Tailoring Multiple Myeloma Therapy for Special Populations

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Disclosures for Palumbo Antonio, MD

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Scientific Advisory Board	No relevant conflicts of interest to declare

Presentation includes discussion of the off-label use of a drug or drugs

Discontinuation Reduces Dose-Intensity

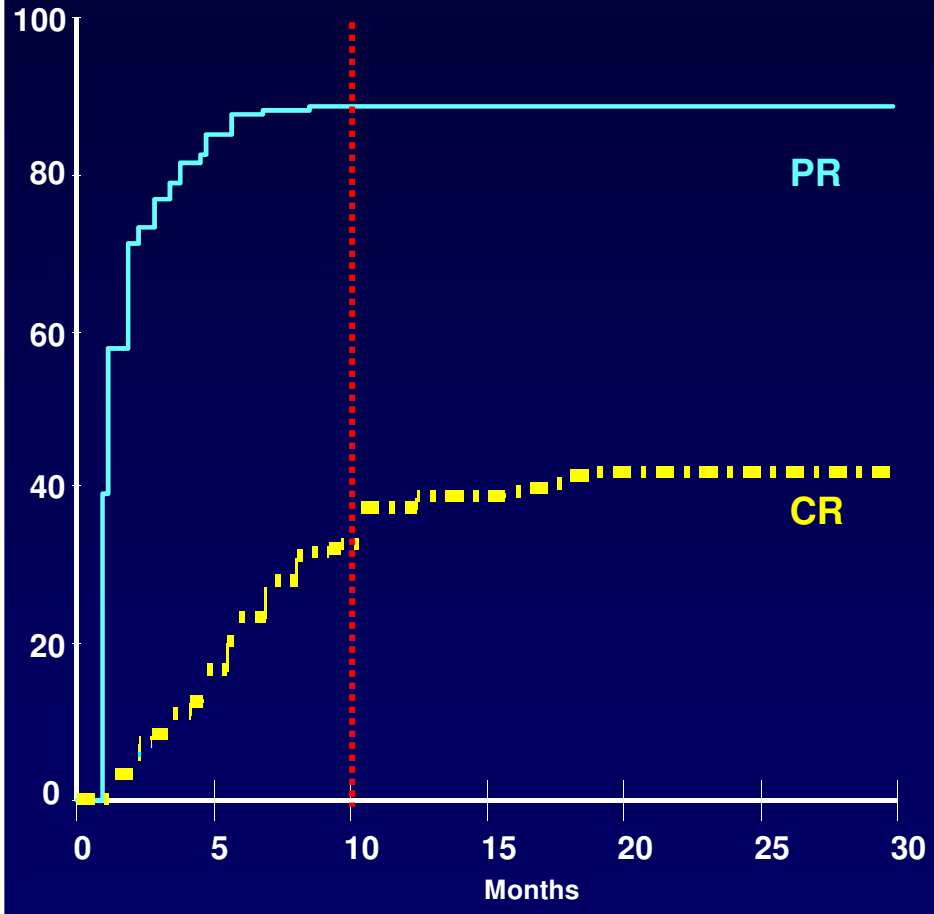
	3 Drug	2 Drug
Discontinuation %		
65 years - 75 years	17	10
>75 years	34	16
Cumulative dose intensity %		
65 years - 75 years	88	97
>75 years	56	97

Palumbo A, et al. *Haematologica.* 2011;96(suppl 2): Abstract 0514.

Time to PR and Time to CR

Bortezomib-Paradigm

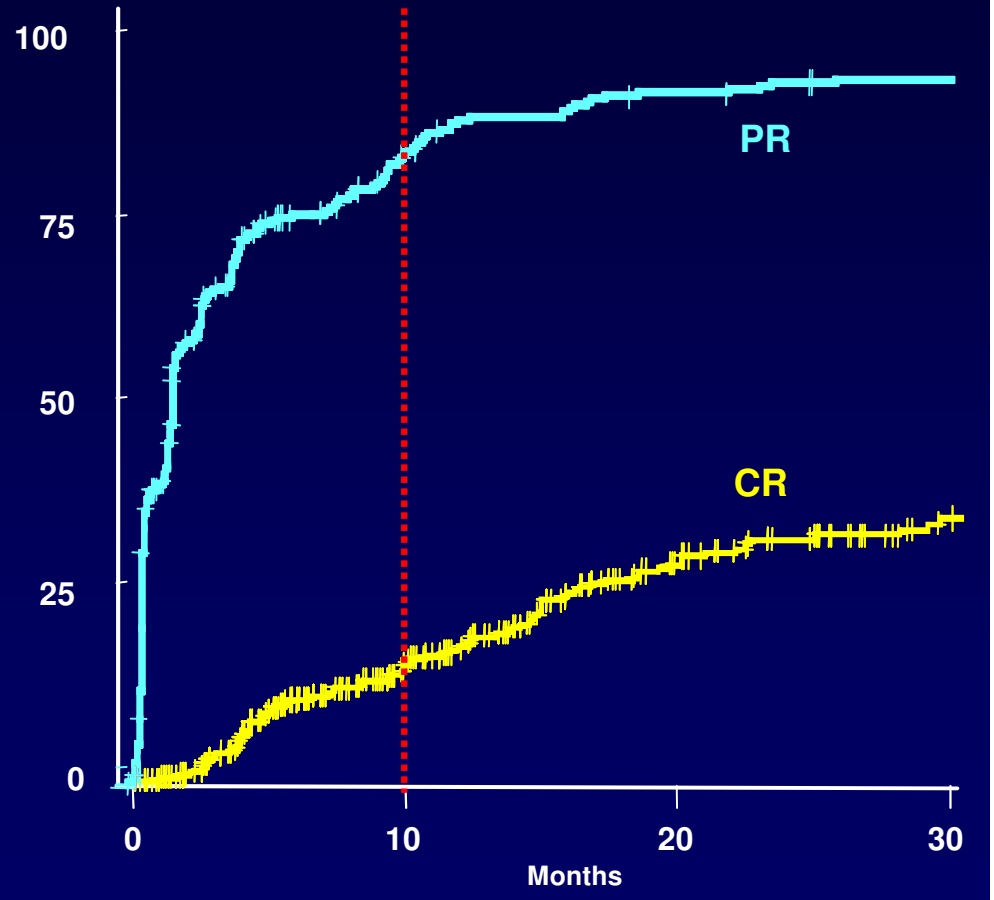
VMPT-VT



Palumbo A,et al. *J Clin Oncol*. 2010;28(34):5101-5109.

Lenalidomide-Paradigm

MPR vs MEL200



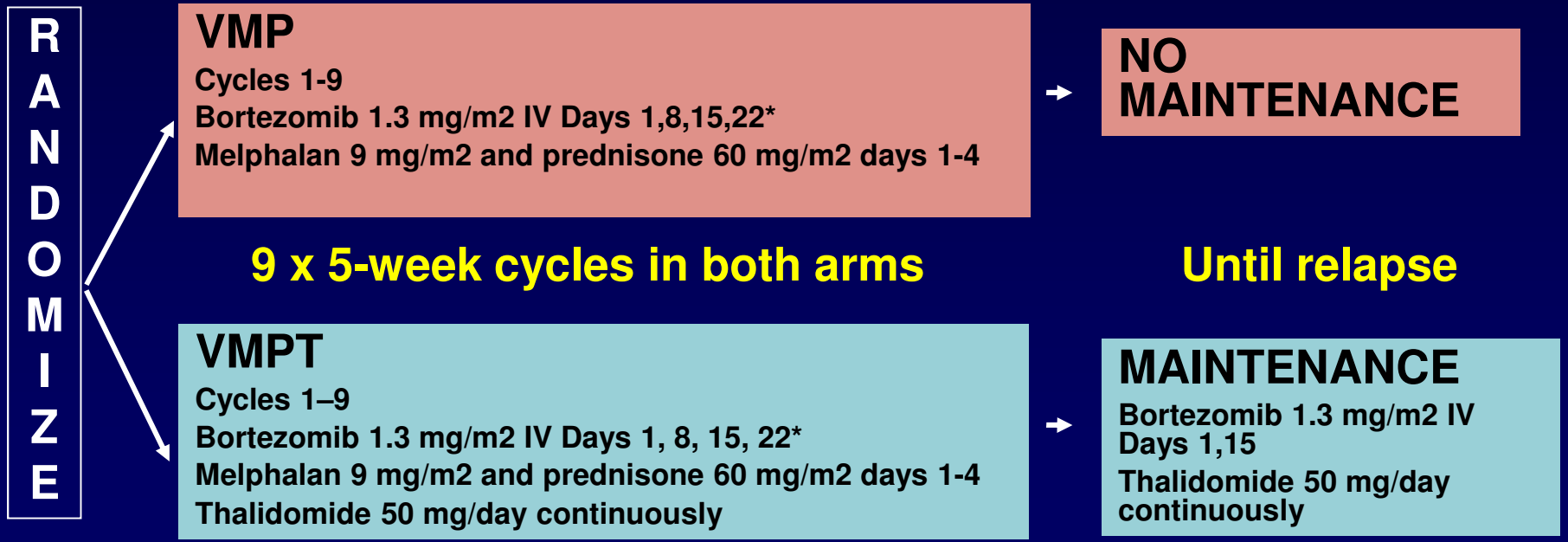
Palumbo A, et al. *Blood*. 2011;118: Abstract 3069.

PR, partial response; CR, complete response; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance; MPR, melphalan-prednisone-lenalidomide; MEL200, melphalan 200 mg/m2

New Treatment Options

Bortezomib-Melphalan-Prednisone-Thalidomide: VMPT-VT vs VMP

- **511 patients** (≥65 years) randomized from 61 Italian centers
- Patients: symptomatic MM/end-organ damage with measurable disease
  - ≥65 years or <65 years and not transplant-eligible; creatinine <2.5 mg/dL



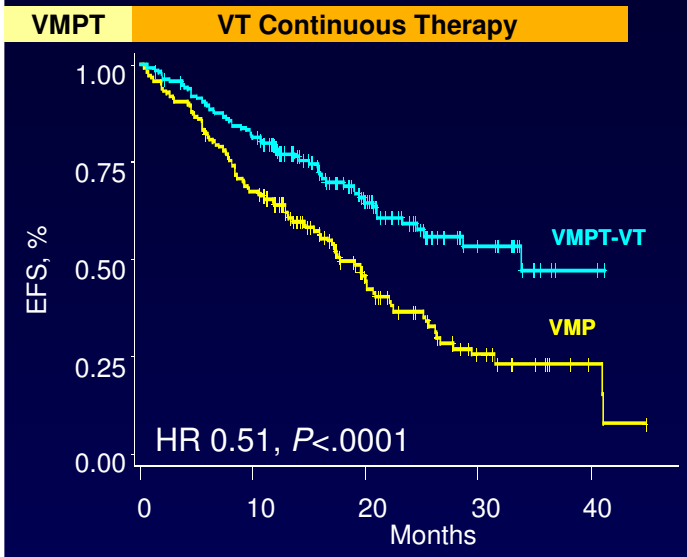
*66 VMP patients and 73 VMPT-VT patients were treated with twice weekly infusions of bortezomib

VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance; VMP, bortezomib-melphalan-prednisone-lenalidomide

Palumbo A, et al. *J Clin Oncol.* 2010;28(34):5101-5109.

VMPT-VT: Landmark Analysis

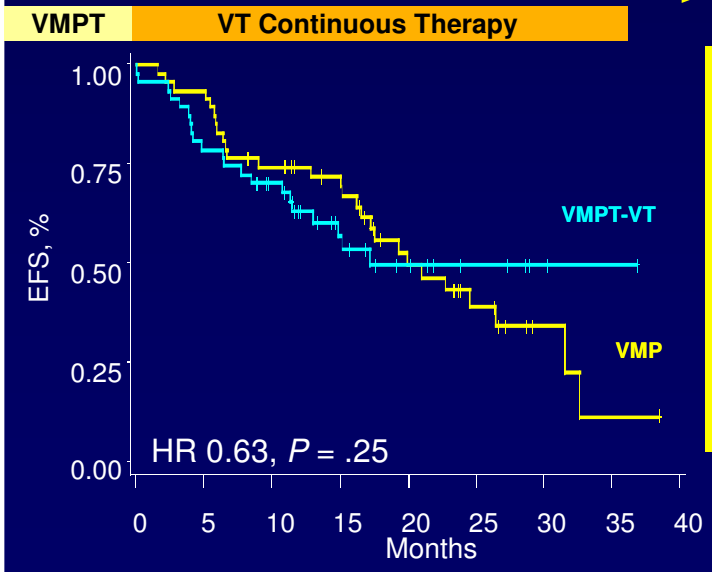
65–75 years of age



TOTAL		INDUCTION		MAINTENANCE	
Disc. for AEs	Bort. dose intensity*	Disc. for AEs	Bort. dose intensity*	Disc. for AEs	Bort. dose intensity*
25%	81%	**17%**	**89%**	12%	77%

*** Cumulative dose**

>75 years of age

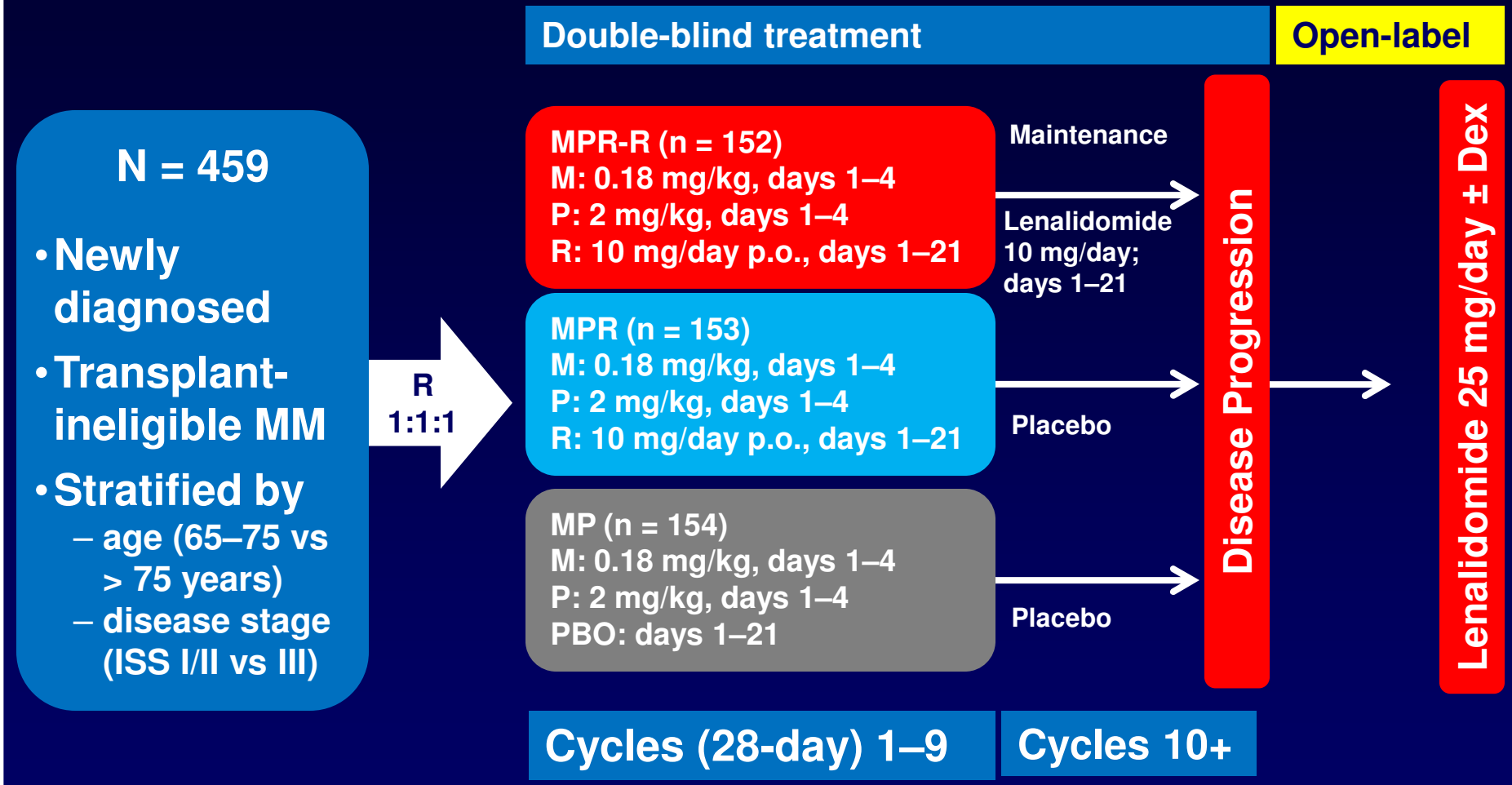


TOTAL		INDUCTION		MAINTENANCE	
Disc. for AEs	Bort. dose intensity*	Disc. for AEs	Bort. dose intensity*	Disc. for AEs	Bort. dose intensity*
35%	58%	**29%**	**63%**	14%	49%

*** Cumulative dose**

Palumbo A, et al. *Blood*. 2010;116: Abstract 620.

Melphalan-Prednisone-Lenalidomide: MPR-R vs MPR vs MP



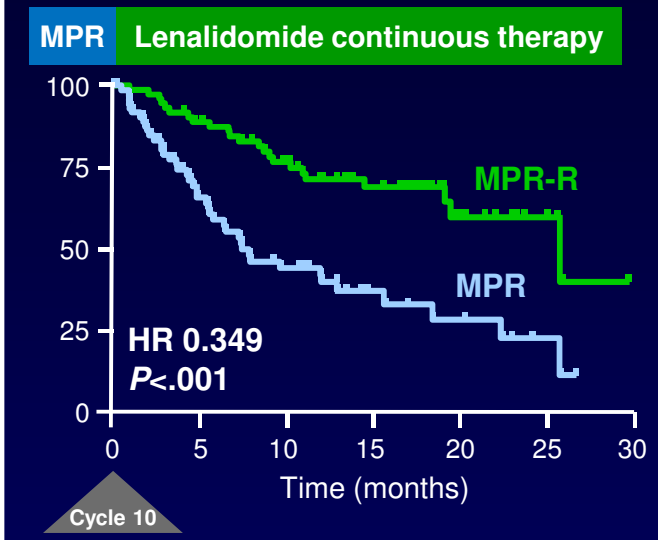
* All patients received thromboprophylaxis during induction; thromboprophylaxis could be continued during maintenance at physician's discretion.

MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide maintenance; MPR, melphalan-prednisone-lenalidomide; MP, melphalan-prednisone; PBO, placebo

Palumbo A, et al. *N Engl J Med*. 2012;366(19):1759-69.

MPR-R: Landmark PFS Analysis By Age

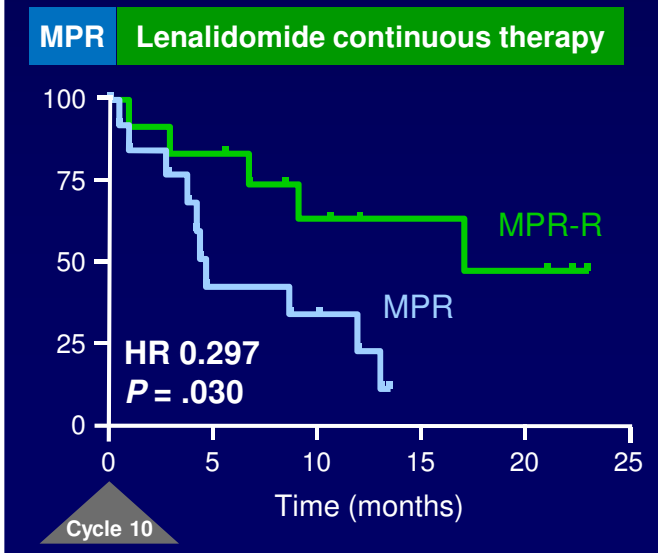
65-75 years of age



INDUCTION				MAINTENANCE	
Disc. for AEs %	*Dose intensity - %			Disc. for AEs %	*Dose intensity - %
	Len	Mel	Pred		Len
12	88	91	94	8	92

* Median relative dose

>75 years of age



INDUCTION				MAINTENANCE	
Disc. for AEs %	*Dose intensity - %			Disc. for AEs %	*Dose intensity - %
	Len	Mel	Pred		Len
28	76	85	89	17	87

* Median relative dose

Palumbo A, et al. *Haematologica*. 2011;96(Suppl 2): Abstract 514.

Frail Patients

Age-Adjusted Therapy

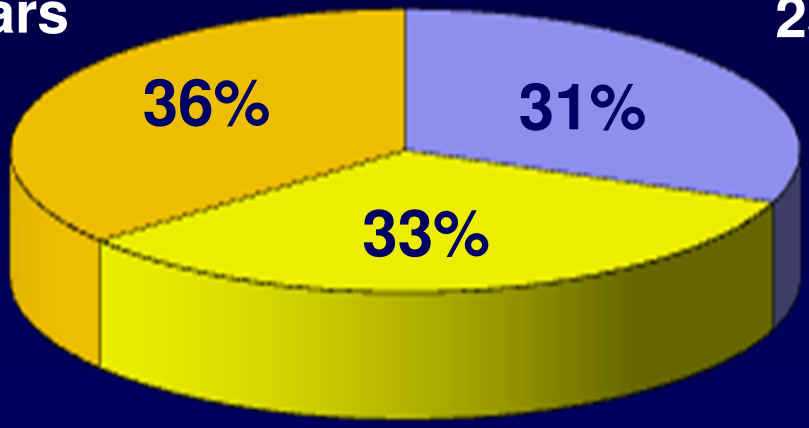
INCIDENCE: 2002 8.9/100.000

Full-dose chemotherapy

65-74 years

Autologous transplant

25-64 years

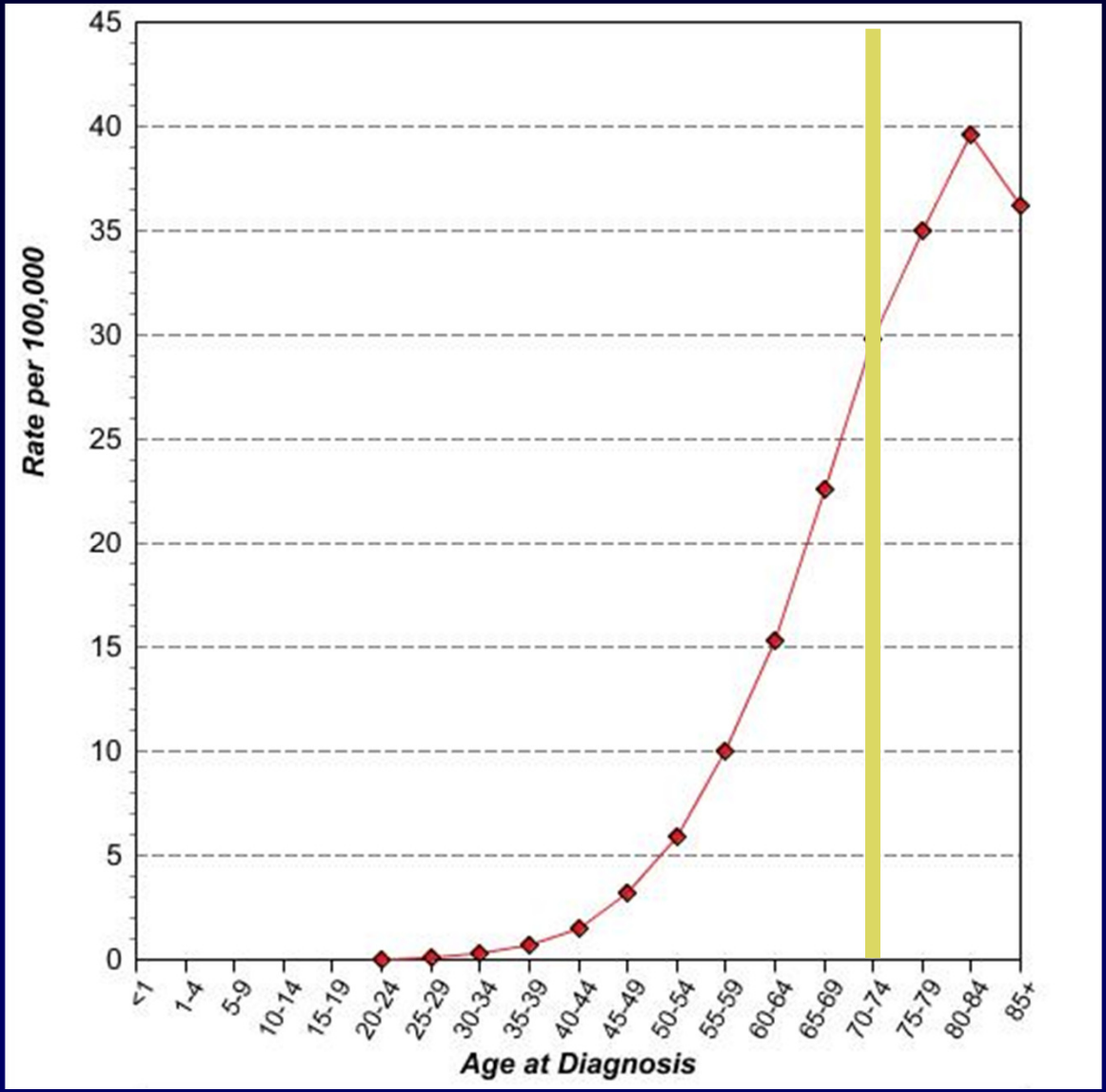


75-101 years

Reduced-dose chemotherapy

Regione Piemonte, Assessorato Sanità 2006

Age-Specific (Crude) SEER Incidence Rates: Multiple Myeloma



Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics. Available at: http://www.cancer.gov/aboutnci/servingpeople/snapshots/myeloma.pdf. 2010.

Period Life Expectancy 2007

Period Life Table, 2007						
	Male			Female		
Age	Death probability*	Number of lives^	Life expectancy	Death probability*	Number of lives^	Life expectancy
0	0.007379	100,000	75.38	0.006096	100,000	80.43
25	0.001446	97,834	51.78	0.000528	98,746	56.35
50	0.005512	92,224	28.99	0.003255	95,530	32.69
65	0.016723	79,684	17.19	0.010698	87,473	19.89
70	0.025579	72,066	13.73	0.017163	81,944	16.05
75	0.04001	61,612	10.62	0.027709	73,679	12.55
80	0.064457	47,974	7.9	0.045561	61,930	9.43
85	0.105937	31,699	5.65	0.078471	46,123	6.77
90	0.174013	15,722	3.92	0.13619	27,333	4.69
95	0.27075	4,794	2.75	0.222541	10,824	3.26
100	0.361644	754	2.07	0.311697	2,411	2.39

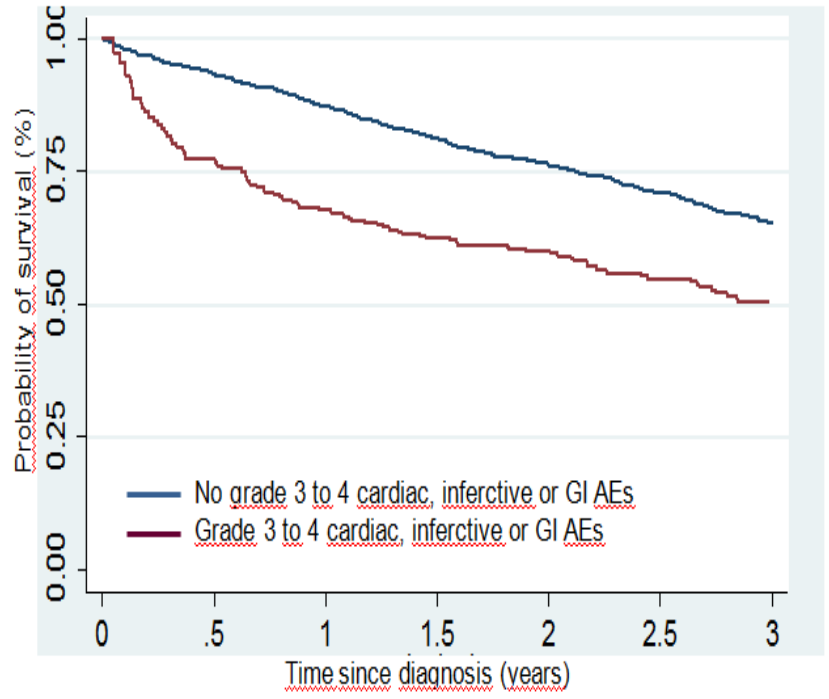
* Probability of dying within one year

^Number of survivors alive out of 100,000

Note: The period life expectancy at a given age for 2007 represents the average number of years of life remaining if a group of persons at that age were to experience the mortality rates for 2007 over the course of their remaining life.

Table extracted from U.S. Social Security life tables data. Available at: http://www.ssa.gov/oact/STATS/table4c6.html. Accessed March 29, 2012.

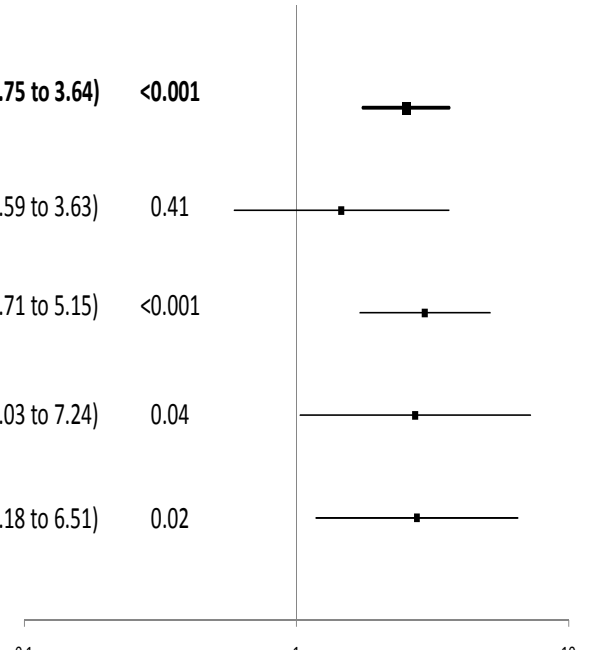
Grade 3-4 Cardiac, Infective, GI Adverse Events Impact on Survival of 1435 Myeloma Patients Multivariate Analysis



No. at Risk

No cardiac, infective, GI Aes	1435	1145	1030	929	775	563	368
Cardiac, infective, GI Aes	0	141	149	153	136	107	82

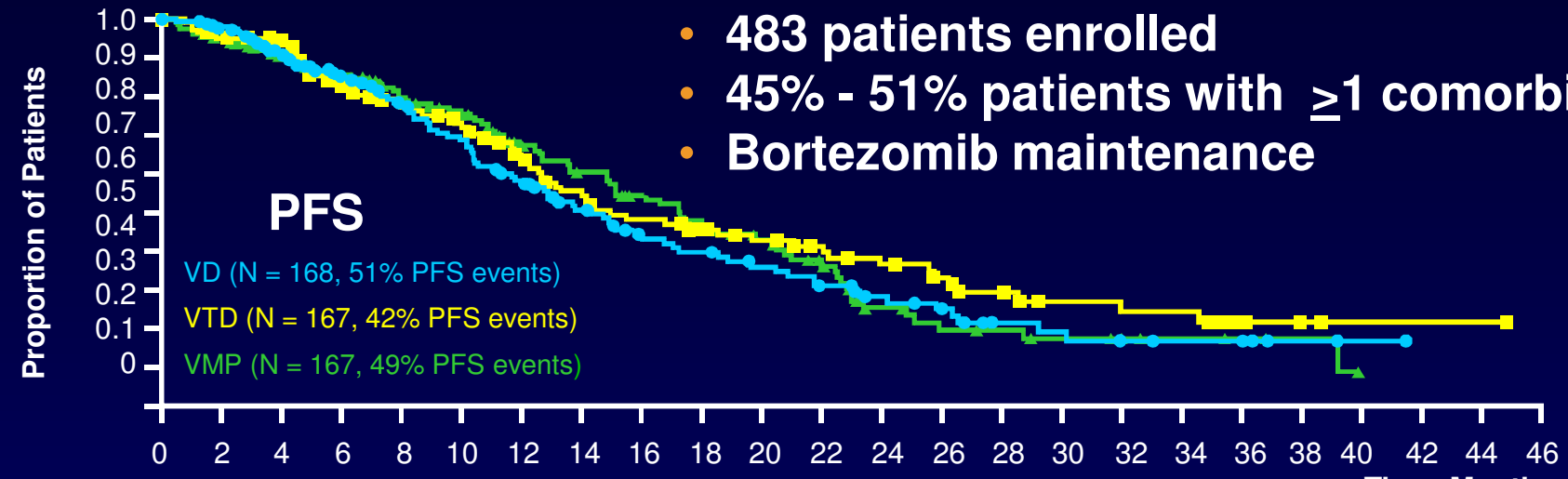
	HR (95% CI)	P value
All	**2.53 (1.75 to 3.64)**	**<0.001**
MP	1.46 (0.59 to 3.63)	0.41
MPT	2.96 (1.71 to 5.15)	<0.001
VMP	2.73 (1.03 to 7.24)	0.04
VMPT/VTP	2.77 (1.18 to 6.51)	0.02

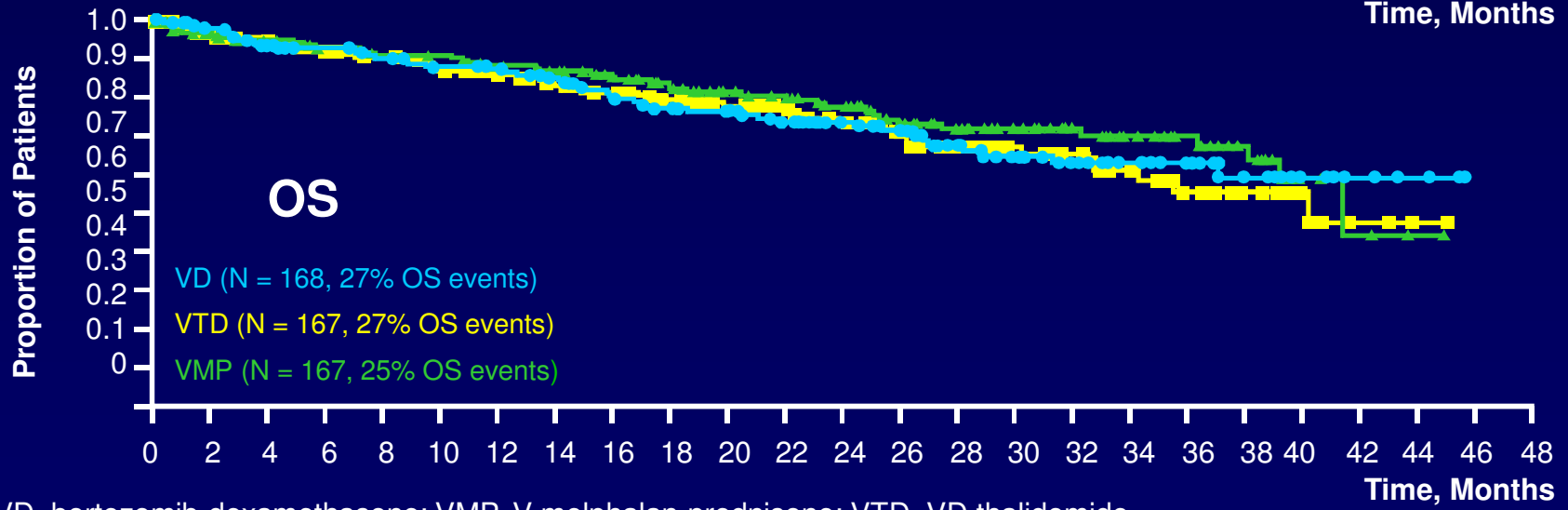


Unpublished data.

VD vs VMP vs VTD Phase IIIb Randomized Study

- 483 patients enrolled
- 45% - 51% patients with ≥1 comorbidity
- Bortezomib maintenance





VD, bortezomib-dexamethasone; VMP, V melphalan-prednisone; VTD, VD thalidomide

Niesvizky R, et al. *Blood.* 2010;116: Abstract 619.

Lenalidomide-Prednisone Melphalan-Prednisone-Lenalidomide

Cycles (28-day) 1-4	Cycles (28-day) 5-10
RP **R:** 25 mg/d, days 1-21 **P:** 50 mg 3 times/week	**MPR** M: 2 mg 3 times/week **P: 50** mg 3 times/week **R:** 10 mg/d, days 1-21

M, melphalan; P, prednisone; R, lenalidomide;

Falco P, et al. *Leukemia.* 2013;27(3):695-701.

Treatment Algorithm

Dose Level – 0	Dose Level – 1	Dose Level – 2
Lenalidomide 25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Thalidomide 100 mg/d	50 mg/d	50 mg/every other day
Bortezomib 1.3 mg/m^2 d 1, 8, 15, 22 / 5 wks	1.0 mg/m^2 d 1,8,15,22 / 5 wks	1.3 mg/m^2 d 1,15 / 4 wks
Melphalan 0.2 mg/kg/d d 1-4 / 5 wks	0.15 mg/kg d 1-4 / 5 wks	0.10 mg/kg d 1-4 / 5 wks
Prednisone 2 mg/kg/d d 1-4 / 5 wks	1.5 mg/kg/d d 1-4 / 5 wks	1 mg/kg/d d 1-4 / 5 wks

Palumbo A, et al. *N Engl J Med*. 2011;364(11):1046-1060.

Charlson Index

Assigned Weight	Conditions
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

Assigned weights for each condition that a patient has. The total equals the score.
Example: chronic pulmonary (1) and lymphoma (2) = total score (3)

Charlson M, et al. *J Chronic Dis*. 1987;40(5):373-383.

Activity of Daily Living (ADL)

Bathing (tub bath, shower, sponge bath)	Score
- Needs no assistance (gets into/outside of a bathtub without needing any help)	1
- Receives assistance in bathing only one part of the body (eg. back)	1
- Need assistance in bathing more than one part of the body	0
Dressing (taking cloths from the wardrobe/drawers and getting dressed)	
- Takes clothes and gets dress completely autonomously	1
- Takes clothes and gets dress but needs assistance to tie the shoes	1
- Needs assistance in taking clothes or dressing	0
Toileting (going to the toilet room, using toilet, arranging clothes)	
- Goes to the toilet room, uses toilet, arranges clothes without needing assistance (may use cane or walker for support and may use bedpan/urinal at night)	1
- Needs assistance to go to the toilet, using the toilet, and arranging clothes, or in using bedpan/urinal)	0
- Cannot go to the toilet	0
Transferring	
- Moves in and out of bed and uses a chair without assistance (may use cane or walker)	1
- Needs assistance for these movements	0
- Bedridden, cannot get out of bed	0
Continence	
- Controls bowel and bladder completely by self	1
- Occasional “accidents”	0
- Needs supervision to control bowel and bladder, uses a catheter, is incontinent	0
Feeding	
- Feeds self without any assistance	1
- Needs help only in cutting meat of buttering bread	1
- Needs complete assistance to eat, is partially or completely fed parenterally	0

Only one per each category can be selected. The maximum total score is 6

Katz S, et al. *JAMA.* 1963;185:914-919.

Instrumental Activity of Daily Living (IADL)

ABILITY TO USE TELEPHONE

1 ❑ Operates telephone on own initiative-looks up and dials numbers, etc…
1 ❑ Dials a few well-known numbers
1 ❑ Answers telephone but does not dial
0 ❑ Does not use telephone at all

SHOOPPING

1 ❑ Takes care of all shopping needs independently
0 ❑ Shops independently for small purchases
0 ❑ Needs to be accompanied on any shopping trip
0 ❑ Completely unable to shop

FOOD PREPARATION

1 ❑ Plans, prepares and serves meals
0 ❑ Prepares adequate meals if with supplied with ingredients
0 ❑ Heats, servese and prepares meals, or prepares meals or preapares meals but does not maintain adequate diet
0 ❑ Needs to aheve meals prepare and serve

HOUSEKEEPING

1 ❑ Maintains house alone or with occasional assistance (e.g. "heavy work domestic help"
1 ❑ Performs light daily tasks such as dish washing, bed making
1 ❑ Performs light daily tasks but cannot maintain accettable level of cleanliness
0 ❑ Needs help with all home maintenance tasks
0 ❑ Does not participate in any housekeeping tasks

LAUNDRY

1 ❑ Does personal laundry completely
1 ❑ Launders small items-rinses stockings, etc.
0 ❑ All laundry must be done by others

MODE OF TRANSPORTATION

1 ❑ Travels independently on public transportation or drives own car
1 ❑ Arranges own travel via taxi, but does not otherwise use public transportation
1 ❑ Travels on public transportation when accompanied by another
0 ❑ Travel limited to taxi or automobile with assistance of another

RESPONSIBILITY OF OWN MEDICATIONS

1 ❑ Is responsible for taking medication in correct dosage at correct time
0 ❑ Takes responsibility if medication is prepared in advance in separate dosage
0 ❑ Is not capable of dispensing own medication

ABILITY TO HANDLE FINANCE

1 ❑ Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank) collects and keeps tracks of income
1 ❑ Manage day-to-day purchases, but needs help with banking, major purchases, etc.
0 ❑ Incapable of handling money

Only one per each category can be selected.

The maximum total score is 8

Lawton MP, et al. *Gerontologist.* 1969;9(3):179-186.

New Treatment Algorithm for Elderly MM

Patient Status Assessment

- Age
- ADL
- IADL
- Charlson comorbidity score

Fit	Unfit	Frail
Age <80 yr	Fit >80 yr	Unfit >80 yr
ADL 6	ADL 5	ADL ≤4
IADL 8	IADL 6-7	IADL ≤5
Charlson 0	Charlson 1	Charlson ≥2
Go-go	***moderate-go***	***slow-go***
Full-dose regimens Dose level 0	Reduced-dose regimens Dose level -1	Reduced-dose Palliative approach Dose level -2

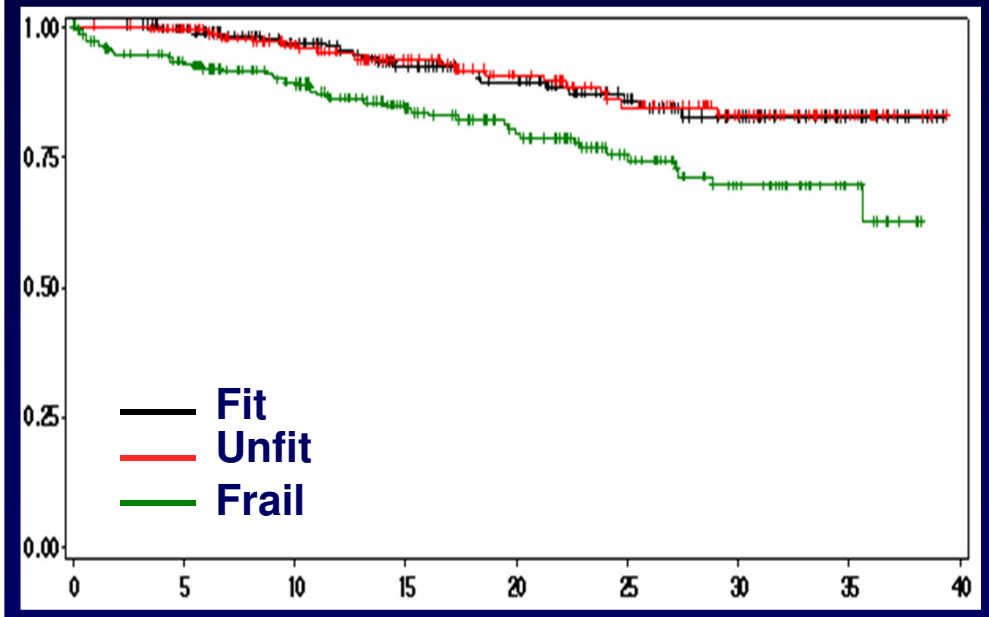
ADL, activity of daily living; IADL, instrumental activity of daily living; ASCT, autologous stem cell transplantation

Fit vs Unift vs Frail Patients With MM

Large cohorts treated with reduced-intensity regimens

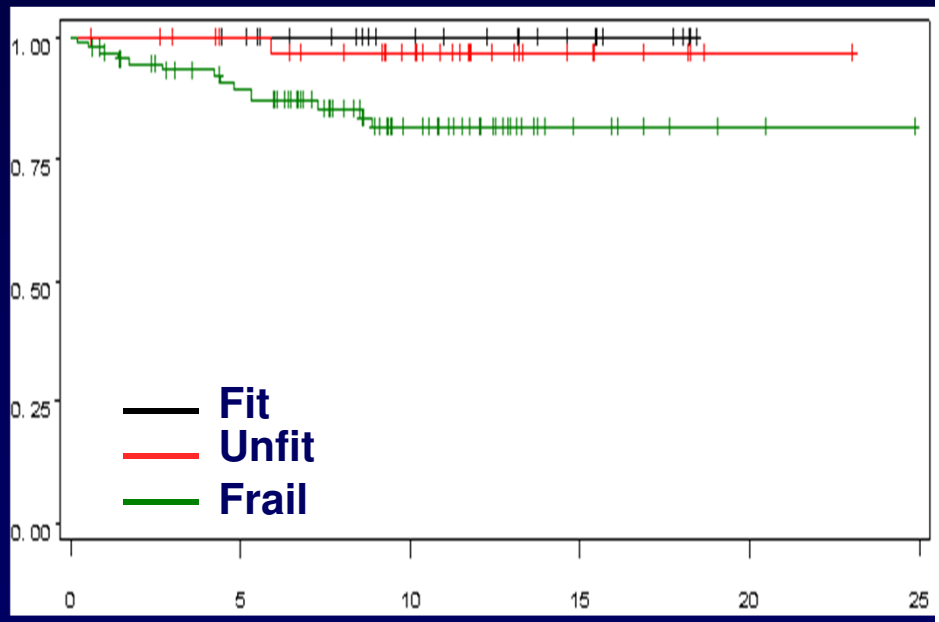
Lenalidomide regimens
650 patients; median follow-up 19 mos

OS @ 24 mos
Fit/unfit patients = 87%; frail = 77% (*P* = .0006)



Bortezomib regimens
150 patients; median follow-up 10 mos

OS @ 24 mos
Fit/unfit patients= 96%; frail= 85% (*P* = .014)



Fit: age <80 years and adl = 6 and IADL = 8 and Charlson = 0

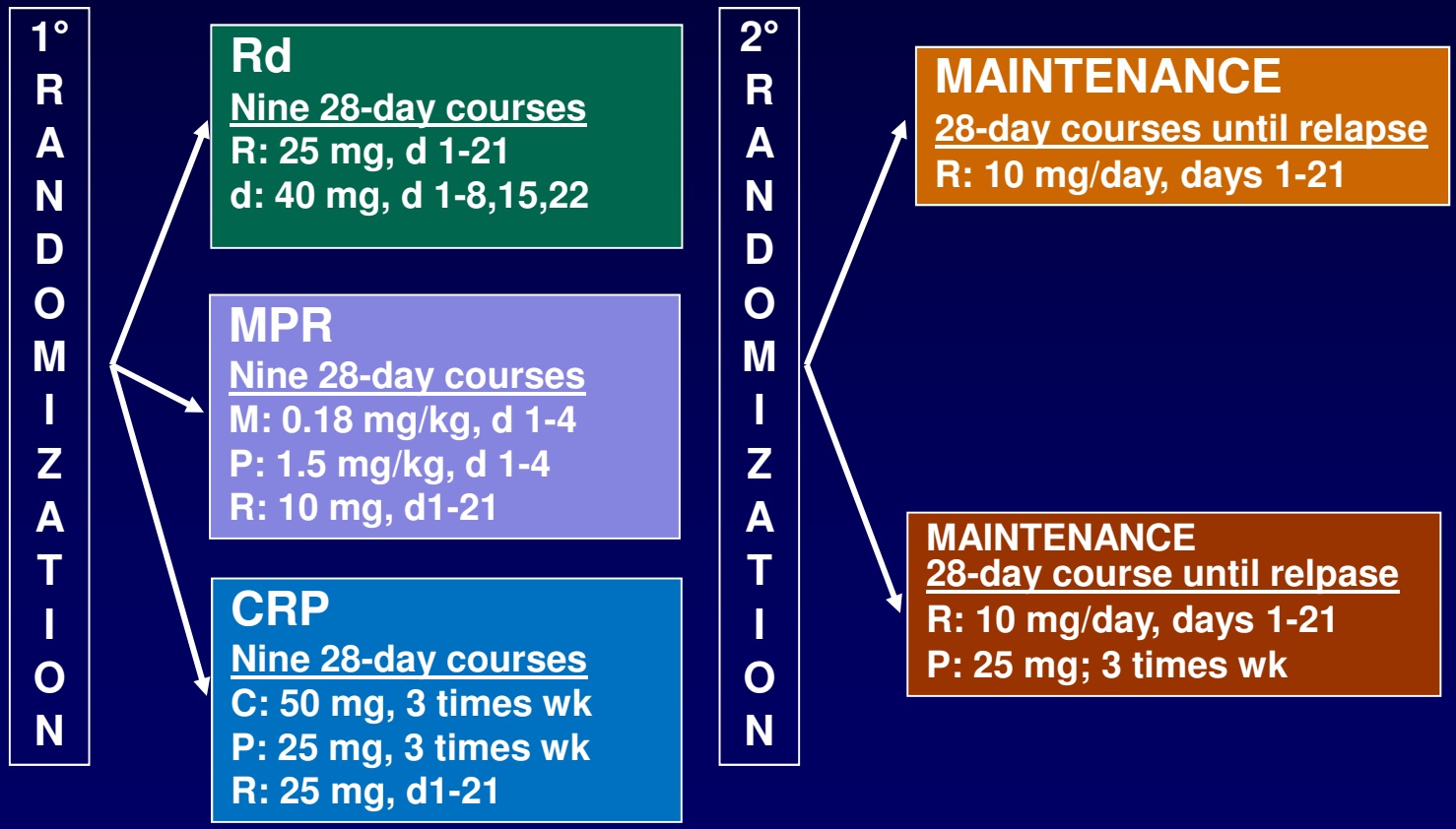
Unfit: fit age ≥80 years or adl = 5-6 or IADL = 6-7 or Charlson = 1

Frail: unfit age ≥80 or adl ≤4 or IADL ≤5 or Charlson ≥2

RD vs MPR vs CRP
Age >65 Years

Treatment Schedule

- **650 patients (older than 65 years) randomized from 5 countries**
- **Patients: symptomatic disease, organ damage, measurable disease**



C, cyclophosphamide; R, lenalidomide; M, melphalan; P, prednisone

Outcome in Fit vs Unfit vs Frail Patients

	Rd		MPR		CPR	
	Fit (n = 62)	Frail (n = 89)	Fit (n = 67)	Frail (n = 84)	Fit (n = 64)	Frail (n = 83)
GR ≥3 AEs %						
Hematologic	29	30	58	63	36	28
Nonhematologic	22	25	21	32	17	29
Response rates %						
≥ VGPR	34	37	33	29	36	21
≥ PR	77	69	79	68	78	70

Fit patient < fit 80 years or ADL = 6 or IADL = 8 or Charlson = 0

Frail patient > unfit 80 years or ADL ≤4 or IADL ≤5 or Charlson >2

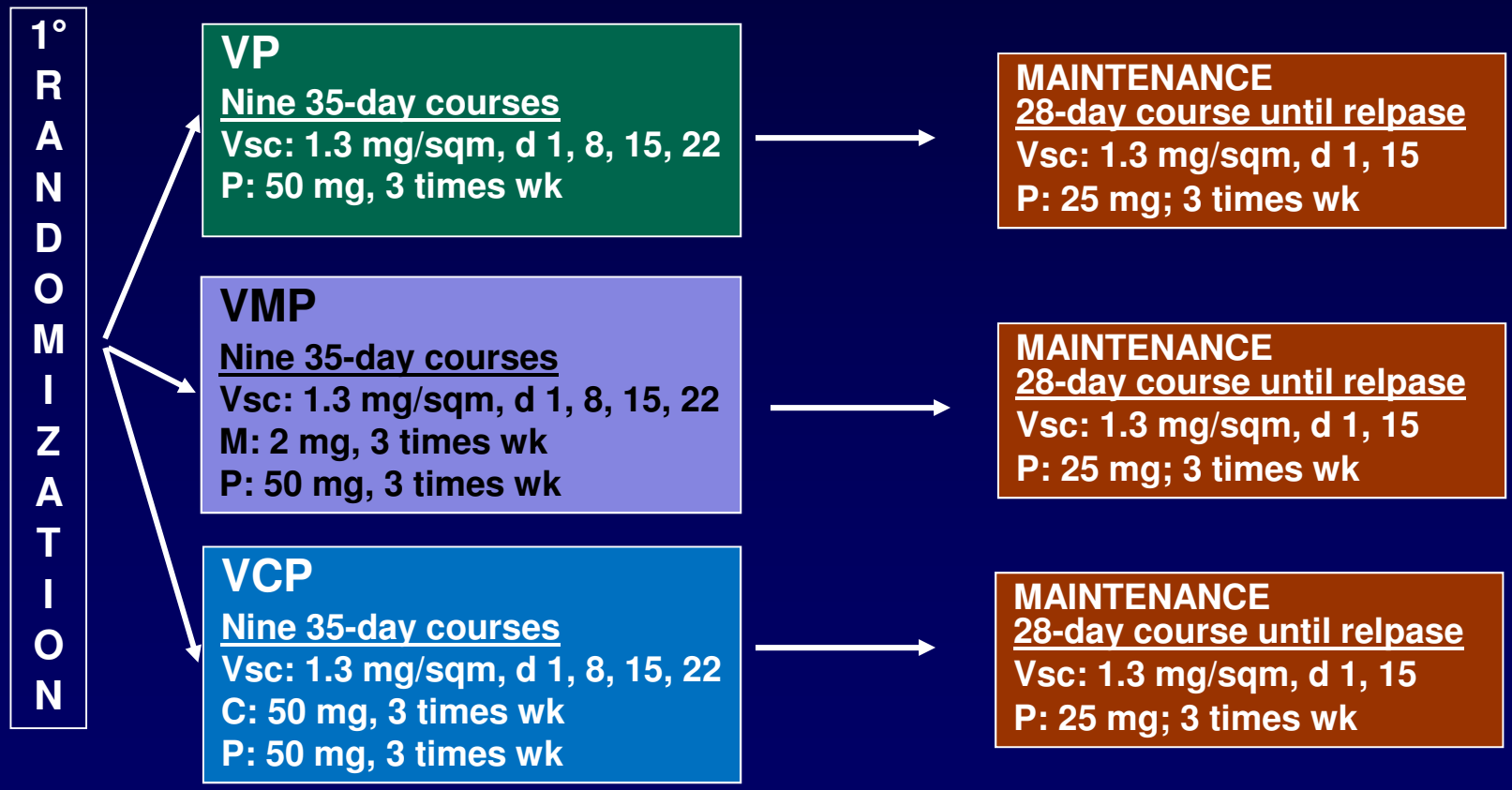
C, cyclophosphamide; R, lenalidomide; M, melphalan; P, prednisone; GR, grade; AE, adverse event; ≥ VGPR, at least very good partial response; ≥ PR, at least partial response

Subcutaneous
VP vs VMP vs VCP
Age >75 years

Treatment Schedule

Treatment Schedule

- **150** patients (>75 years) randomized from 3 countries
- Patients: Symptomatic disease, organ damage, measurable disease



Vsc, subcutaneous bortezomib, cyclophosphamide; M, melphalan; P, prednisone

Outcome in Fit vs Frail Patients

	VP		VMP		VCP	
	Fit (n = 11)	Frail (n = 40)	Fit (n = 19)	Frail (n = 31)	Fit (n = 22)	Frail (n = 29)
Safety %						
GR 3-5 AEs	36	30	32	48	27	52
Discont for Aes	9	15	21	23	9	21
Response rates %						
≥ PR	82	60	58	77	68	52

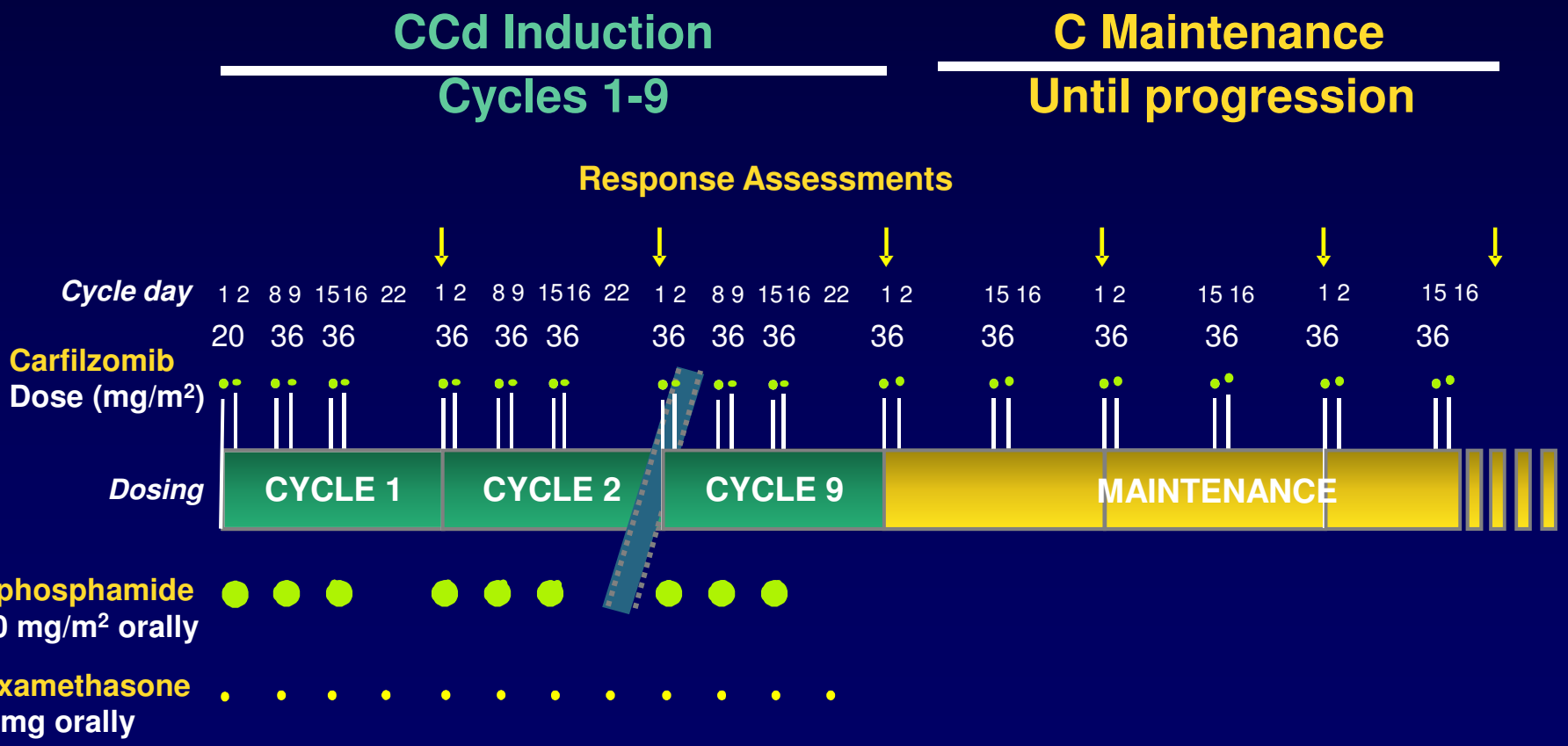
Frail defined as: age ≥ 80 years or ADL ≤4 or IADL ≤5 or Charlson ≥2

V, subcutaneous bortezomib; C, cyclophosphamide; M, melphalan; P, prednisone; GR, grade; AE, adverse event; ≥ PR, at least partial response

Carfilzomib, Cyclophosphamide, and Dexamethasone (CCd) for NDMM

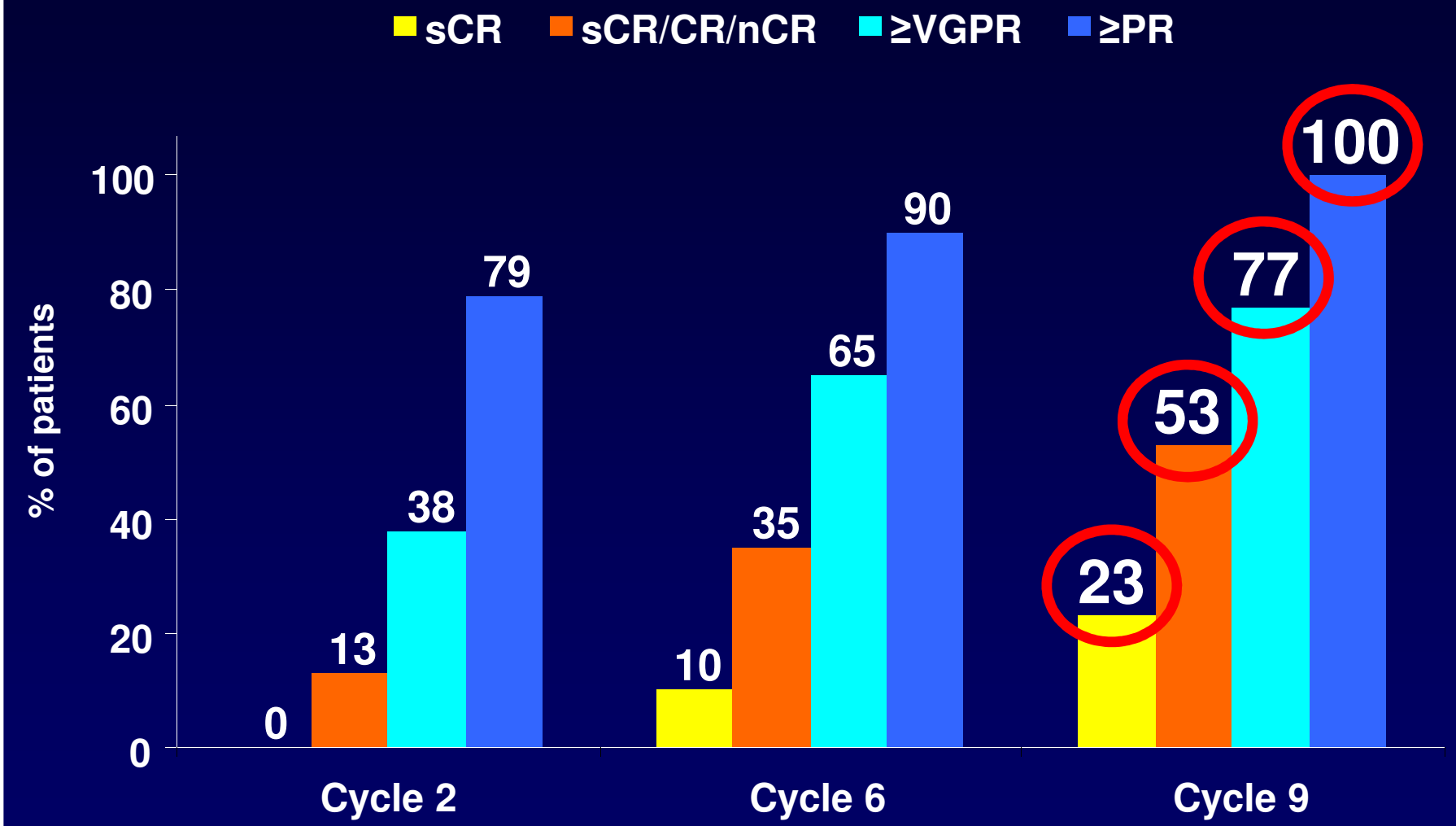
Study Design

- Phase II
- Multicenter (10 centers)



Palumbo A, et al. *Blood.* 2012;120: Abstract 730.

Response Rate by Treatment Duration

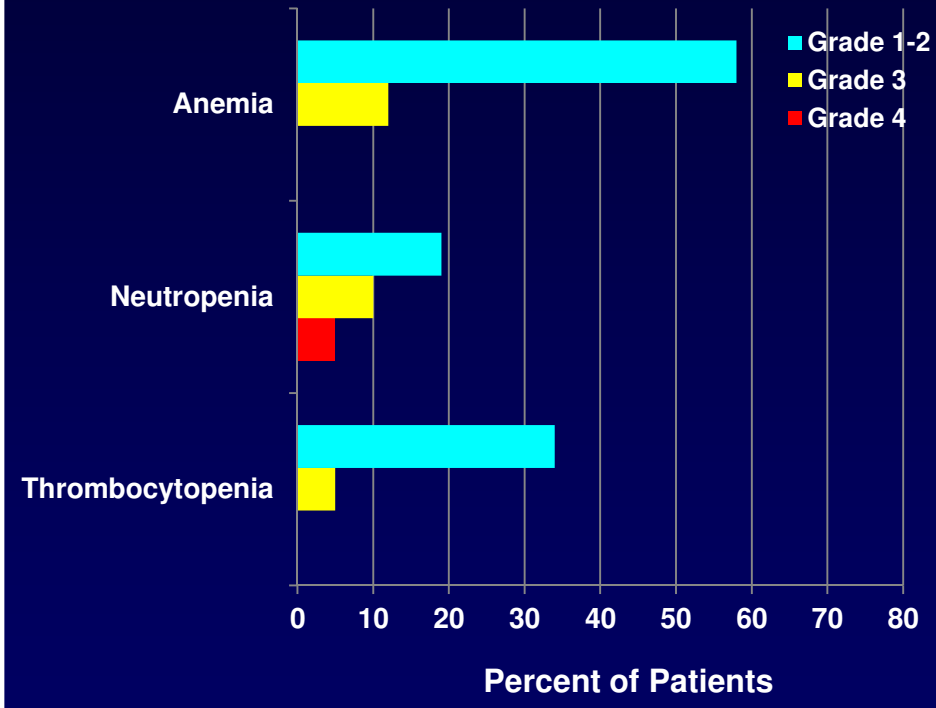


sCR, stringent complete response; CR, complete response; nCR, near complete response; ≥VGPR, at least very good partial response; ≥ PR, at least partial response

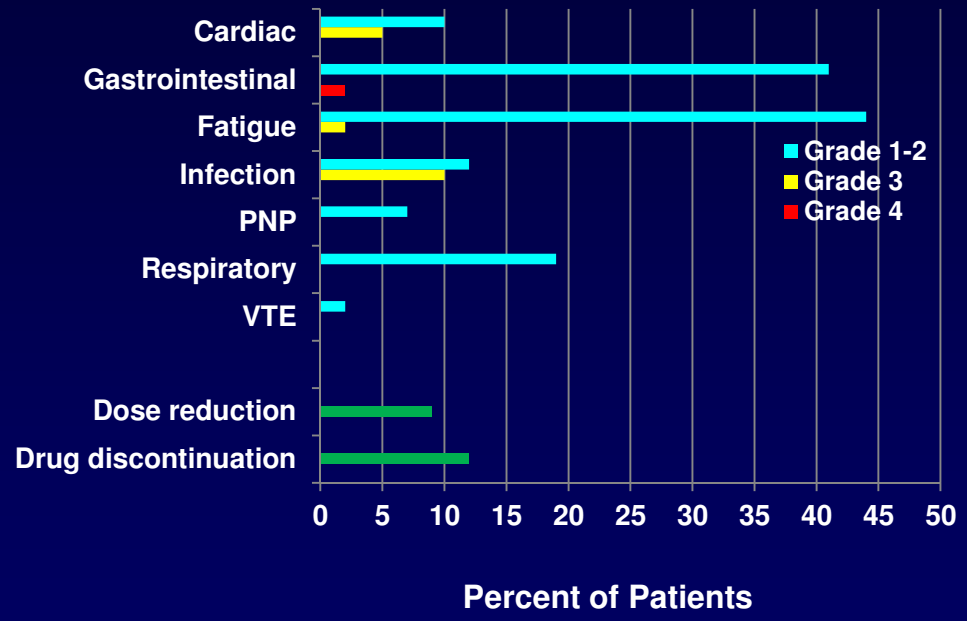
Palumbo A, et al. *Blood.* 2012;120: Abstract 730.

Adverse Events – All Grades

Hematologic



Nonhematologic



No difference between patients younger and older than 75 years

Palumbo A, et al. *Blood.* 2012;120: Abstract 730.

Outcome In Fit Vs Unfit Vs Frail Patients

	CCd		
	Fit (n = 23)	Unfit (n = 20)	Frail (n = 15)
≥1 nonhematologic AE %	17	20	20
Discontinuation rate[a], %	13	10	7
Carfilzomib dose intensity, %	22	27	19

Unfit defined as: fit patient >80 years or ADL 5 or IADL 6-7 or Charlson 1

Frail defined as: unfit patient >80 years or ADL ≤4 or IADL ≤5 or Charlson >2

CCd, carfilzomib-cyclophosphamide-dexamethasone; AE, adverse event; [a]Discontinuation due to AEs; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living

Conclusion

PATIENT STATUS ASSESSMENT

- Age > 80 years
- ADL, activity of daily living
- IADL, instrumental activity of daily living
- Charlson comorbidity score

- Lower doses
- 2 drug combination
- 2 drugs → 3 drugs or higher doses

Rd **Vd** **CCd**

Lower frequency of SAE

Better outcome in frail patients

Rd, Lenalidomide Dex; Vd, Bortezomib Dex ; CCd, Carfilzomib Cyclophosphamide Dex