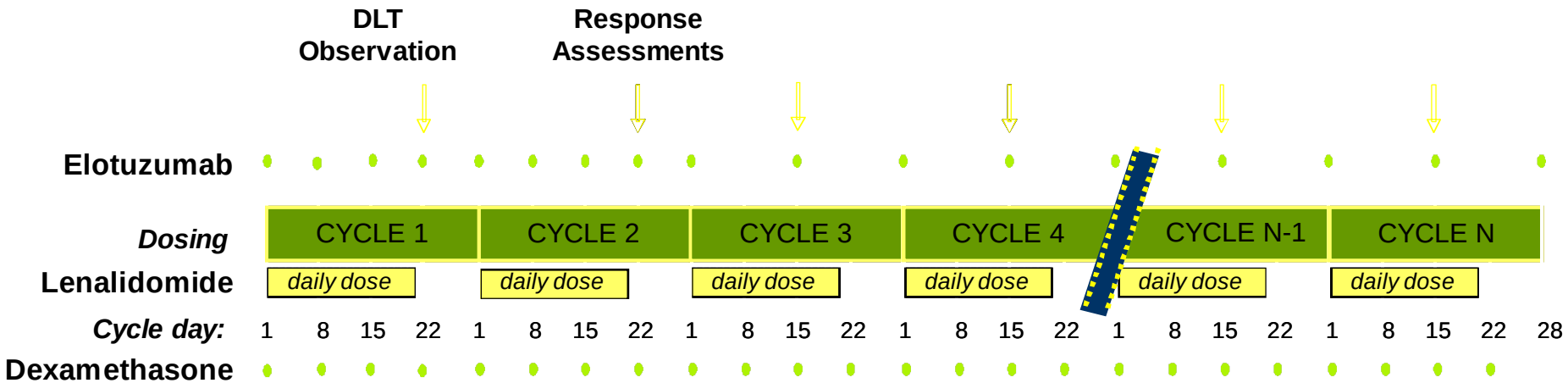
- Rd+CFZ Ph 1
- 16 cycles Dex 1,8,15,22 cycles 1-4; d1 only cycles 5-16
- R d1-21; CFZ 1,2,8,9,15,16 cycles 1-8; 1,2,15,16 cycles 9-16
- N=32, 28 prior IMiD
- MTD R 25, CFZ 27/M2 ≥VGPR 38%, ≥PR 59% ≥MR 72% Ph3 CFZ Rd vs Rd

Elotuzumab

- Anti CS-1 humanized monoclonal expressed on PC's NK's & CD8 T cells
- Phase 1 study IV q 2 weeks
- MTD was not reach @ 20 mg/kg (1.6 g for an 80kg male vs 750 mg rituximab and 30 mg tiw for alemtuzumab)
- N=34 ORR 0

Blood 120: 552-9; 2012

Phase 1b/2 Study Schema



- Phase 1b 3+3 dose escalation cohorts evaluating elotuzumab 5, 10, and 20 mg/kg IV in combination with lenalidomide 25 mg PO and low-dose dexamethasone PO
  - First 5 patients limited to 6 cycles of therapy; remaining 23 treated until disease progression or unacceptable toxicity, if earlier
- Phase 2 randomizing (1:1) approximately 60 patients to either 10 or 20 mg/kg elotuzumab

DLT, dose-limiting toxicity.

Blood 2010:116a,abstract 1936

Best Confirmed Response (IMWG Criteria)

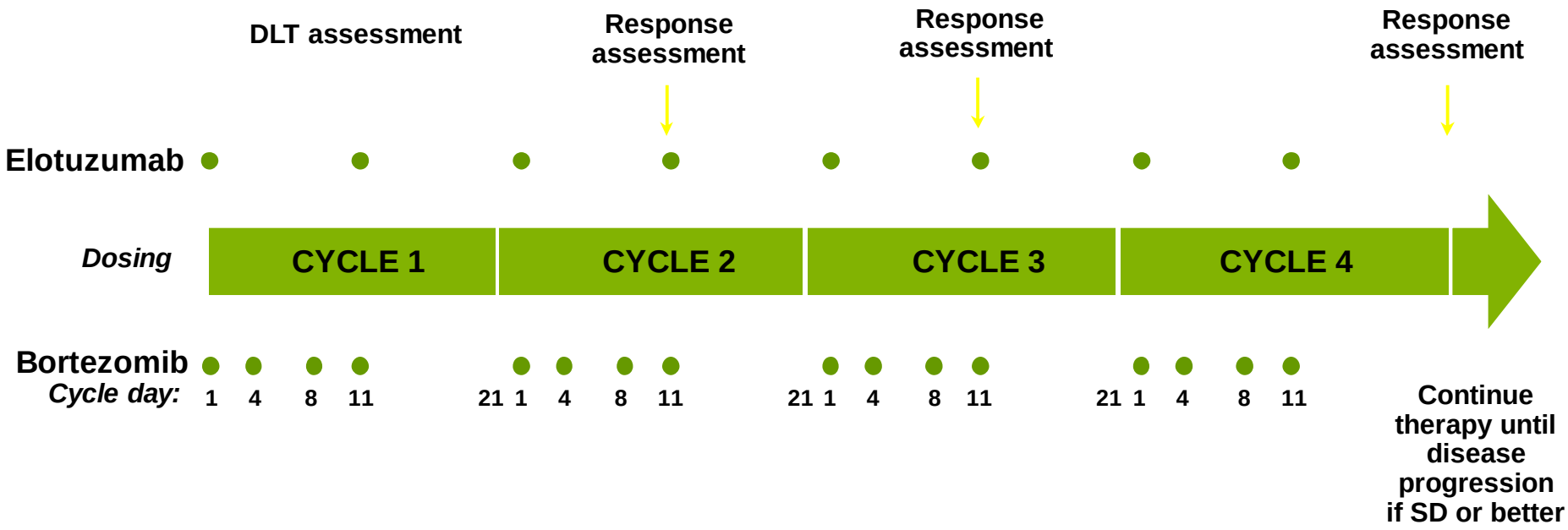
	Total Patients (%)	**Lenalidomide-Naïve Patients (%)**
Total ITT	28	22
ORR (≥ PR)	23 (82)	21 (95)
CR	1 (4)	1 (5)
VGPR	7 (25)	6 (27)
PR	15 (54)	14 (64)
SD	4 (14)	1 (5)
PD	1 (4)	0

Blood 2010:116a,abstract 1936

ORR by Prior Lines of Therapy

Prior Lines of Therapy	All Patients		Lenalidomide-Naïve Patients	
	Total	RR (%)	Total	RR (%)
1	7	6 (86)	6	6 (100)
2	5	4 (80)	3	3 (100)
3	4	4 (100%	4	4 (100)
≥4	12	9 (75)	9	8 (89)
Median: 3	28	23 (82)	22	21 (95)

Study Schema



- 3+3 dose escalation with elotuzumab 2.5, 5, 10, and 20 mg/kg IV in combination with bortezomib 1.3 mg/m^2 IV
- Expansion phase with 12 additional patients at elotuzumab 20 mg/kg
- Dexamethasone 20 mg PO added at cycle 2 or 3 on days 1, 2, 4, 5, 8, 9, 11, 12 if disease progression noted

Blood 2010; 116a abstract 3023

DLT, dose-limiting toxicity.

Efficacy

Best Confirmed Response

Parameter	Response by EBMT (%)	Response by Combined Uniform Criteria (%)
Total patients*	27	27
(≥ PR)	13 (48)	15 (56)
(≥ MR)	17 (63)	19 (70)
CR	2 (7)	2 (7)
SD	7 (26)	5 (19)
PD	3 (11)	3 (11)

Conclusion

- There is more that we do not know than we know
- For now Len maintenance is not standard of care for all myeloma patients. Longer follow up on any possible survival benefits and late toxicities (SPM) required
- This is not to say that Len maintenance is wrong, it could be completely right but longer time necessary to buy in

Conclusion

- Triplet induction with novel agents is clearly better than doublets of standard therapy (VAD)
- Triplet induction with novel agents may not produce better OS than doublets.
- Time with neurotoxicity is a real issue as survival imporves.
- New drug development is rapid & exciting

- The ability to successively salvage patients with new more active agents hold out the hope of pushing survivals to the point where myeloma becomes a truly chronic disease.