Trattamento del Mieloma Multiplo nel paziente non candidabile al trapianto: dalla prima linea alla recidiva

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Goals of therapy in elderly patients

- Rapid symptom control
- Optimal quality of life
- Few and acceptable side effects
- Best possible quality of response
- Long PFS
- Long OS
- Cure ?

Characteristics of the Elderly Patient

Chronological age does not necessarily correlate with biological age

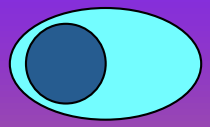
All three individuals are 70 years old

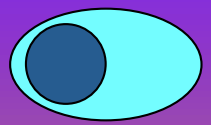
Fit

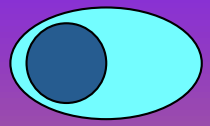
Minor morbidity

significant morbidity

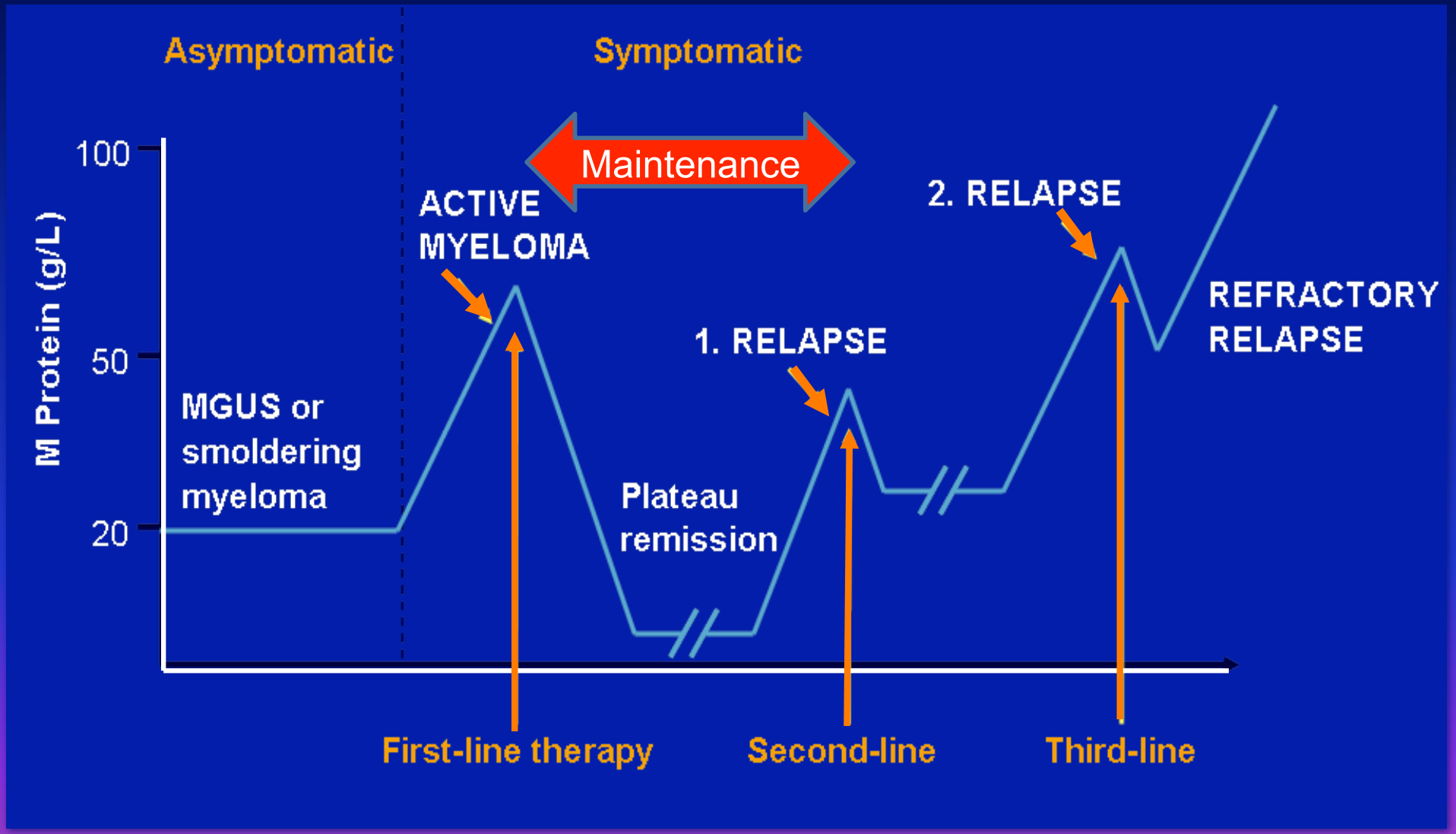
The variation in biological fitness in a specific age cohort increases with rising age, but the ‚biology' of myeloma cells does not vary with age







The natural course of multiple myeloma



Drug combinations for elderly patients

Possible options

1-drug*	2 - drugs	3- drugs	4 - drugs
Dex	Bendamustine+P	MPT	VMPT
Thal	VD	VMP	
	MP*	CTD	
	Thal-Dex	VTD	
	Len-Dex	VRD	

*only exceptional cases

Most commonly used combinations contain 2-3 drugs

1L Therapy for MM NO ASCT elderly pts in Italy

VMP

è indicato per il trattamento di pazienti adulti con mieloma multiplo precedentemente non trattato non eleggibili a chemioterapia ad alte dosi con trapianto di cellule staminali ematopoietiche.

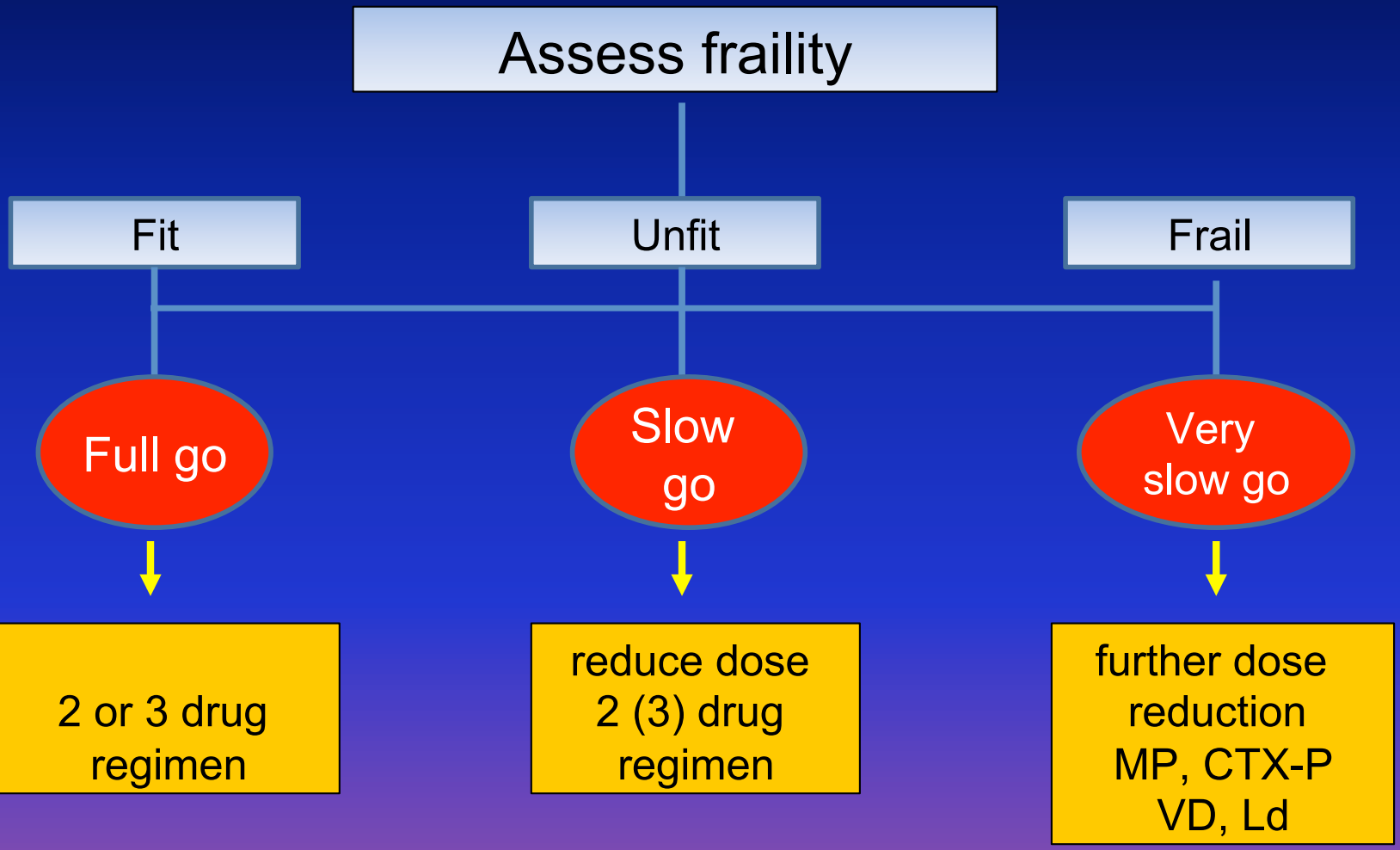
MPT

è indicato per il trattamento di prima linea di pazienti con mieloma multiplo non trattato di età ≥ 65 anni o non idonei a chemioterapia a dosi elevate.

Rd

è indicato per il trattamento di pazienti adulti con mieloma multiplo non precedentemente trattato che non sono eleggibili al trapianto

Treatment of patients with multiple myeloma not eligible for transplantation



Instruments for assessing frailty and allocation to treatment groups

Assess
- 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	Reduced-dose regimens	Reduced-dose Palliative approach
Dose level 0	Dose level -1	Dose level -2

Palumbo A et al. IMW 2013

Adaptation of dose according to risk factors

Agent	Dose level 0	Dose level-1	Dose level - 2
Dexamethasone	40 mg	20 mg	10 mg
Melphalan	0.25 mg/kg or 9 mg/m^2	0.18 mg/kg or 7.5 mg/m^2	0.13 mg/kg or 5 mg/m^2
Thalidomide	100 mg	50 mg	50 mg/qod
Lenalidomide	25 mg	15 mg	10 mg
Bortezomib	1.3 mg twice weekly, sc	1.3 mg weekly, sc	1.0 mg weekly, sc
Prednisone	60 mg/m^2	30 mg/m^2	15 mg/m^2
Cyclophosphamide	100 mg	50 mg	50 mg/qod

Palumbo et al.,BLOOD 2011

Comorbidities relevant for treatment selection in myeloma

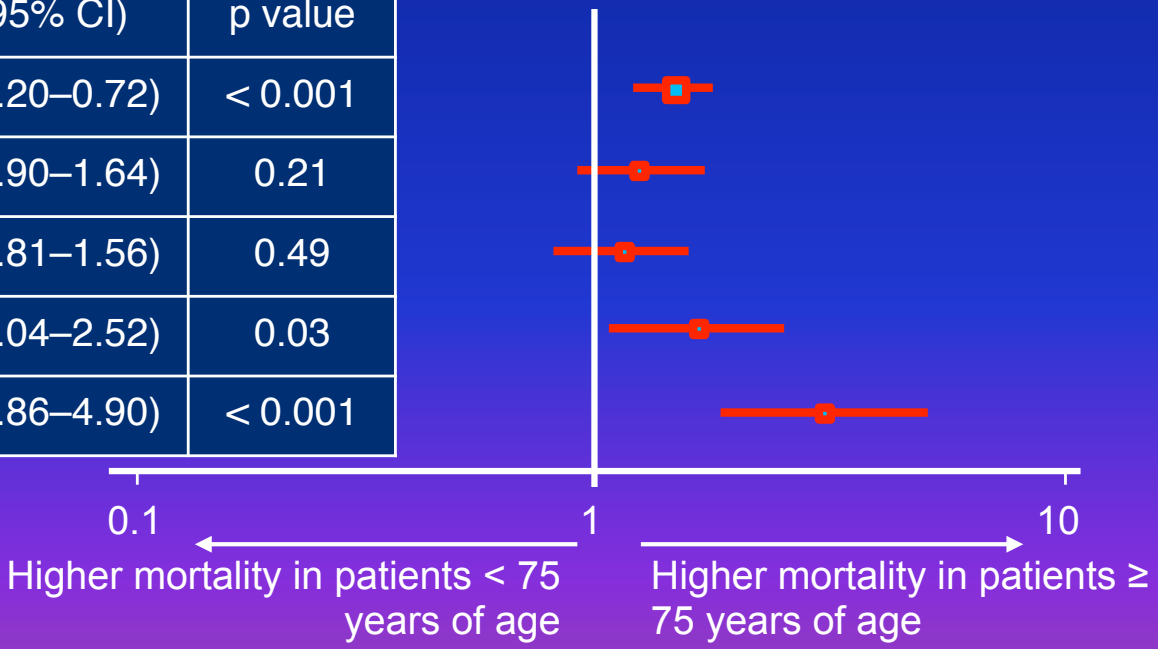
Polyneuropathy	Avoid bortezomib (or use once weekly sc)
Renal impairment	Consider dose adaptations when using lenalidomide
Bone marrow insufficiency	Careful dosing of cytoreductive drugs, consider single agent dexamethasone
Cardiac arrhythmias/ dysfunction	Cave: Thalidomide & high dose dexamethasone
Immune system	Careful dosing of cytoreductive drugs
Diabetes	Cave: high dose dexamethasone
Cognitive function/ compliance	Consider iv regimens

Higher risk of mortality in patients ≥ 75 years of age

Retrospective meta-analysis of 4 EU phase III trials (N = 1,435) with MP, MPT, VMP, and VMPT

- **Median follow up 33 months**
- **Median OS in total population 50 months**
- **Estimated 3-year OS 68% in patients < 75 years of age vs 57% in patients ≥ 75 years of age (HR 1.44, CI 1.20-1.72, p < 0.001)**

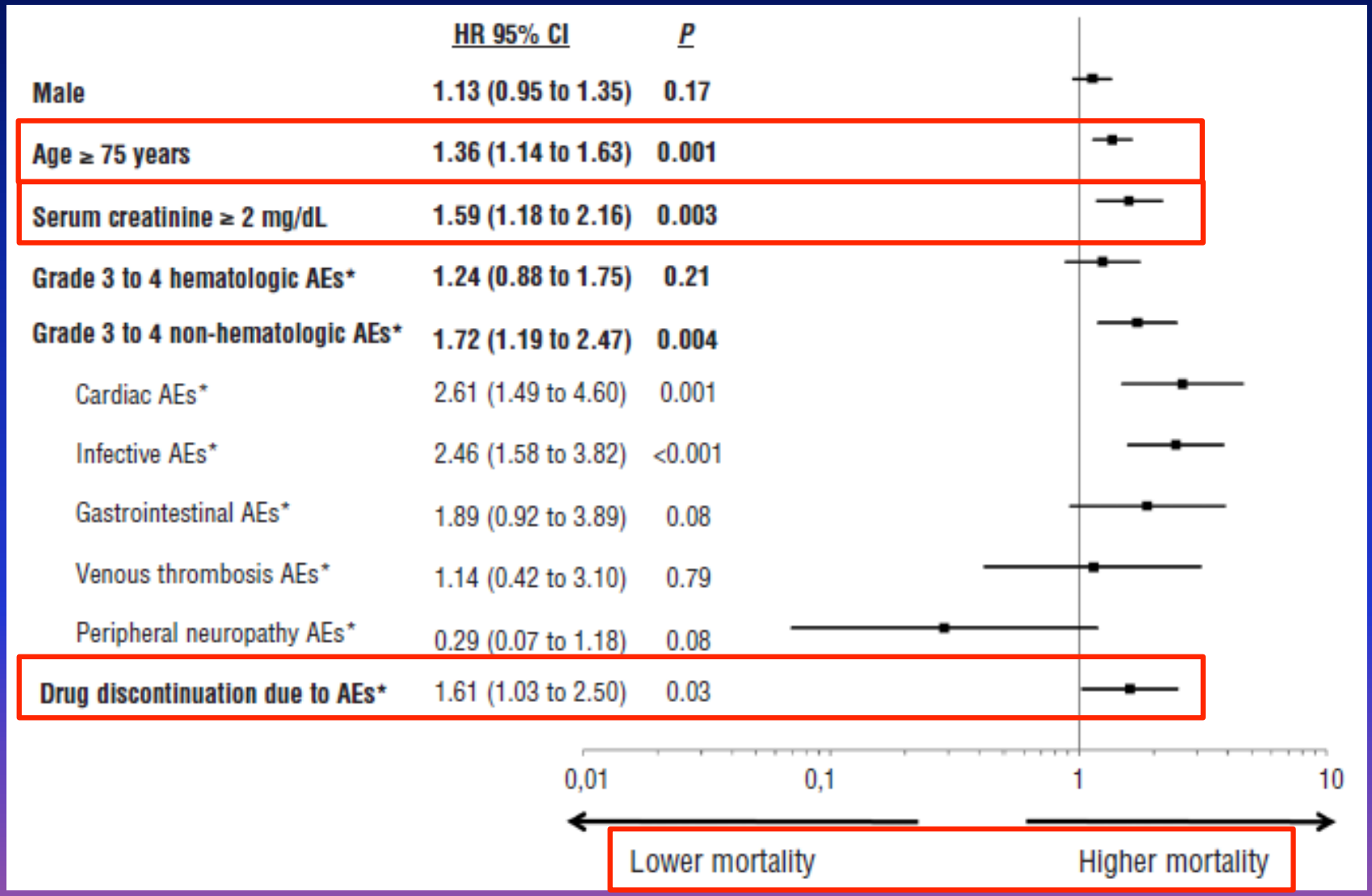
	HR (95% CI)	p value
All	1.44 (1.20–0.72)	< 0.001
MP	1.21 (0.90–1.64)	0.21
MPT	1.12 (0.81–1.56)	0.49
VMP	1.62 (1.04–2.52)	0.03
VTP/VMPT	3.02 (1.86–4.90)	< 0.001



Bringhen S, et al. *Haematologica*. 2013;98:980-7.

Age and Organ Damage Correlate with Poor OS: Meta-analysis of 4 Randomized Trials

- **n=1435 (≥ 65 yrs): MPT vs MP, VMP vs MP, VMP vs VMPT-VT**

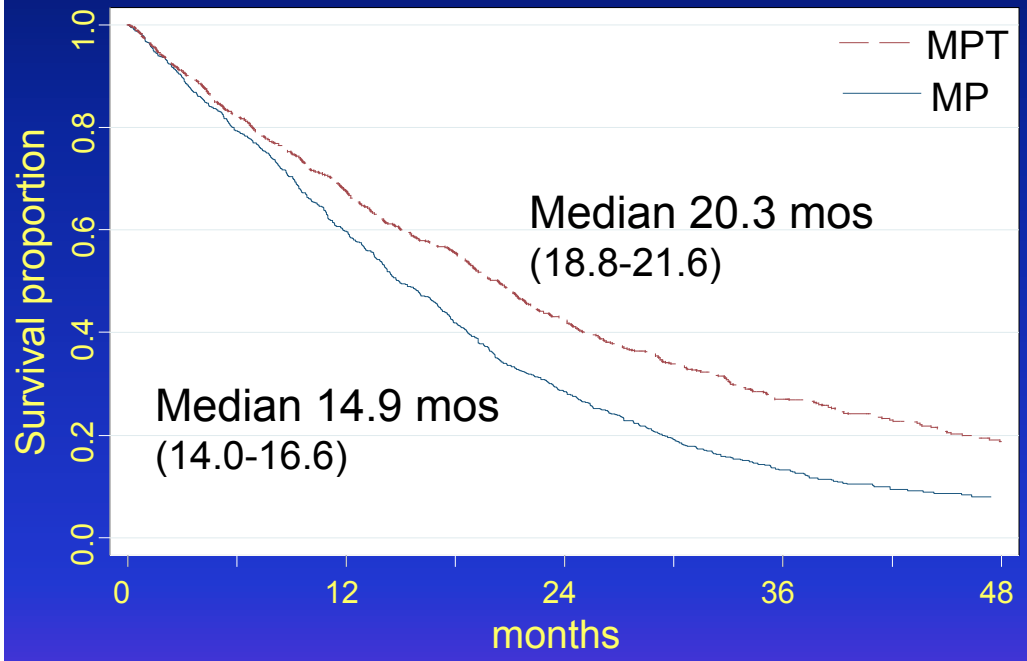


Bringhen et al. Haematologica 2013;98(6):980-987

MPT vs MP: Meta-analysis of 1685 individual-patient data of 6 randomized trials

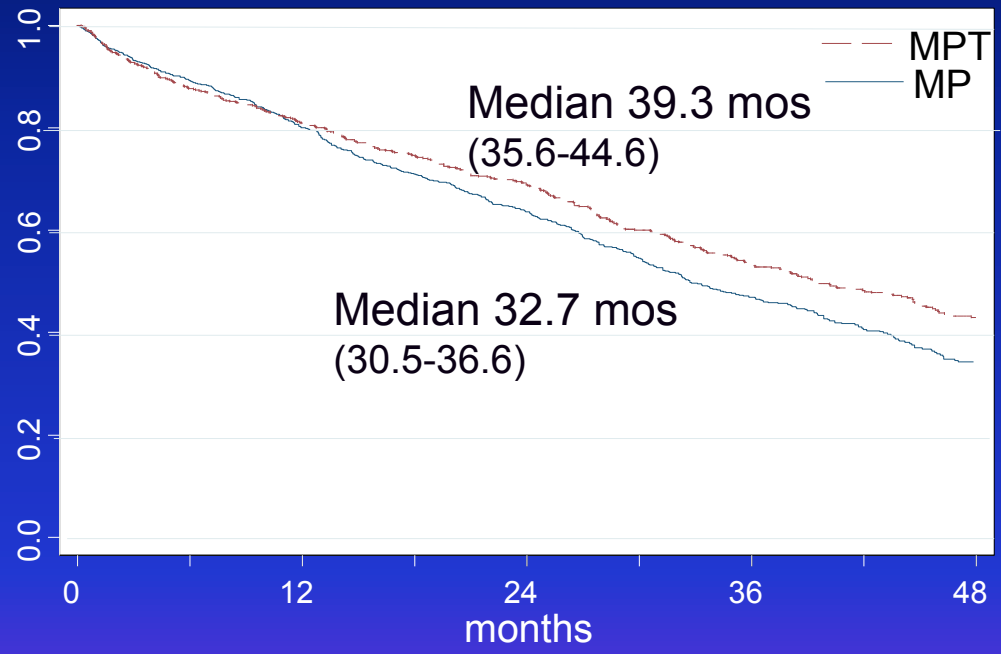
PFS

HR=0.67 in favor of MPT, p<0.0001



OS

HR=0.83 in favor of MPT, p=0.005*



*Cox model for treatment, with analysis stratified by study using a random effects (frailty) model

Fayers et al. Blood 2011, accepted for publication 30 May 2011

MPT: Pros and Cons

Pros

- Survival benefit
- Oral regimen
- Not expensive

Cons

- Thalidomide toxicity
- Suboptimal in cytogenetic high risk group
- Shorter survival after relapse

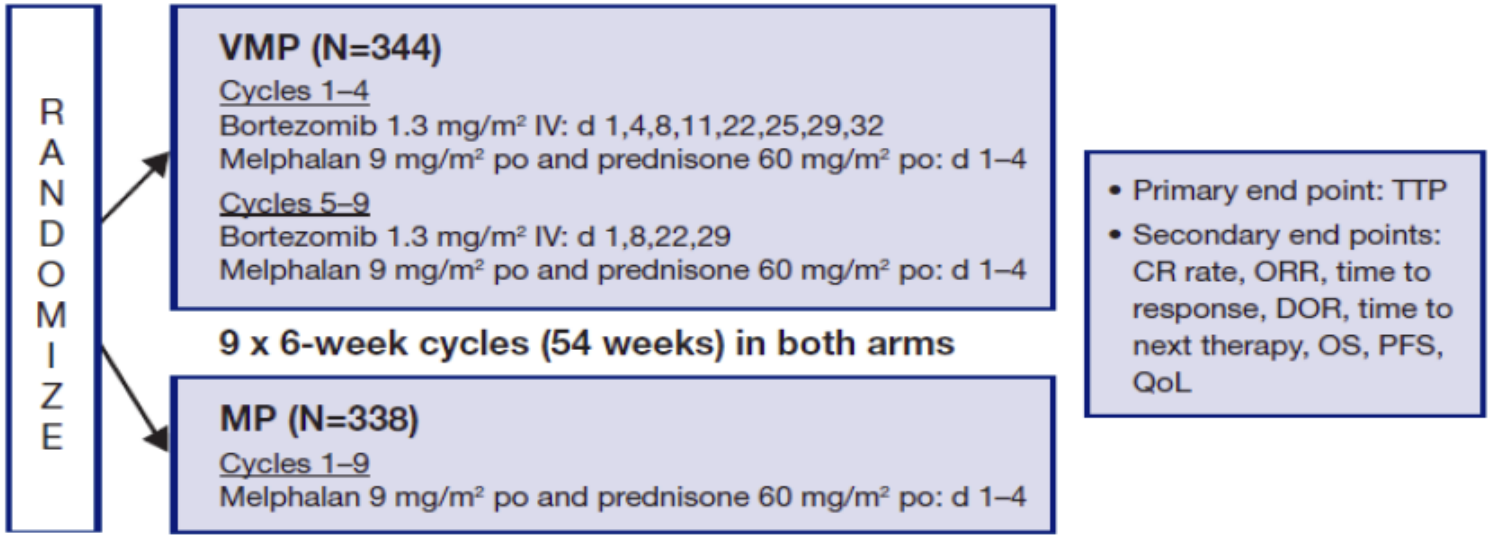
VISTA:VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D., Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D., Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D., for the VISTA Trial Investigators*

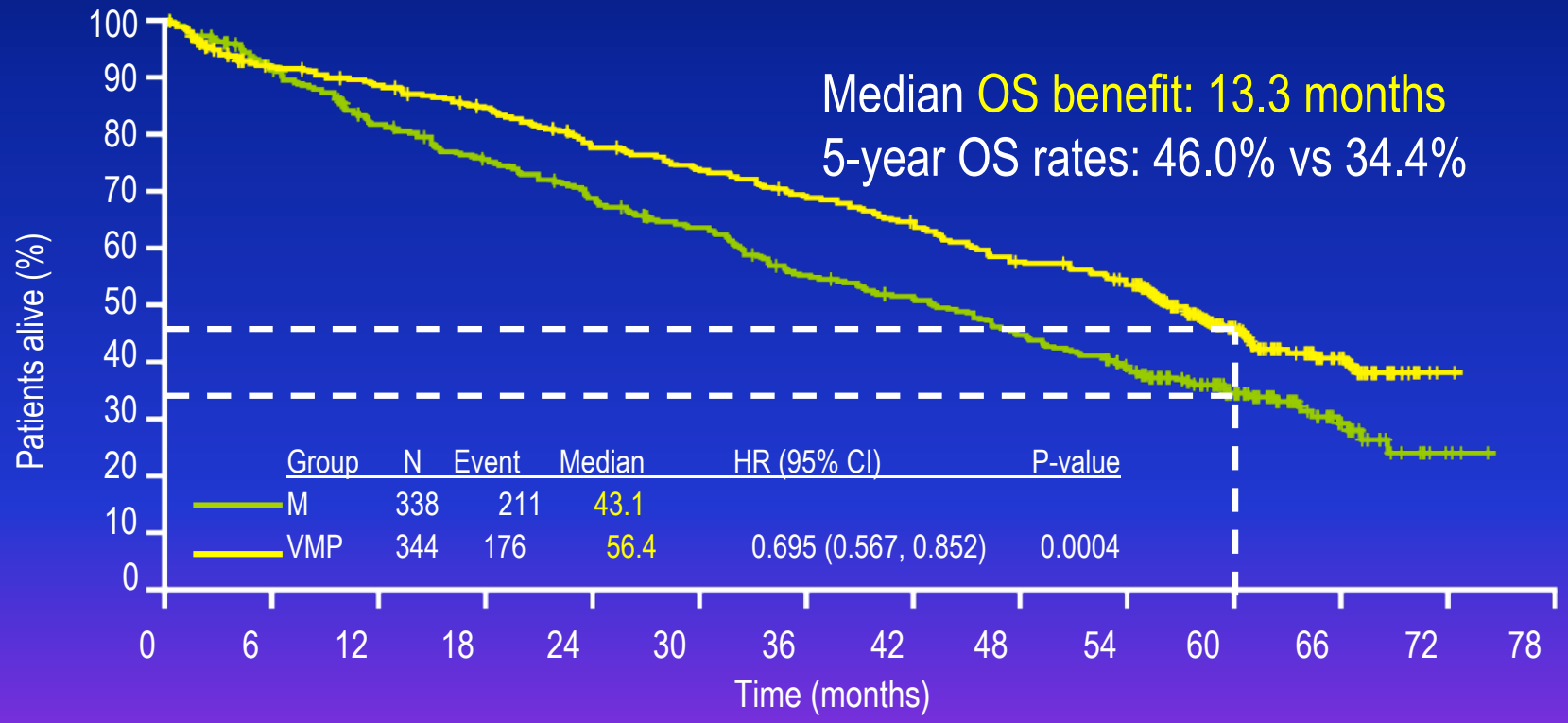


San Miguel NEJM 2008

MP vs. VMP (VISTA) Final updated OS analysis

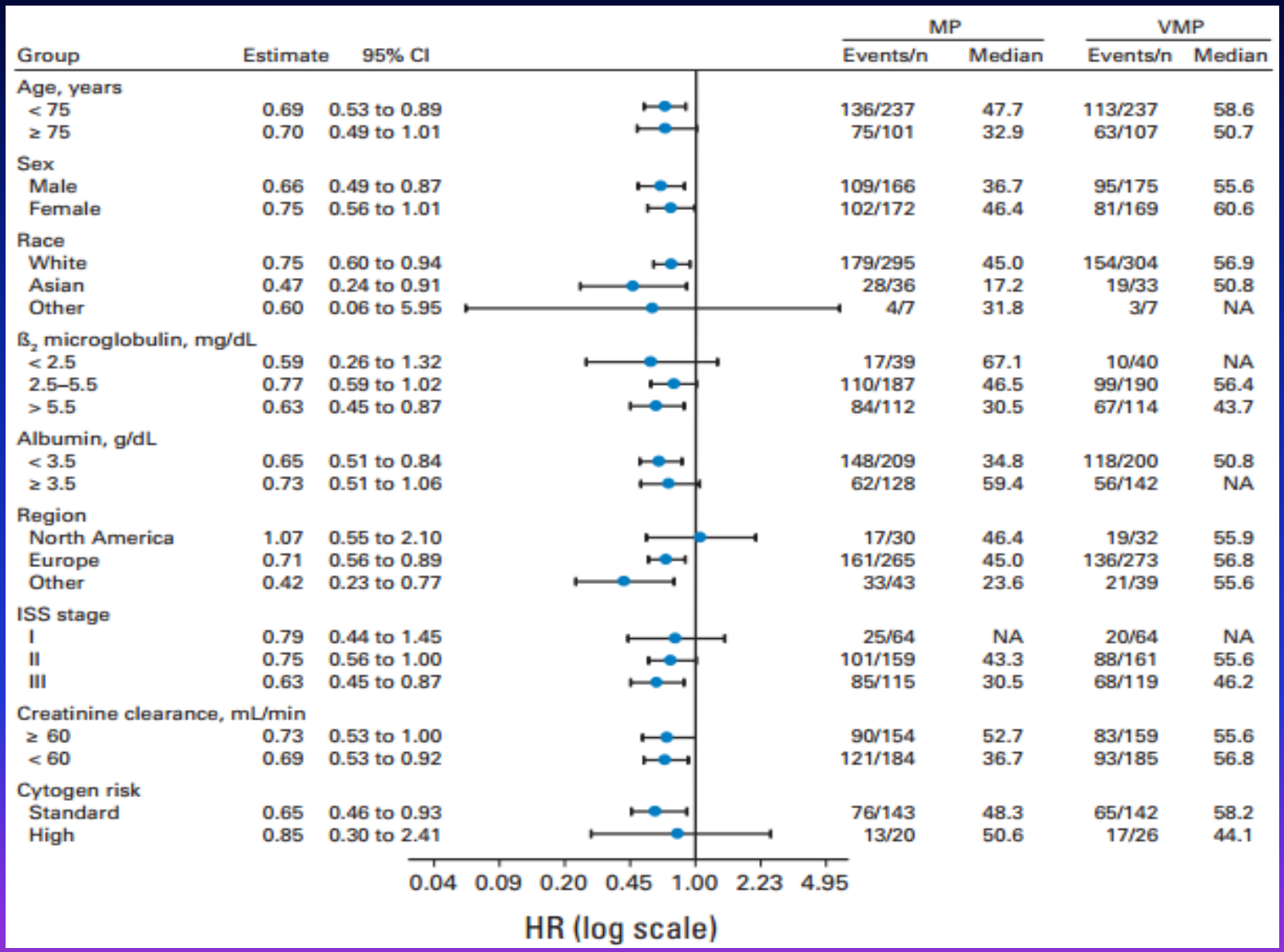
Median follow-up 60.1 months

•31% reduced risk of death



San Miguel et al. JCO 2013

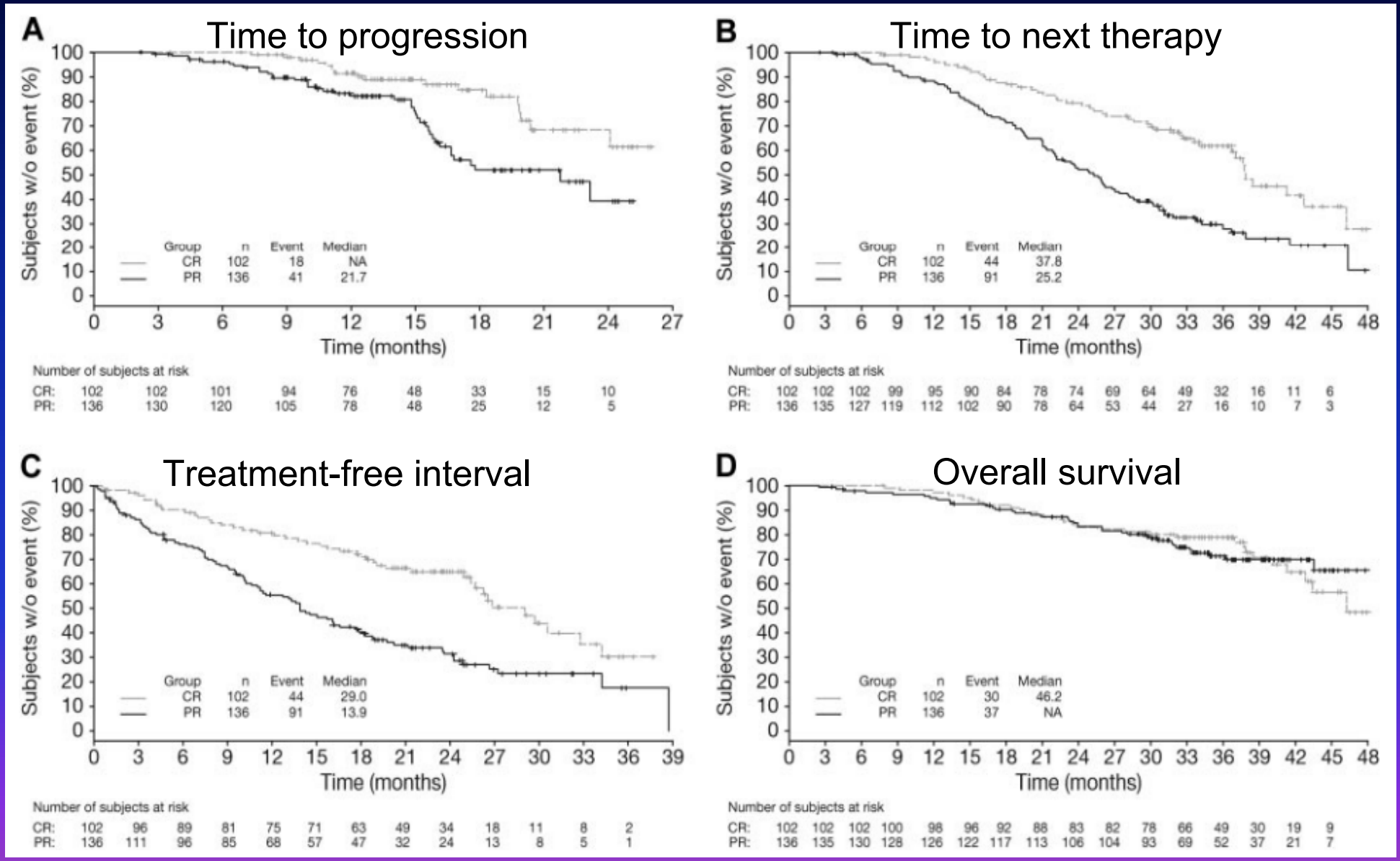
Overall survival in different subgroups: VMP vs. MP



Group	Estimate	95% CI	MP Events/n	MP Median	VMP Events/n	VMP Median
Age, years						
< 75	0.69	0.53 to 0.89	136/237	47.7	113/237	58.6
≥ 75	0.70	0.49 to 1.01	75/101	32.9	63/107	50.7
Sex						
Male	0.66	0.49 to 0.87	109/166	36.7	95/175	55.6
Female	0.75	0.56 to 1.01	102/172	46.4	81/169	60.6
Race						
White	0.75	0.60 to 0.94	179/295	45.0	154/304	56.9
Asian	0.47	0.24 to 0.91	28/36	17.2	19/33	50.8
Other	0.60	0.06 to 5.95	4/7	31.8	3/7	NA
$ß_2$ microglobulin, mg/dL						
< 2.5	0.59	0.26 to 1.32	17/39	67.1	10/40	NA
2.5–5.5	0.77	0.59 to 1.02	110/187	46.5	99/190	56.4
> 5.5	0.63	0.45 to 0.87	84/112	30.5	67/114	43.7
Albumin, g/dL						
< 3.5	0.65	0.51 to 0.84	148/209	34.8	118/200	50.8
≥ 3.5	0.73	0.51 to 1.06	62/128	59.4	56/142	NA
Region						
North America	1.07	0.55 to 2.10	17/30	46.4	19/32	55.9
Europe	0.71	0.56 to 0.89	161/265	45.0	136/273	56.8
Other	0.42	0.23 to 0.77	33/43	23.6	21/39	55.6
ISS stage						
I	0.79	0.44 to 1.45	25/64	NA	20/64	NA
II	0.75	0.56 to 1.00	101/159	43.3	88/161	55.6
III	0.63	0.45 to 0.87	85/115	30.5	68/119	46.2
Creatinine clearance, mL/min						
≥ 60	0.73	0.53 to 1.00	90/154	52.7	83/159	55.6
< 60	0.69	0.53 to 0.92	121/184	36.7	93/185	56.8
Cytogen risk						
Standard	0.65	0.46 to 0.93	76/143	48.3	65/142	58.2
High	0.85	0.30 to 2.41	13/20	50.6	17/26	44.1

San Miguel et al., JCO 2013

VMP induced CR is associated with improved outcome



Harousseau JL et al., BLOOD 2010

VISTA EA

Table 3. Adverse Events (Safety Population).*

Events	Bortezomib Group (N=340)			Control Group (N=337)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
Any event	338 (99)	181 (53)	96 (28)	326 (97)	148 (44)	92 (27)
Hematologic events†						
Thrombocytopenia	178 (52)	68 (20)	58 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	34 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal events						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Infections						
Pneumonia	56 (16)	16 (5)	6 (2)	36 (11)	13 (4)	4 (1)
Herpes zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Nervous system disorders						
Peripheral sensory neuropathy	151 (44)	43 (13)	1 (<1)	16 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0
Other conditions						
Pyrexia	99 (29)	8 (2)	2 (1)	64 (19)	6 (2)	2 (1)
Fatigue	98 (29)	23 (7)	2 (1)	86 (26)	7 (2)	0
Anorexia	77 (23)	9 (3)	1 (<1)	34 (10)	4 (1)	0
Asthenia	73 (21)	20 (6)	1 (<1)	60 (18)	9 (3)	0
Cough	71 (21)	0	0	45 (13)	2 (1)	0
Insomnia	69 (20)	1 (<1)	0	43 (13)	0	0
Peripheral edema	68 (20)	2 (1)	0	34 (10)	0	0
Rash	66 (19)	2 (1)	0	24 (7)	1 (<1)	0
Back pain	58 (17)	9 (3)	1 (<1)	62 (18)	11 (3)	1 (<1)
Dyspnea	50 (15)	11 (3)	2 (1)	44 (13)	5 (1)	3 (1)
Hypokalemia	44 (13)	19 (6)	3 (1)	25 (7)	8 (2)	2 (1)
Arthralgia	36 (11)	4 (1)	0	50 (15)	2 (1)	1 (<1)
Deep-vein thrombosis	4 (1)	3 (1)	0	6 (2)	2 (1)	0

San Miuel NEJM 2008

How to reduce toxicity of Bortezomib and and maintain efficacy?

- Bortezomib once weekly
  - longer duration of therapy
  - similar cumulative dose
  - similar efficacy
  - less toxicty (G3/4 neurotoxicity)

- Bortezomib subcutaneously
  - 10 times lower serum peak concentration
  - similar area under the curve
  - less neurotoxicity
  - similar efficacy

FIRST: Phase 3 trial of Lenalidomide + low-dose Dex vs MPT (IFM 07-01; MM-020)

Centres in EU, Switzerland, APAC, USA, and Canada

Inclusion criteria
N = 1,623

- Previously untreated MM
- Age > 65 years or not eligible for a transplant
- No neuropathy of grade > 2

RANDOMIZATION

Rd (28-day cycle; until disease progression)
Lenalidomide 25 mg/day, days 1–21
Dexamethasone* 40 mg/day, days 1, 8, 15, and 22

Rd (28-day cycle; up to 18 cycles)
Lenalidomide 25 mg/day, days 1–21
Dexamethasone* 40 mg/day, days 1, 8, 15, and 22

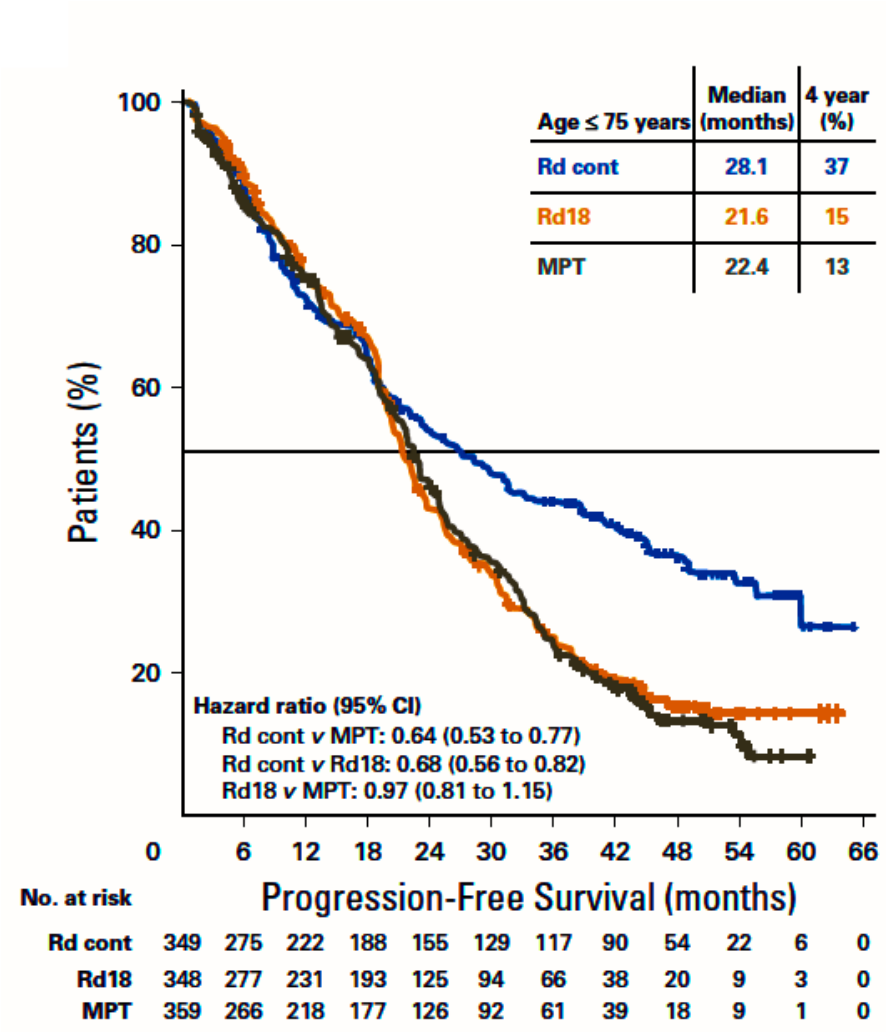
MPT (6-week cycle; up to 12 cycles)
Melphalan* 0.25 mg/kg/day, days 1–4
Prednisone 2.0 mg/kg/day, days 1–4
Thalidomide* 200 mg/day

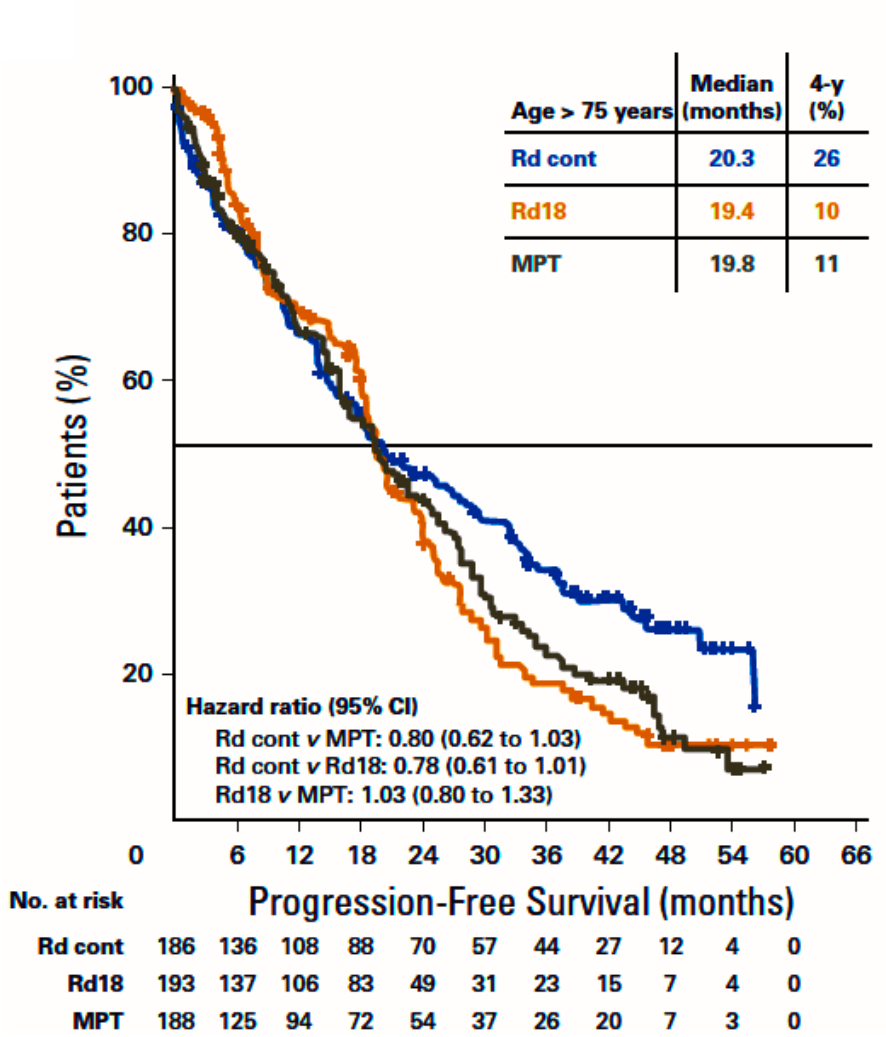
Primary end-point: PFS

*In patients aged > 75 years: Dex 20 mg/day, melphalan 0.20 mg/kg/day, thalidomide 100 mg/day

NCT00689936. Available from: www.clinicaltrials.gov.

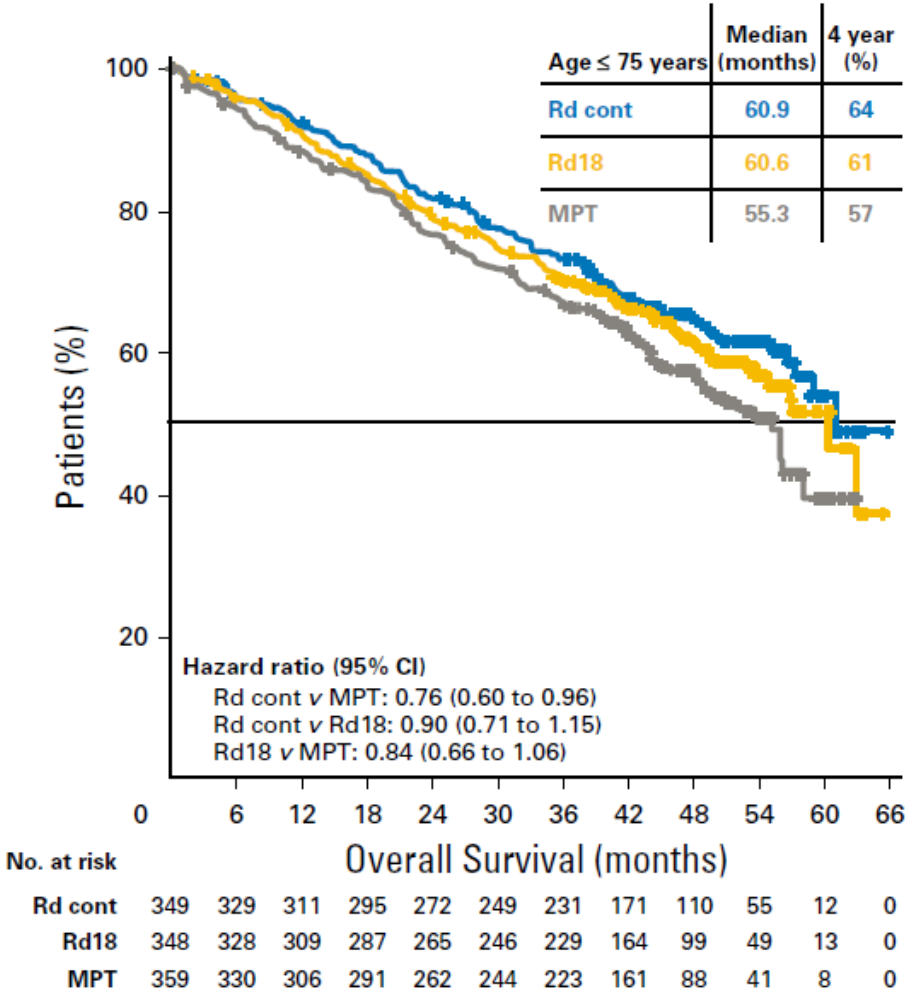
PFS by age: median follow up 45,5 months

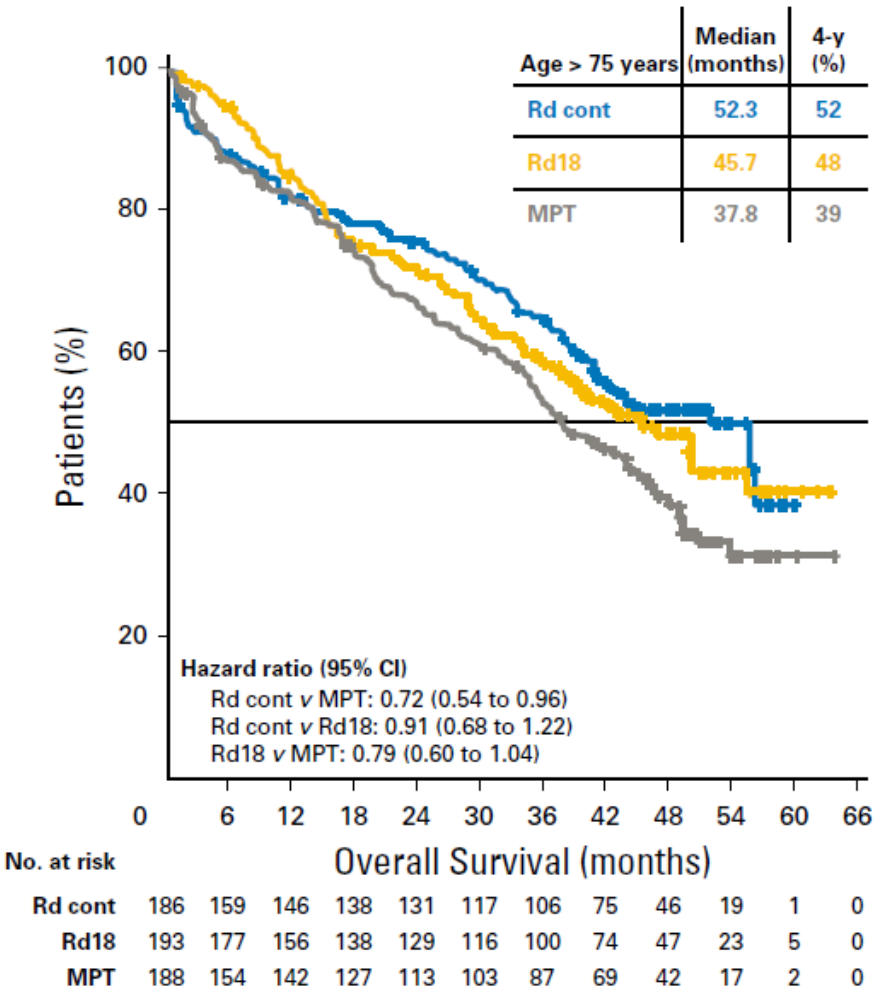




Hulin et al. JCO 2016;34:3609-3617

OS by age: median follow up 45,5 months





Hulin et al. JCO 2016;34:3609-3617

Toxicities

TEAE or SPM	No. (%)					
	Age ≤ 75 Years			Age > 75 Years		
	Rd Continuous (n = 347)	Rd18 (n = 348)	MPT (n = 357)	Rd Continuous (n = 185)	Rd18 (n = 192)	MPT (n = 184)
Grade 3 to 4 hematologic TEAEs*						
Neutropenia	98 (28)	87 (25)	169 (47)	53 (29)	56 (29)	74 (40)
Anemia	63 (18)	41 (12)	70 (20)	36 (19)	44 (23)	32 (17)
Thrombocytopenia	28 (8)	30 (9)	47 (13)	17 (9)	13 (7)	13 (7)
Leukopenia	17 (5)	21 (6)	39 (11)	7 (4)	9 (5)	14 (8)
Grade 3 to 4 nonhematologic TEAEs*						
Infection	105 (30)	73 (21)	57 (16)	54 (29)	45 (23)	36 (20)
Cardiac disorder	41 (12)	22 (6)	22 (6)	22 (12)	17 (9)	24 (13)
Fatigue	23 (7)	27 (8)	17 (5)	17 (9)	19 (10)	14 (8)
Back pain	21 (6)	26 (7)	18 (5)	18 (10)	8 (4)	10 (5)
Peripheral sensory neuropathy	5 (1)	2 (1)	36 (10)	1 (1)	0 (0)	15 (8)
TEAEs of special interest						
Cataract	27 (8)	11 (3)	1 (< 1)	6 (3)	3 (2)	2 (1)
DVT	23 (7)	11 (3)	10 (3)	6 (3)	9 (5)	4 (2)
PE	13 (4)	10 (3)	17 (5)	7 (4)	6 (3)	3 (2)
SPM						
Invasive SPM	13 (4)	19 (6)	22 (6)	8 (4)	14 (7)	8 (4)
Hematologic malignancy	2 (1)	2 (1)	9 (3)	1 (1)	0	3 (2)
Solid tumor	11 (3)	18 (5)	13 (4)	7 (4)	14 (7)	5 (3)
Noninvasive SPM (NMSC)	17 (5)	13 (4)	15 (4)	10 (5)	7 (4)	11 (6)

Hulin C. et al, VOLUME 34 • NUMBER 30 • OCTOBER 20, 2016

Riepilogo studi prima linea pazienti No-ASCT

	VISTA (VMP arm) San Miguel	VMP (OW) Palumbo	FIRST (Continuous Rd) Facon	VMPT-VT Palumbo	VMP-VT Mateos
CR	30%	24%	15.1%	38%	42%
PFS	**21.7m**	**24.8m**	**26m**	**35.3m**	**37m**
OS	**Median: 56.4m**	**Median: 60.6m**	**Median: 59m**	**Median: NR**	**Median: 63m**
	5-year OS: 46.0%	**5-year OS: 51%**	**4-yearOS: 59%**	**5-year OS: 61%**	**5-year OS: 69%**

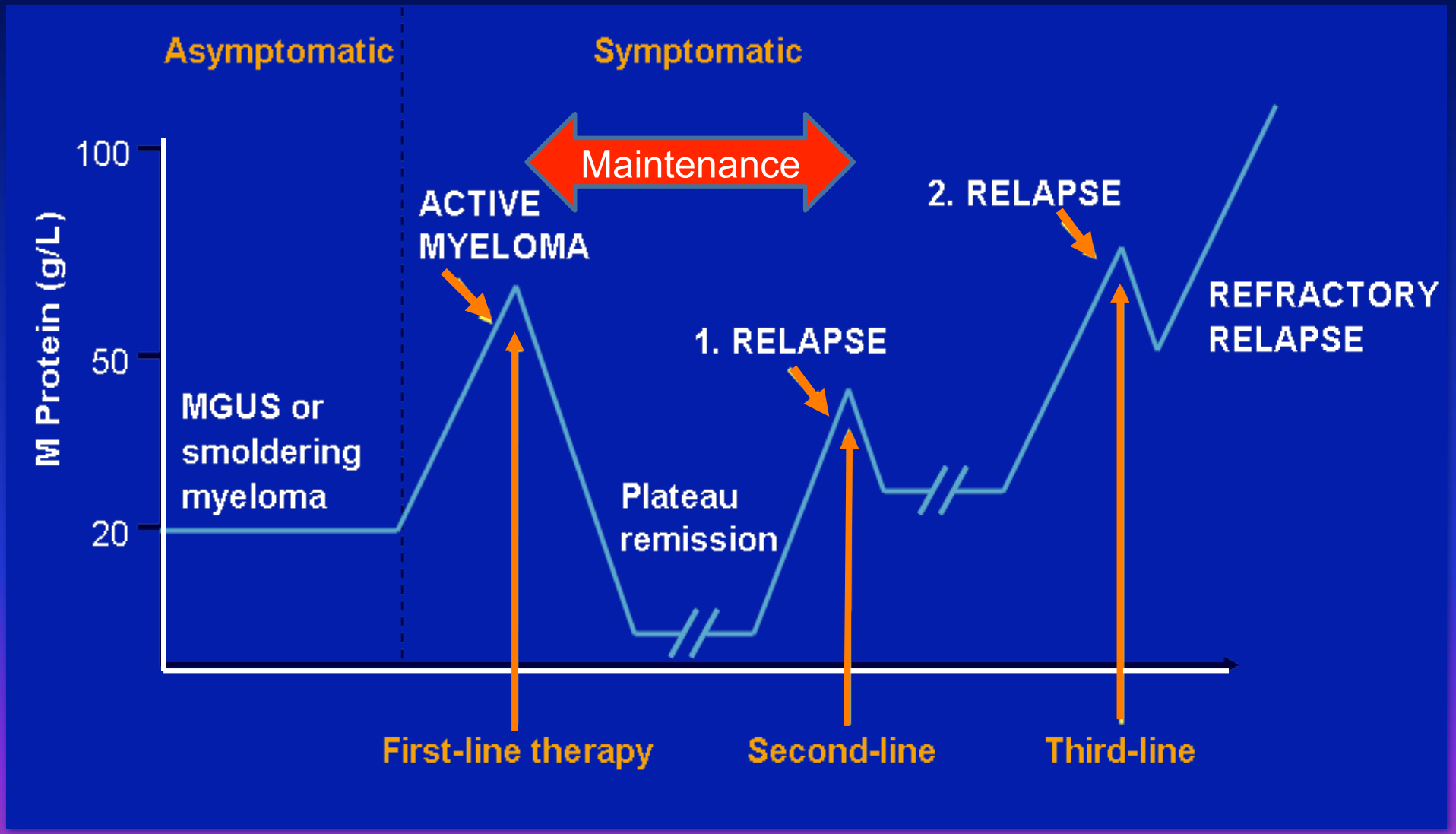
N. Cicli definiti

Trattamento continuo

Maintenance studies - summary

Thalidomide	↑ PFS no improvement in OS ↑ Reduced OS after relapse Negative impact on high risk pts
Clinical practice recommendations	50 mg for ≈ 12 mos may be considered
Lenalidomide	↑ PFS -no improvement in OS -increased risk for SPM
Bortezomib-thalidomide	Tendency for ↑ PFS and ↑ OS but not significant superior over VP

The natural course of multiple myeloma



Treatment of relapsed/refractory MM
General considerations

Components of initial therapy

- Alkylating-based
- Dexamethasone-based
- IMiD-based
- Bortezomib-based

Efficacy of initial therapy

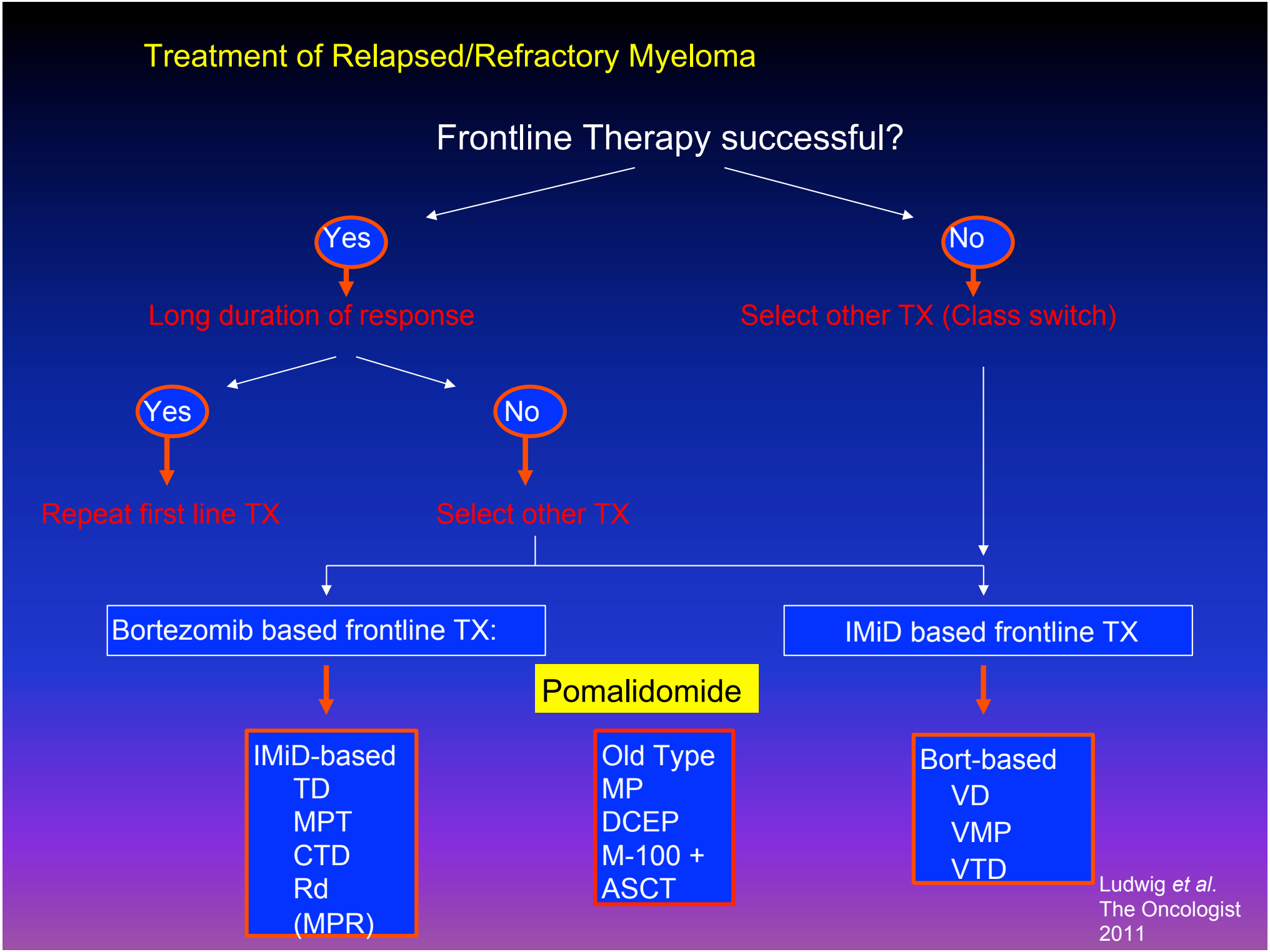
- Quality of response
- Tolerance of tretament
- Duration of respose

Patient status and type of relapse

- Age, performance status, glucose metabolism
- Aggressive vs non-aggressive relapse
- Bone marrow reserve
- Renal function impairment
- Pre-existing peripheral neuropathy
- Oral vs. iv therapy

IMiD, immunomodulatory derivative; MM, multiple myeloma

Treatment of Relapsed/Refractory Myeloma



Ludwig *et al.*
The Oncologist
2011

Retreatment with bortezomib: a meta-analysis including 23 studies

- 23 trials, 1051 patients
- Patients refractory or not refractory to bortezomib
  - 11 studies including bortezomib-refractory pts
  - 6 studies excluding bortezomib-refractory pts
  - 6 studies missing information on bortezomib-refractory pts
- Combinations
  - Bortezomib ± Dex: 4 studies
  - Bortezomib + combination therapy: 19 studies

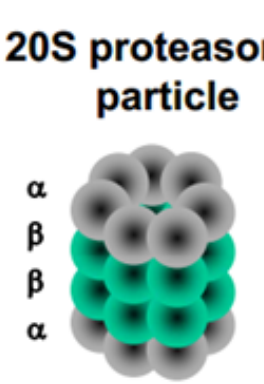
Knopf et al. IMW 2013 (Abstract P-228), poster presentation

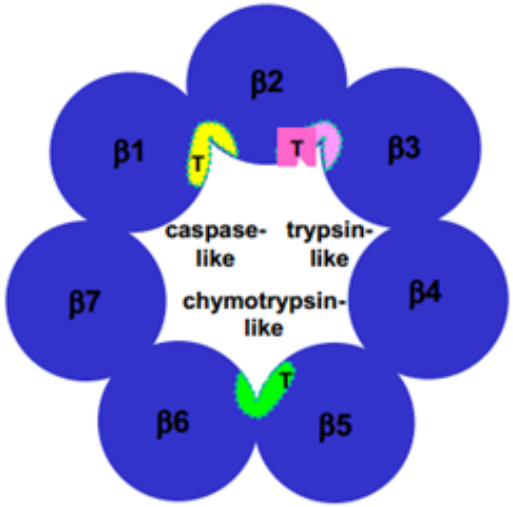
Results of meta-analysis of retreatement with bortezomib in different risk groups

Variable	ORR	TTP (months)	OS (months)
Relapsed	57%	8.5	19.7
Relapsed/>refractory	19%	5.9	20.4
≤ 4 prior TX lines	43%	8.2	20.0
> 4 prior TX lines	29%	7.1	13.3
Boz + Dex	51%	7.9	19.2
Combination	36%	7.1	16.2
Pooled analysis	51%	8.4	19.2

Knopf et al., IMW 2013

Carfilzomib a second generation proteasome inhibitor





β-subunit ring

Three distinct N-terminal threonine protease active sites

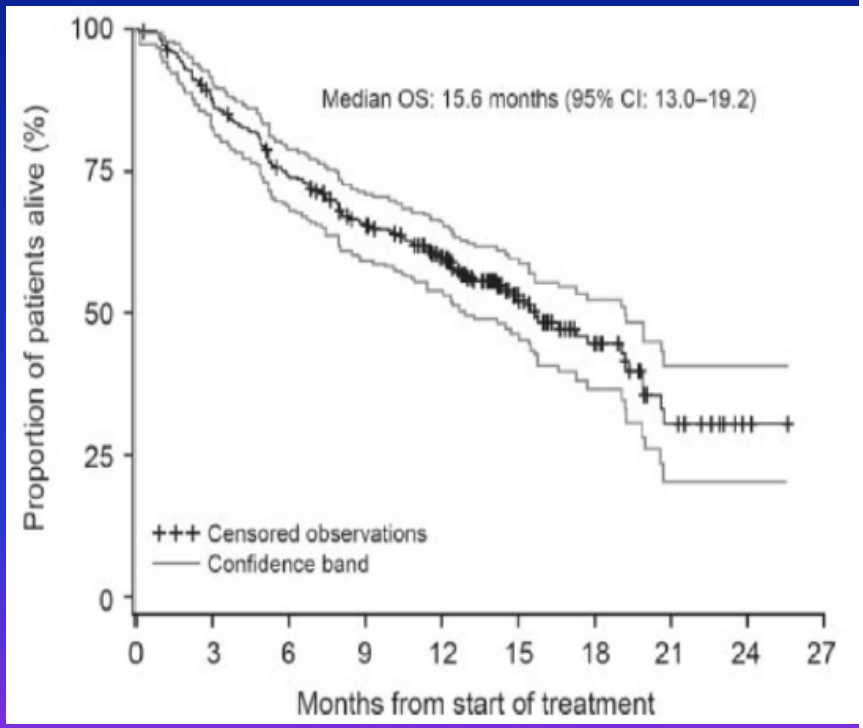
IC_{50}s (nM)	Chymotrypsin-like	Caspase-like	Trypsin-like
Carfilzomib	6	2400	3600
Bortezomib	7	74	4200

Single agent Carfilzomib in relapsed/refractory patients

Progressive disease at enrollment, Relapsed from > 2 prior TX lines, Must include bortezomib

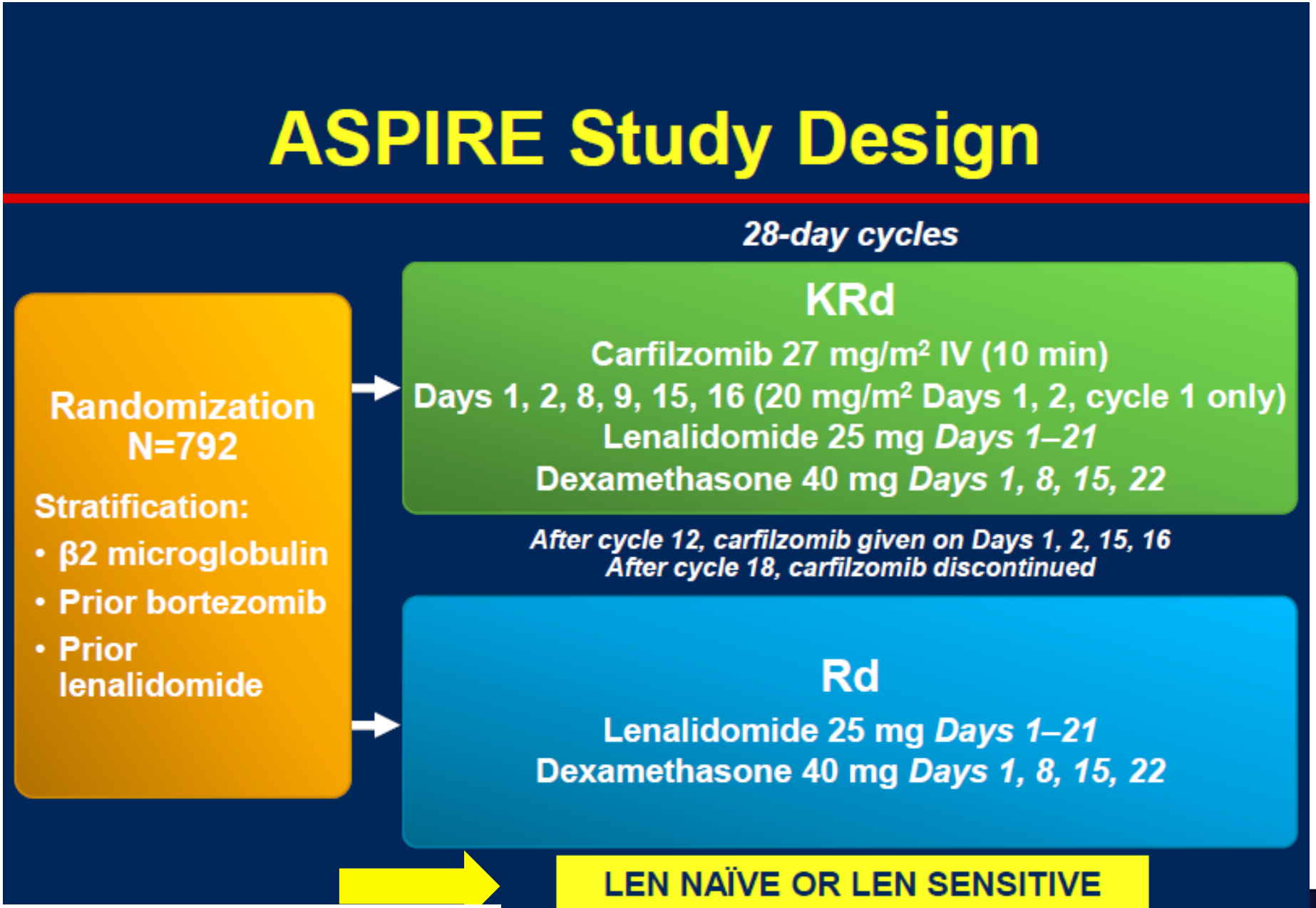
Must include thalidomide or lenalidomide, Refractory to last line

Response category	All patients (n=267)	High risk cytogenetics (n=71)
CR	0.4%	0
VGPR	5.1%	4.2%
PR	18.3%	25.4%
MR	13.2%	4.2%
ORR	37%	29.5%
PFS(median)	3.7 mos	3.6 mos
DOR (median)	7.8 mos	6.9 mos



Siegel D et al., BLOOD 2012

Carfilzomib KRd - Relapse



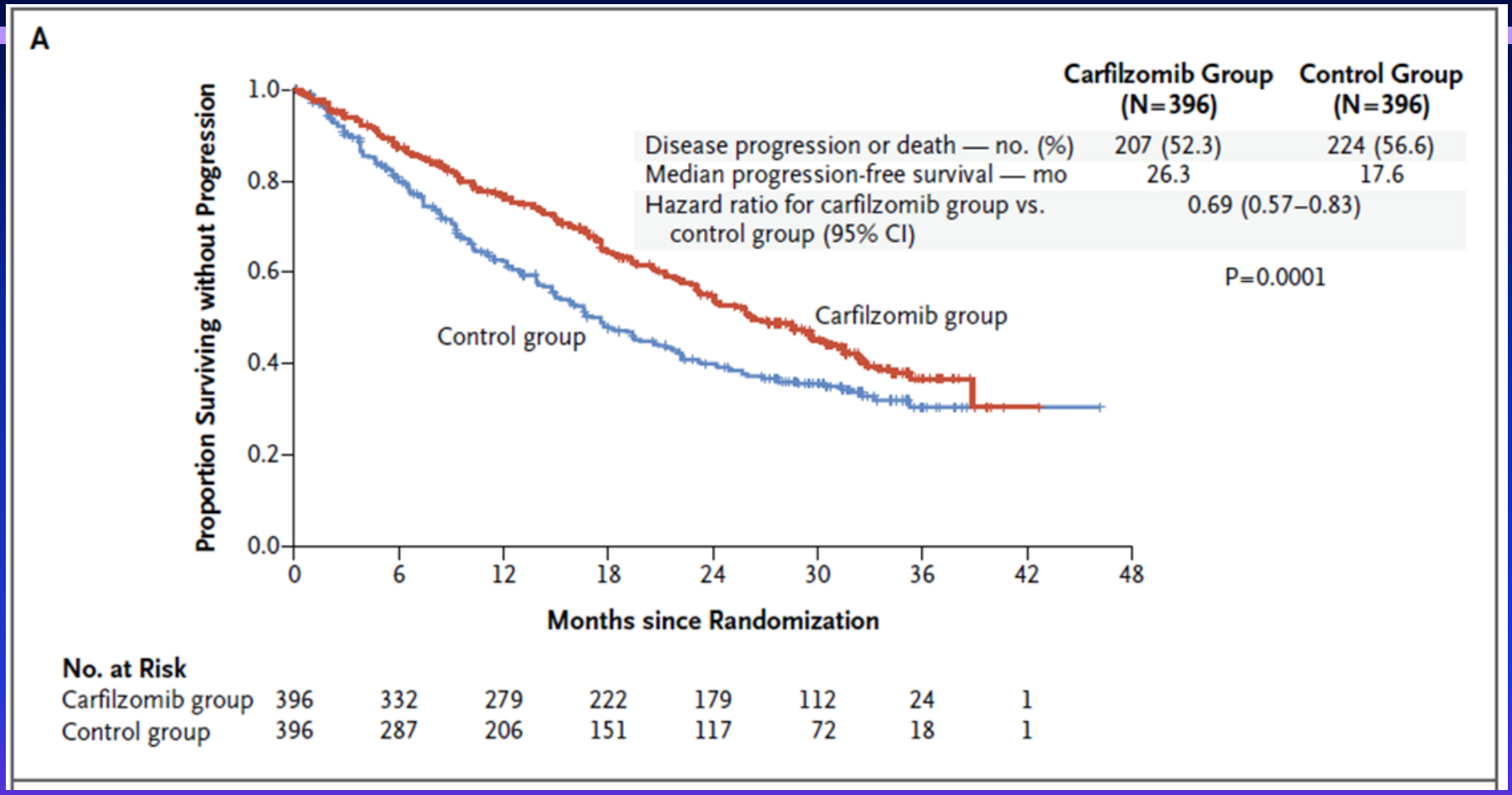
In both groups Rd beyond cycle 18 until disease progression

Patient and Disease Characteristics at Baseline
ITT Population (N=792)

Characteristic	KRd (n=396)	Rd (n=396)
Presence of neuropathy at baseline, %	36.4	34.6
Number of prior regimens, median (range)	2 (1–3)	2 (1–3)
Prior therapies, %		
Transplant	54.8	57.8
Bortezomib	65.9	65.7
Non-responsive to prior bortezomib*	15.2	14.6
Lenalidomide	19.9	19.7
Any IMiD	58.8	57.8
Refractory to prior IMiD in any prior regimen	21.5	22.2
Bortezomib and IMiD	36.9	35.1
Non-responsive to prior bortezomib* and refractory to prior IMiD	6.1	6.8

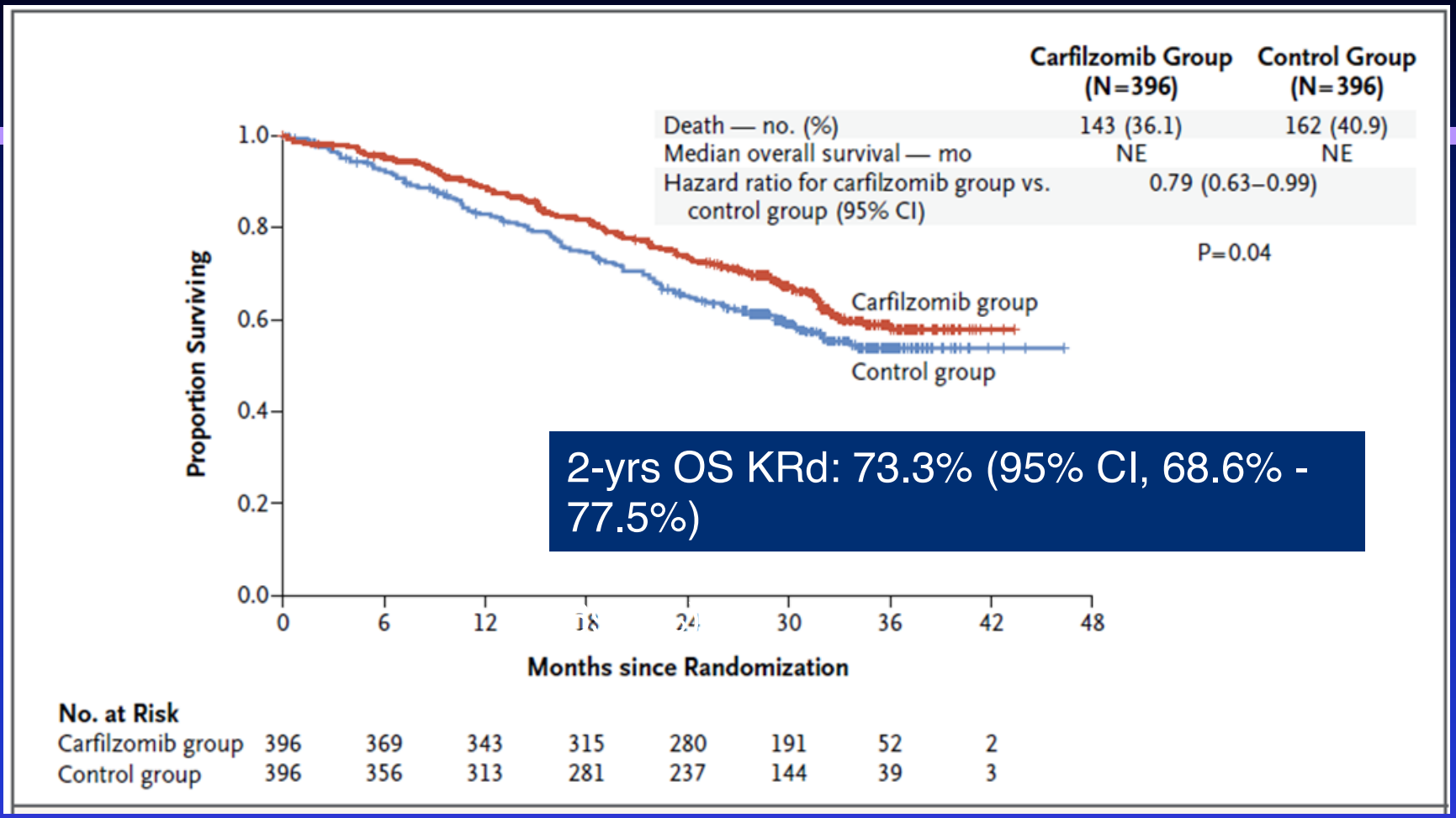
*Non-responsive is defined as less-than-minimal response to any bortezomib-containing regimen, disease progression during any bortezomib-containing regimen, or disease progression within 60 days after the completion of any bortezomib-containing

Primary Endpoint: PFS



Stewart AK et al. N Engl J Med 2015;372:142-52.

Secondary Endpoint: OS



2-yrs OS KRd: 73.3% (95% CI, 68.6% - 77.5%)

- Primary objective met → Interim analysis of OS conducted
- As of June 16, 2014, a total of 305 deaths (60% of the prespecified 510 events required for final analysis)
- **Median follow-up was 32.3 months in KRd and 31.5 months in Rd.**

Stewart AK et al. N Engl J Med 2015;372:142-52.

Secondary Endpoint: Safety profile

	Carfilzomib Group (n=392)		Control Group (n=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Most common events, no. (%)				
Hematologic adverse event				
Anemia	167 (42.6)	70 (17.9)	155 (39.8)	67 (17.2)
Neutropenia	148 (37.8)	116 (29.6)	131 (33.7)	103 (26.5)
Thrombocytopenia	114 (29.1)	65 (16.6)	88 (22.6)	48 (12.3)
Nonhematologic adverse event				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Peripheral edema	85 (21.7)	5 (1.3)	75 (19.3)	2 (0.5)
Nasopharyngitis	84 (21.4)	1 (0.3)	63 (16.2)	0
Constipation	79 (20.2)	1 (0.3)	67 (17.2)	2 (0.5)
Back pain	67 (17.1)	5 (1.3)	78 (20.1)	8 (2.1)
Other adverse events of interest, n (%)				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Peripheral neuropathy†	67 (17.1)	10 (2.6)	66 (17.0)	12 (3.1)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure‡	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Elevated creatinine	26 (6.6)	4 (1.0)	18 (4.6)	1 (0.3)
Cardiac failure§	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Deep vein thrombosis	26 (6.6)	7 (1.8)	15 (3.9)	4 (1.0)
Ischemic heart disease‖	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)
Pulmonary embolism	14 (3.6)	12 (3.1)	9 (2.3)	9 (2.3)
Second primary malignancy¶	11 (2.8)	9 (2.3)	13 (3.3)	11 (2.8)

* Adverse events are listed here if they were reported in at least 20% of patients in either treatment group. Other adverse events of particular clinical relevance are also listed. The safety population included all patients who received at least one dose of a study drug.

- AE more frequently occurred in KRd group by at least 5% point

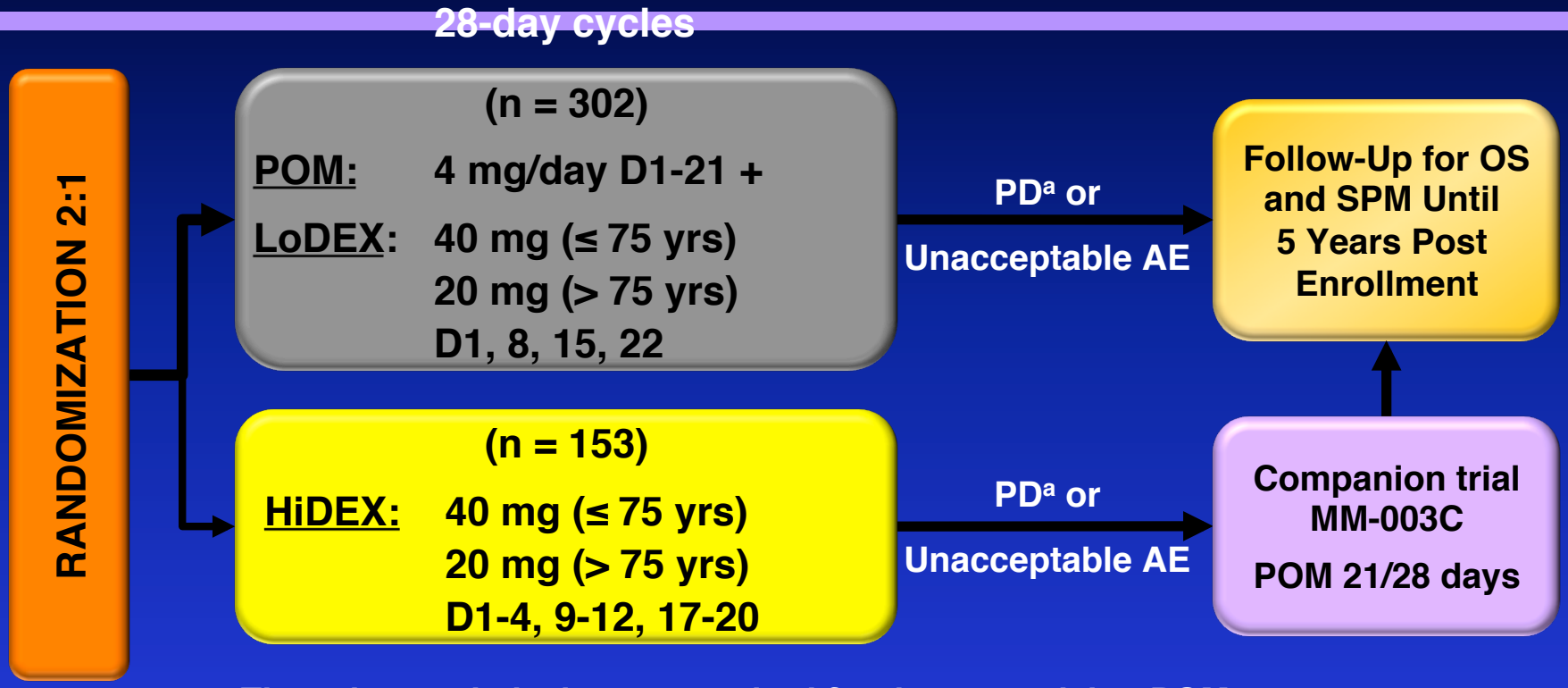
Stewart AK et al. N Engl J Med 2015;372:142-52.

Pomalidomide With Low-Dose Dexamethasone Relapsed and Refractory Multiple Myeloma

- POM was effective in heavily pretreated patients who had already received LEN and bortezomib and who progressed on their last line of therapy
- The combination of POM with LoDEX improves the ORR due to synergy between immunomodulatory agents and glucocorticoids
  - POM + LoDEX, 34%; POM alone, 15%
- Response was durable with POM regardless of the addition of LoDEX
  - POM + LoDEX, 8.3 months ; POM alone, 8.8 months
- POM is generally well tolerated, with low rates of discontinuations due to AEs
    - Age had no impact on ORR, DoR, or safety

Jagannath S, et al. ASH 2012 abstract 450.

MM-003 Design: POM + LoDEX vs. HiDEX



Thromboprophylaxis was required for those receiving POM or at high risk for DVT

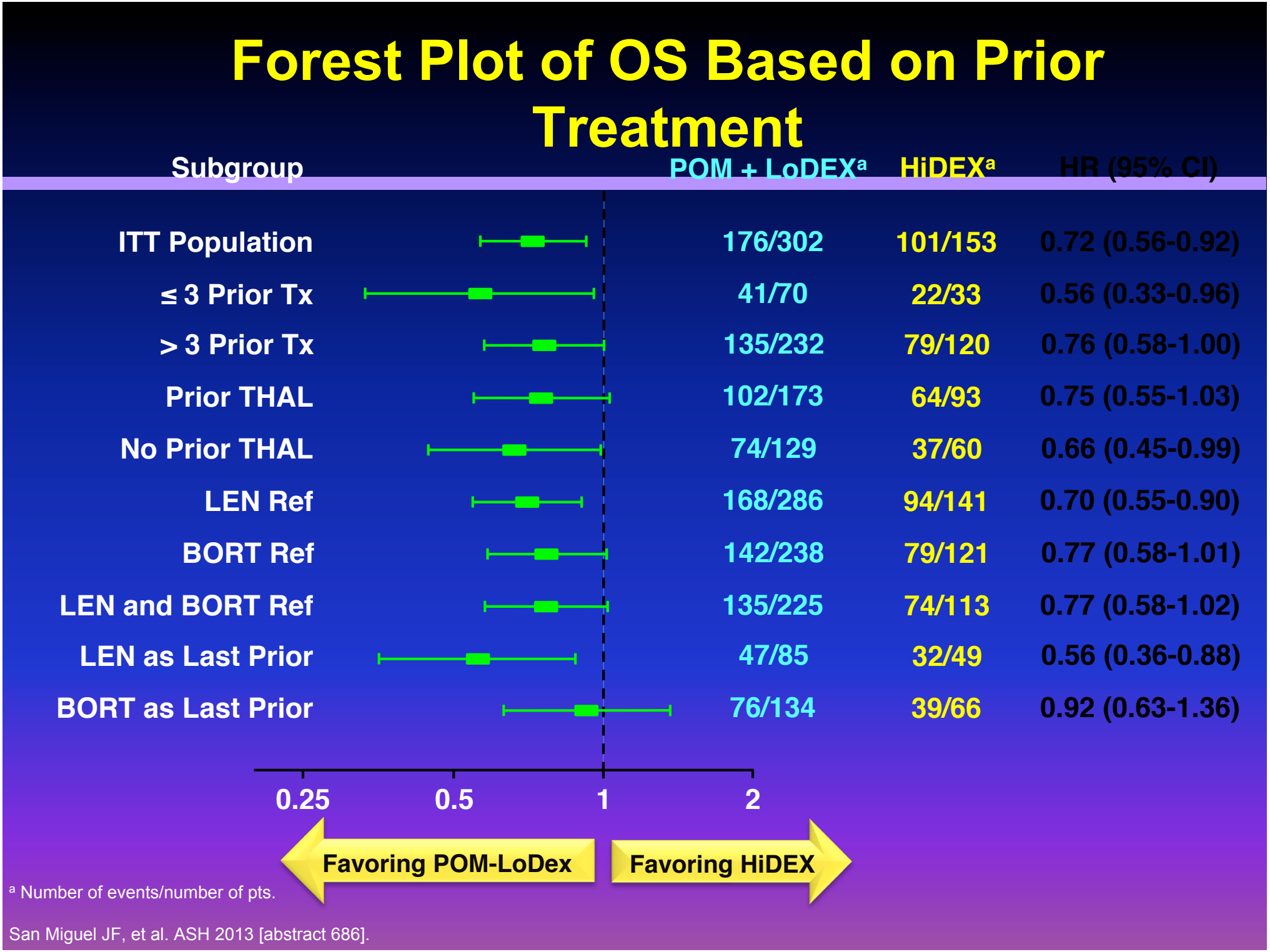
Stratification

- Age (≤ 75 vs. > 75 yrs)
- Number of prior Tx (2 vs. > 2)
- Disease population (primary refractory vs. relapsed/refractory vs. intolerance/failure)

[a] Progression of disease was independently adjudicated in real time.

Dimopoulos MA, et al. ASH 2013 [abstract 408].

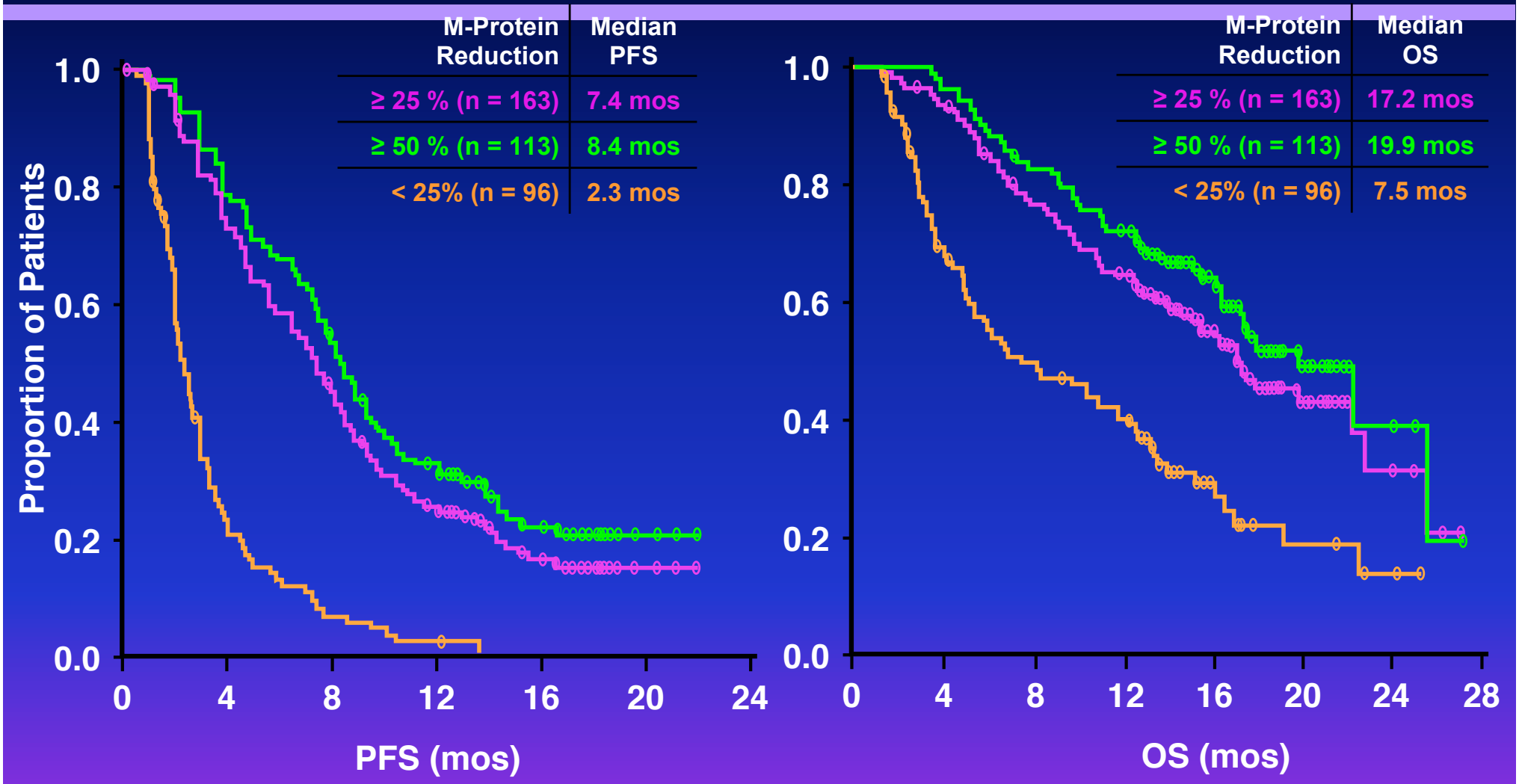
Forest Plot of OS Based on Prior Treatment



[a] Number of events/number of pts.

San Miguel JF, et al. ASH 2013 [abstract 686].

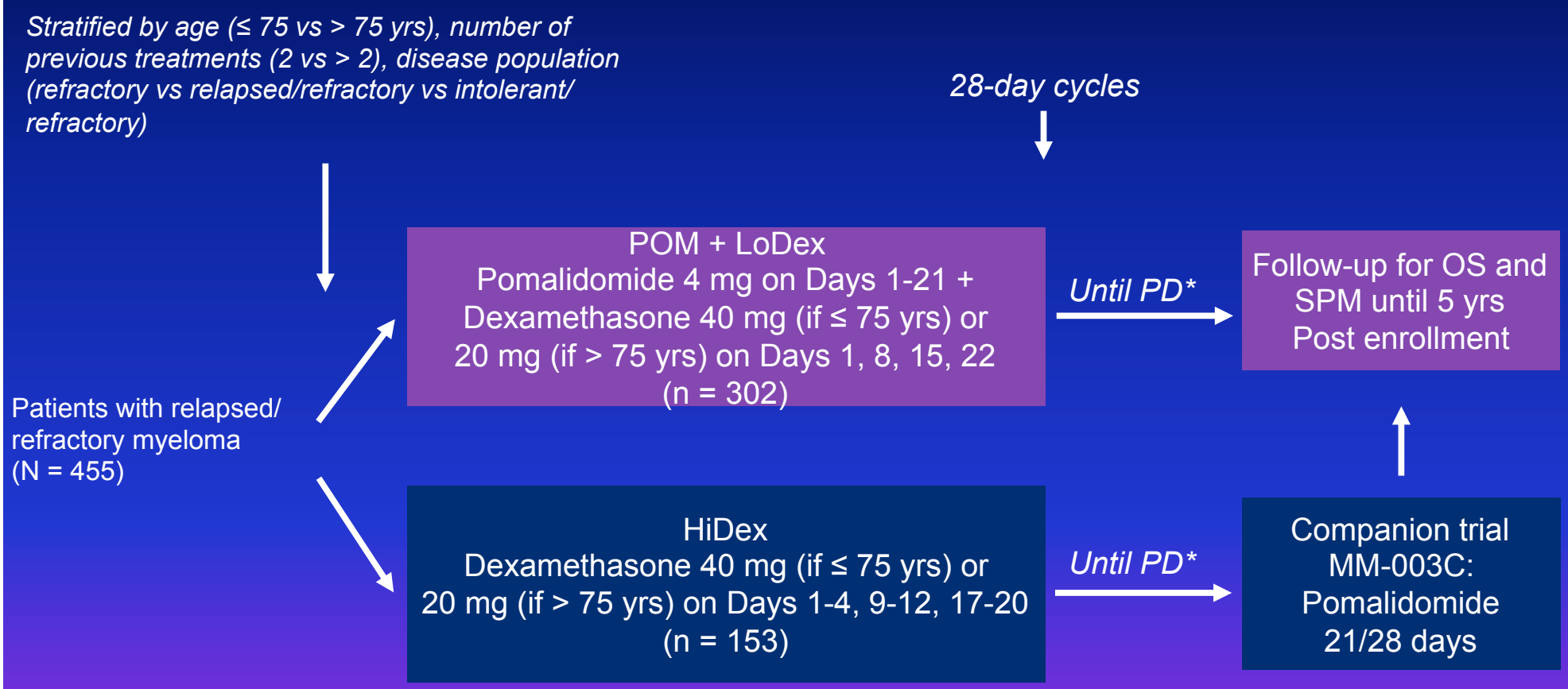
MM-003: PFS and OS by M-Protein Reduction
Patients Assigned to POM + LoDEX



- Median PFS was 4.0 mos and median OS was 13.1 mos overall for POM + LoDEX

San Miguel JF, et al. ASH 2013 [abstract 686].

Pomalidomide + LoDex vs HiDex (MM-003): Phase III Trial Design



- **Primary endpoint: PFS**
- **Secondary endpoints: OS, ORR, DOR, safety**

San Miguel JF, et al. ASCO 2013. Abstract 8510.

*Independently adjudicated in real time.
Thromboprophylaxis indicated for patients receiving pomalidomide or with history of DVT.

Pomalidomide + LoDex vs HiDex Adverse Events (MM-003)

AE, %	POM + LoDex (n = 300)	HiDex (n = 150)
Grade 3/4 hematologic AEs		
▪ Neutropenia	48	16
▪ Anemia	33	37
▪ Thrombocytopenia	22	26
Grade 3/4 nonhematologic AEs		
▪ Infections	30	24
– Pneumonia	13	8
▪ Bone pain	7	5
▪ Fatigue	5	6
▪ Asthenia	4	6
Grade 3/4 AEs of interest		
▪ DVT/PE	1	0
▪ Peripheral neuropathy*	1	1
Discontinuation due to AEs	9	10

*Includes hyperesthesia, peripheral sensory neuropathy, paraesthesia, hypoesthesia, and polyneuropathy.

San Miguel JF, et al. ASCO 2013. Abstract 8510.

New drugs in clinical evaluation

Agent	Mechanism of action
Panobinostat, Vorinostat, Givinostat, Romidepsin	HDAC inhibitor
Perifosine, GSK2110183	Akt inhibitor
Temsirolismus, Everolismus	mTOR inhibitor
Selumetinib	MEK/ERK inhibitor
Plitidepsin (aplidin)	Jun N-terminal Kinase (JNK) activator, anti-angiogenic activity
Dinaciclib	CDK inhibitor
MLN8237	Aurora kinase inhibitor
ARRY-520	Kinesin spindle protein (KSP) inhibitor
Elotuzumab	anti-CS1
Daratumumab	anti-CD38
BHQ880	anti-DKK1
BT062	anti-CD138
Ixazomib	New proteasome inhibitor

Recommendations for clinical practice

- **Assess**
  - comorbidities
  - degree of functional impairment
- **Select most appropriate drug regimen**
- **Adapt dose if required**
- **Consider the increased risk of infections within first weeks/months of therapy**
- **Optimize supportive care**
  - Antibiotics, antivirals, growth factors, anti-thrombotics, bisphosphonates

The future looks bright for elderly myeloma patients

Thank you for your attention