First do no Harm (*Primum non nocere*): Balancing Quality of Life With Quantity of Life

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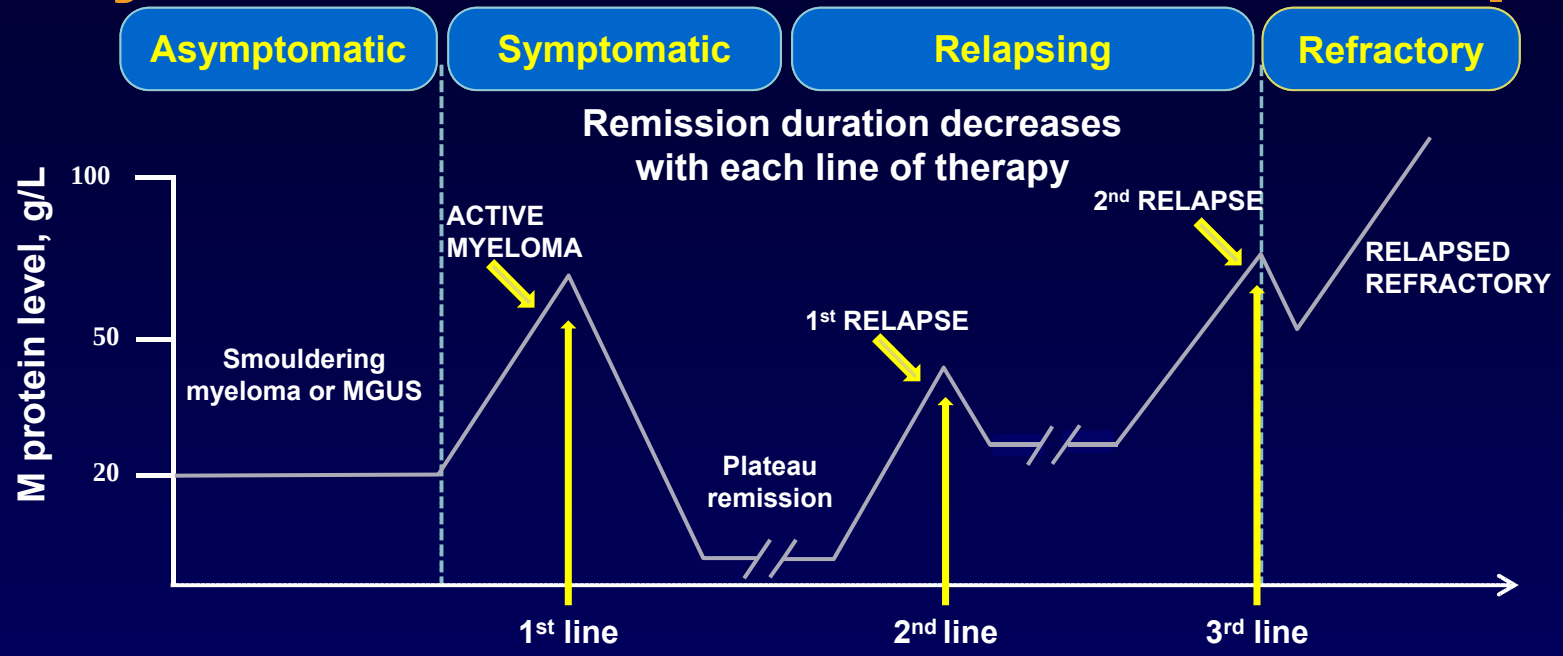
Course of Disease: MM is Characterised by a Pattern of Remission and Relapse



	1st line	2nd line	>3rd line
Median OS, months	20–50	14–16	6–10
Sensitivity to chemotherapy	Sensitive	Resistant	Resistant
Adverse events	Lower risk SAE	High risk SAE	High risk SAE

MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; OS, overall survival; SAE, serious adverse event

Adapted from: Durie BGM. 2008/2009 edition. North Hollywood, CA: International Myeloma Foundation; 2008.

Therapeutic Algorithm

	Young fit	Elderly fit	Elderly unfit/frail
Diagnosis	VTD - ASCT	MPV	Rd
1° Relapse	Bort- Dex	Len-Dex	Bort-Dex
2° Relapse	Len-Dex	Bort-Dex	Len-Dex
3° Relapse	Pom-Dex	Pom-Dex	Pom-Dex
3° Relapse	Carf-Dex	Carfilzomib	Carfilzomib
4° Relapse	Thal-Dex	Thal-Dex	Thal-Dex

ASCT, autologous stem cell transplant; BTZ, bortezomib; CFZ, carfilzomib; CYC, cyclophosphamide; DEX, dexamathasone; DOXO, doxorubicin; LEN, lenalidomide; MPT, melphalan+prednisone+thalidomide; MPV, melphalan+prednisone+thalidomide; POM, pomalidomide; Rd, lenalidomide +dexamethasone; THAL, thalidomide; VTD, bortezomib+thalidomide+dexamethasone

Asymptomatic Progressive Disease

Symptomatic Progressive Disease

Switch -- Rechallenge

When Should We Start/Change Treatment in R/R MM Patients?

1. Asymptomatic progressive disease
   - Confirmed increase >25% M protein

2. Symptomatic progressive disease
   - CRAB criteria

CRAB: C = Calcium (elevated), R = Renal failure, A = Anemia, B = Bone lesions; PDN, prednisone

When to Start Treatment: Asymptomatic Progressive Disease

- Diagnostic criteria
  - No CRAB
  - Confirmed increase >25% M protein
  - Absolute increase >1 g/dl or >500 mg/24 h
  - Bone marrow plasma cell >10%

- Treatment choice
  - Increase dose-intensity

    Len (10mg→25mg) Bort (once → twice weekly)
  - Add 2nd agent corticosteroids

    Dex (40 mg weekly), PDN (50mg bid), Len (10mg→25mg)
  - Add 3rd agent

    Cyclo – Doxo – Len – Bort

Bort, bortezomib

Rajkumar SV, et al. Blood 2011;117: 4691–4695; Palumbo A, et al. N Engl J Med. 2011;364(11):1046–1060

When to Start Treatment: Symptomatic Progressive Disease

- **Diagnostic criteria**
  - **CRAB**
    - **New bone lesion**
    - **Hypercalcemia** (>11.5 mg/dL)
    - **Hemoglobin (<10 g/dL)**
    - **Serum creatinine (>2 mg/dL)**
  - **Confirmed doubling M protein within ≤2 months**
    - **Absolute increase >1 g/dL or >500 mg/24 h**

- **Treatment choice**
  - **Switch bortezomib → lenalidomide combination**
  - **Switch lenalidomide → bortezomib combination**
  - **Introduce pomalidomide combination**
  - **Introduce carfilzomib combination**

Kyle RA, Rajkumar SV. Leukemia 2009;23(1):3–9; Palumbo A, et al. *N Engl J Med.* 2011;364(11):1046-1060.

When to Start Treatment: Switch or Rechallenge

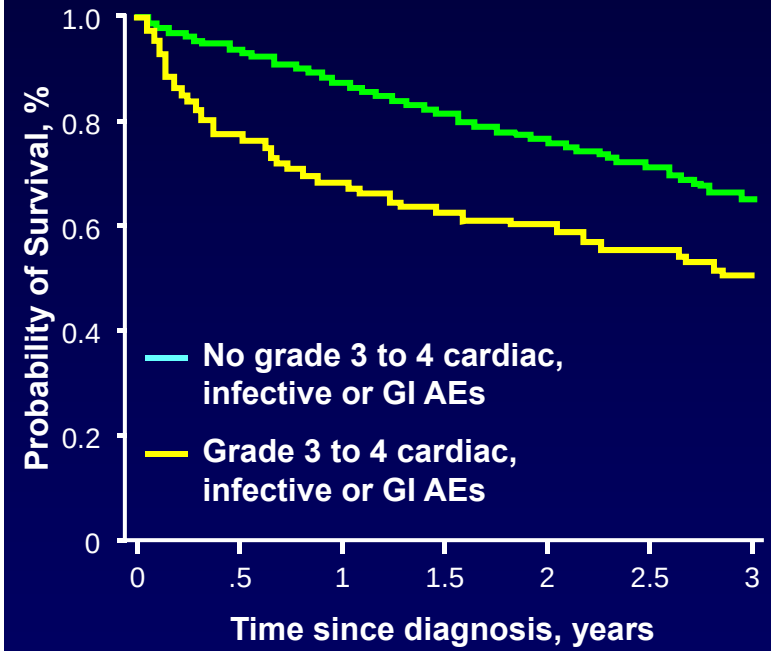
- Previous progression-free survival (PFS) <6 months CRAB
  - Switch bortezomib → lenalidomide combination
  - Switch lenalidomide → bortezomib combination
  - Introduce pomalidomide combination
  - Introduce carfilzomib combination
- Previous PFS/free interval >6 months
  - Rechallenge previous regimen

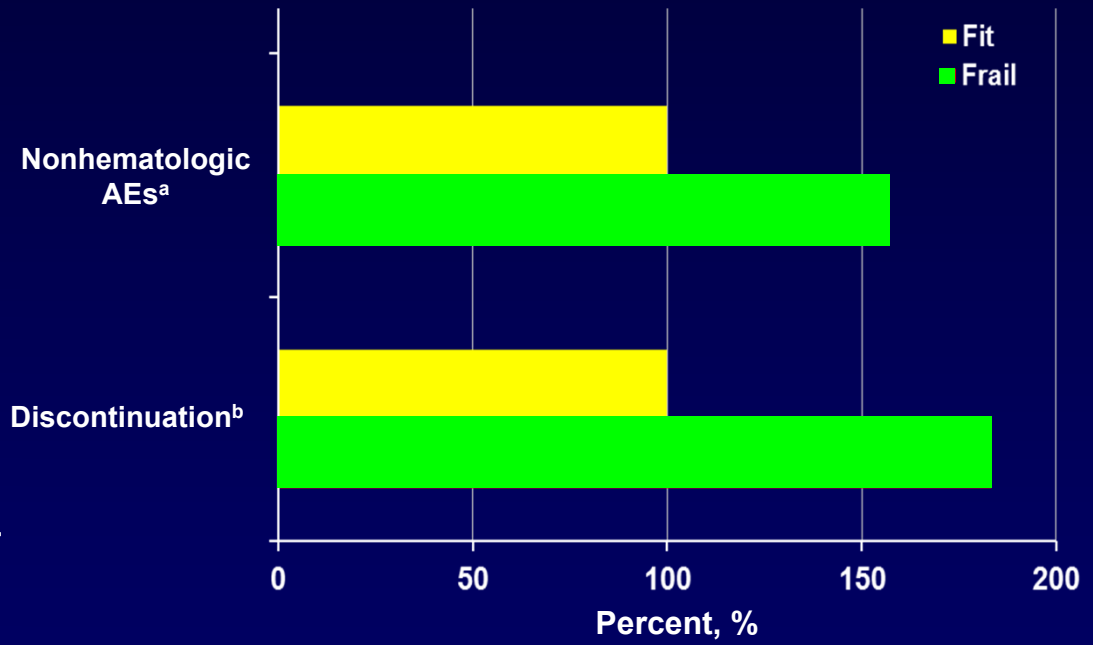
Kyle RA, Rajkumar SV. Leukemia 2009;23(1):3–9; Palumbo A, et al. *N Engl J Med.* 2011;364(11):1046-1060.

In R/R MM Treatment Choice is Mainly Determined By:

1. Disease aggressiveness
2. Age
3. Co-morbidities
4. Patient's choice

Grade 3/4 Cardiac Infective, GI AEs Impact on survival of 1435 myeloma patients: multivariate analysis





[a]at least one adverse event; [b]Due to AEs, withdrawal of consent, patient compliance, unknown; progressive disease was excluded.

GI, gastrointestinal; AE, adverse event

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

New Treatment Algorithm for Elderly MM

Patient Status Assessment

- Age
- ADL
- IADL
- Charlson comorbidity score

FIT	UNFIT	FRAIL
Age <80 years	Fit >80 years	Unfit >80 years
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

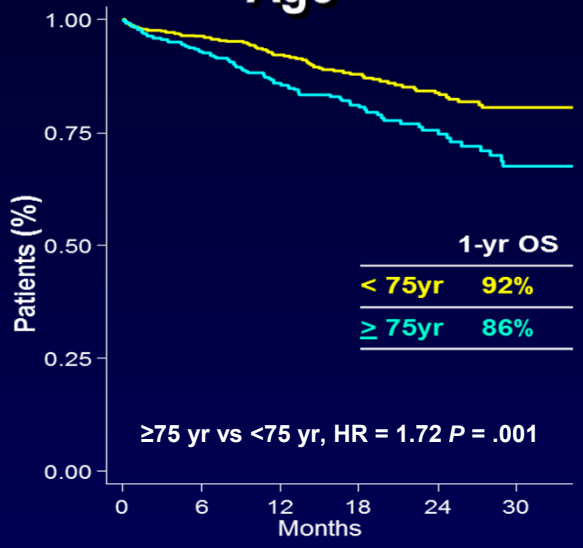
ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living; MM, multiple myeloma

Palumbo A, et al. *Blood.* 2011;118(17):4519-4529

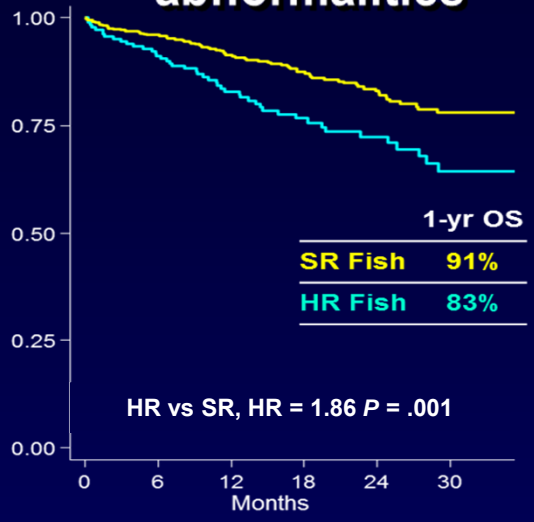
Overall Survival

Subgroup Analysis in All Patients

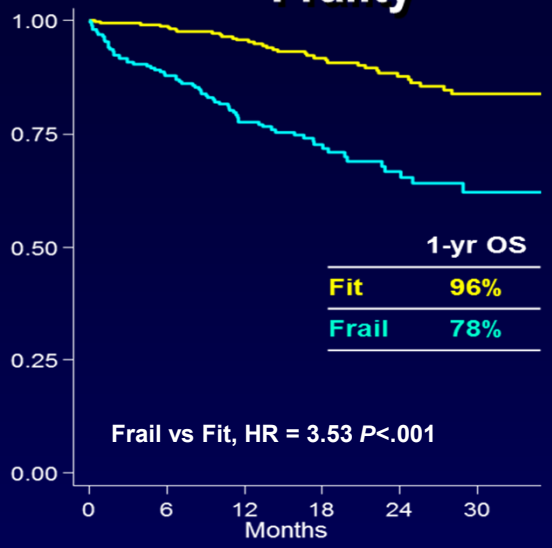
Age



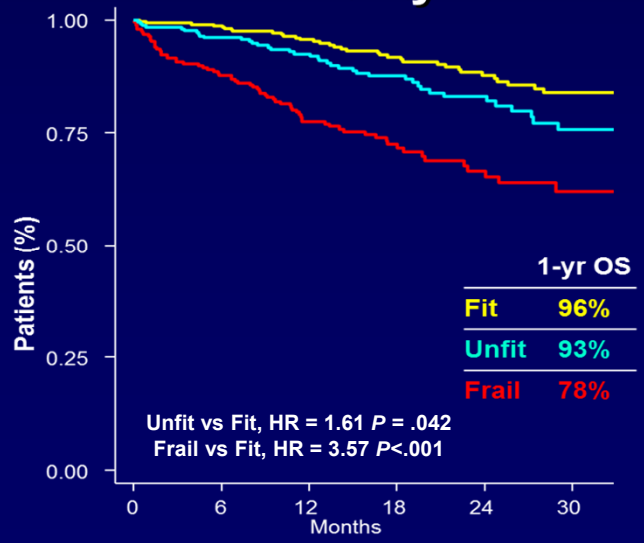
Chromosomal abnormalities



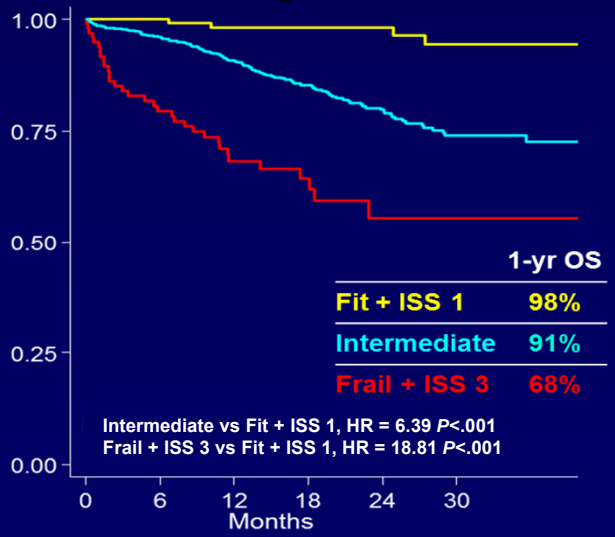
Frailty



Frailty



Frailty + ISS

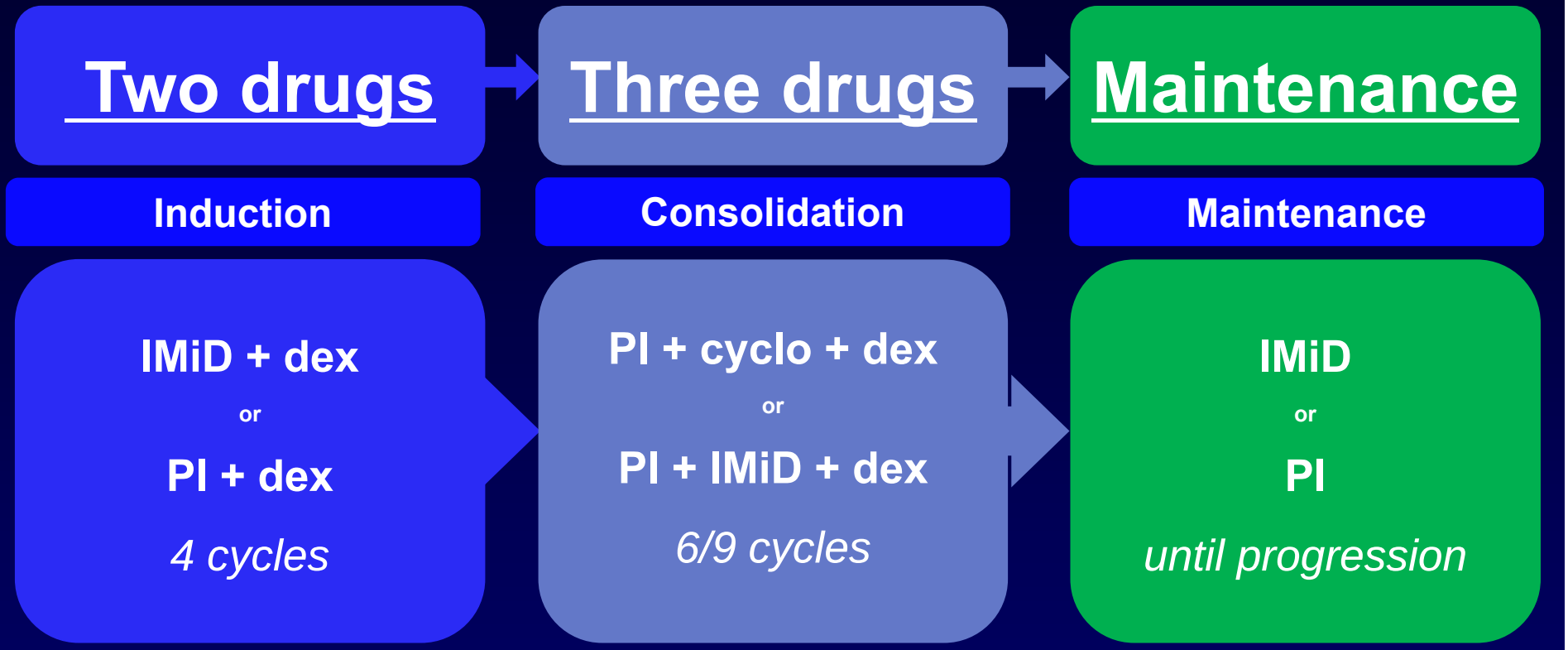


Fit defined as: score=0
Unfit defined as: score=1
Frail defined as: score≥2

FISH, fluorescence *in* situ hybridization; HR, hazard ratio; HR FISH, cytogenetically defined high risk by FISH; SR FISH, cytogenetically defined standard risk by FISH

Larocca A, et al. *Blood.* 2013;122: Abstract 687 and oral presentation.

Treatment Strategy



IMiD, immunomodulatory drug; PI, proteasome inhibitor; dex, dexamethasone; cyclo, cyclophosphamide

Falco P, et al. *Leukemia*. 2013;27(3): 695-701. Palumbo A, et al. *Blood*. 2010;116(21): Abstract 1940.

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Asymptomatic Progressive Disease

Symptomatic Progressive Disease

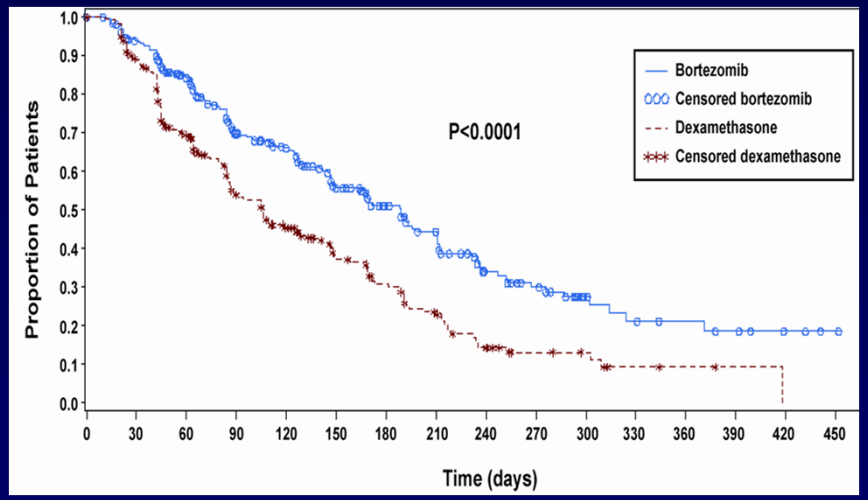
Switch -- Rechallenge

Bortezomib vs Dexamethasone in Relapsed MM

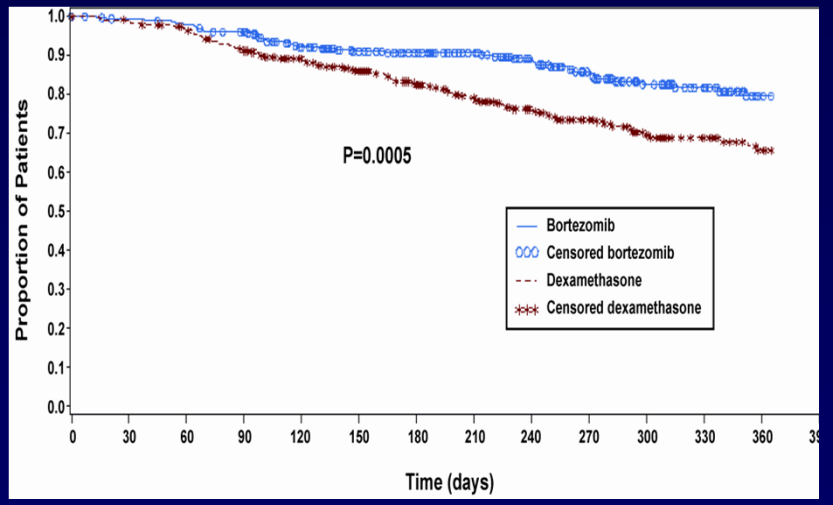
Bortezomib 1.3 mg/m^2 IV push
Days 1, 4, 8, 11 Q3W cycle, 8 cycles

Time to progression (N = 669)

78% improvement in median TTP with bortezomib



1-year survival (N = 669)



Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498

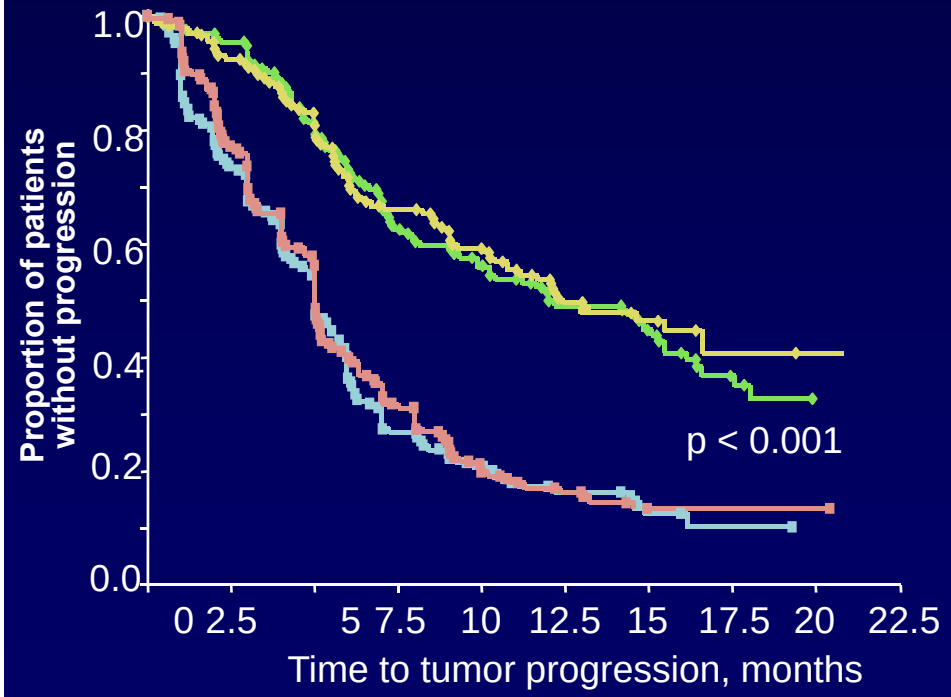
Len/Dex vs Dex in Relapsed MM (MM09-MM010)

Lenalidomide 25 mg d 1–21
Dex 40 mg d 1–4, 9–12, 17–20

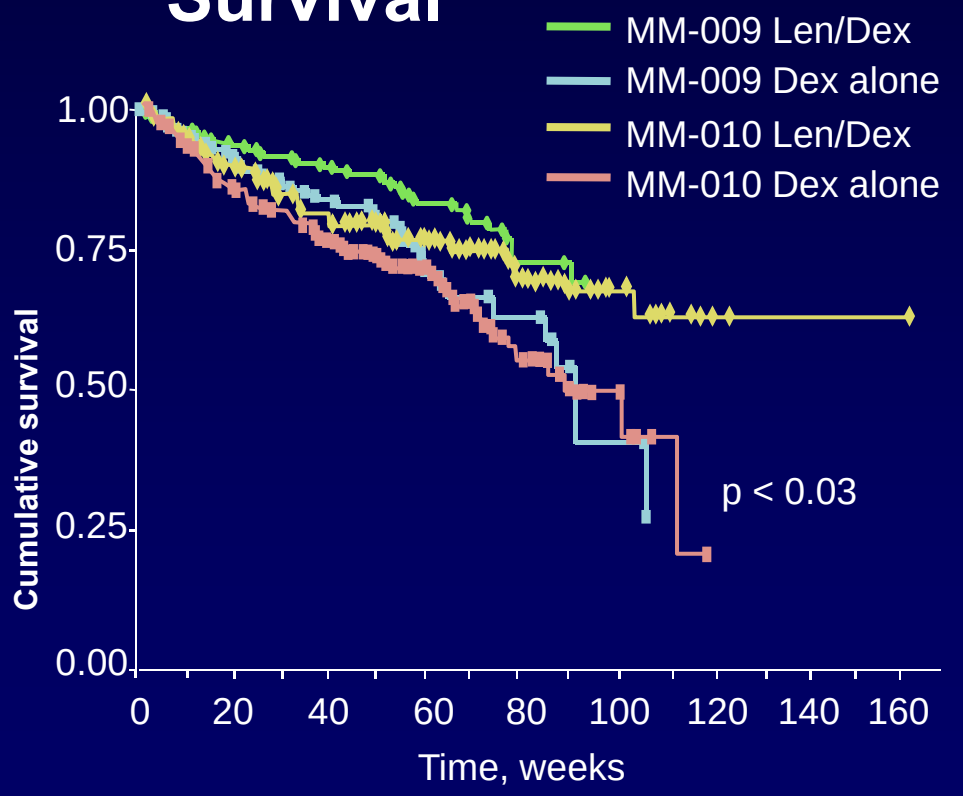
vs

Dex 40 mg d 1–4, 9–12, 17–20

TTP



Survival



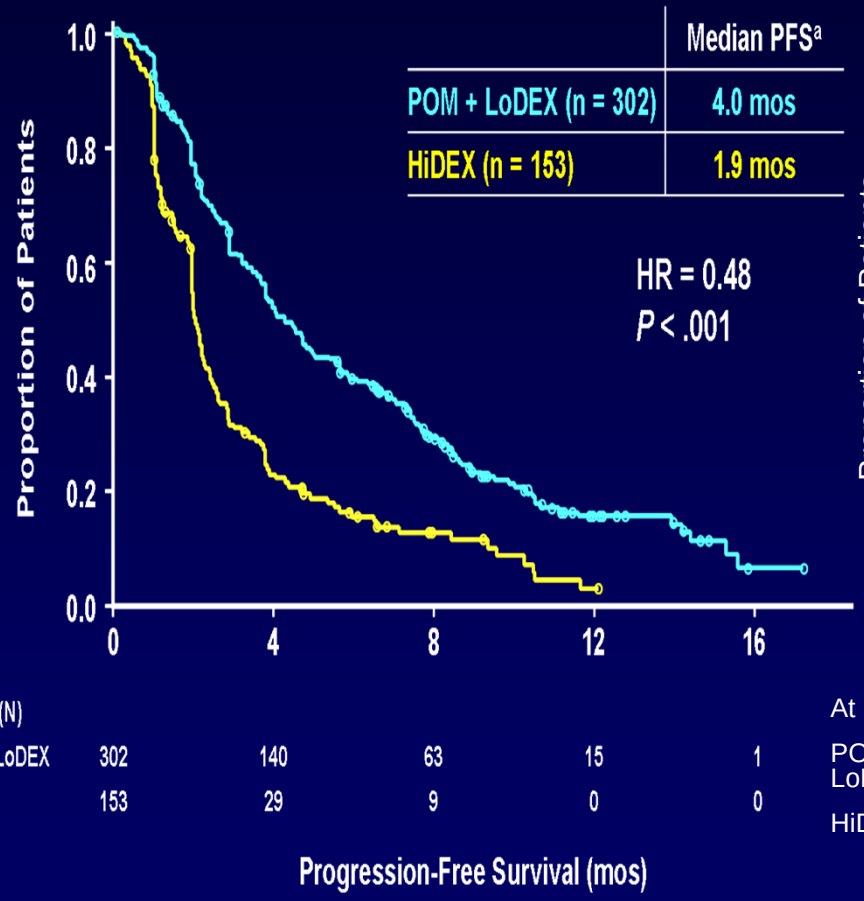
Dimopoulos MA, et al. N Engl J Med. 2007;357(21):2123-2132; Weber DM, et al. J Clin Oncol. 2006;24(18S): Abstract 7521

Current Standard Regimens

Induction regimen	Schedule	
Bortezomib-Dexamethasone[1]	21-day cycles Bor: 1.3 mg/m^2 , d 1-4-8-11	Dex: 40 mg, d 1-4, 9-12
Bortezomib-Cylophosphamide-Dexamethasone[2]	28-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 or 1.5 mg/m^2 d 1-8-15-22 Cycl: 300 mg/m^2 d 1-8-15-(22)	Dex: 40 mg d 1, 8, 15, 22
Bortezomib-Doxorubicin-Dexamethasone[3]	28-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 Dox: 9 mg/m2 d 1-4	Dex. 40 mg d 1, 8, 15, 22
Bortezomib-Thalidomide-Dexamethasone[4]	21-day cycles Bor: 1.3 mg/m^2 d 1-4-8-11 Thal: 100 - 200 mg/d	Dex: 40 mg, d 1-4, 9-12
Bortezomib-Lenalidomide-Dexamethasone[5]	28-day cycles Bor: 1.3 or 1 mg/m^2 d 1-4-8-11 Len: 15 or 25 mg d 1-21	Dex: 40 mg d 1, 8, 15, 22
Lenalidomide-Dexamethasone[6]	28-day cycles Len: 25 mg d 1-21	Dex: 40 mg d 1, 8, 15, 22
Lenalidomide-Cyclophospamide-Dexamethasone[7]	28-day cycles Len: 15 or 25 mg d 1-21 Cycl: 300 mg/m^2 d 1-8-15-(22)	Dex: 40 mg d 1, 8, 15, 22

[1]Harousseau JL, et al. J Clin Oncol. 2010;28(30):4621-4629; [2]Khan ML, et al. Br J Haematol. 2012;156(3):326-333; [3]Sonneveld P, et al. J Clin Oncol. 2012;30(24):2946-5295; [4]Cavo M, et al. Lancet. 2010;376(9758):2075-2085; [5]Richardson PG, et al. Blood 2010; 116(5):679-686.

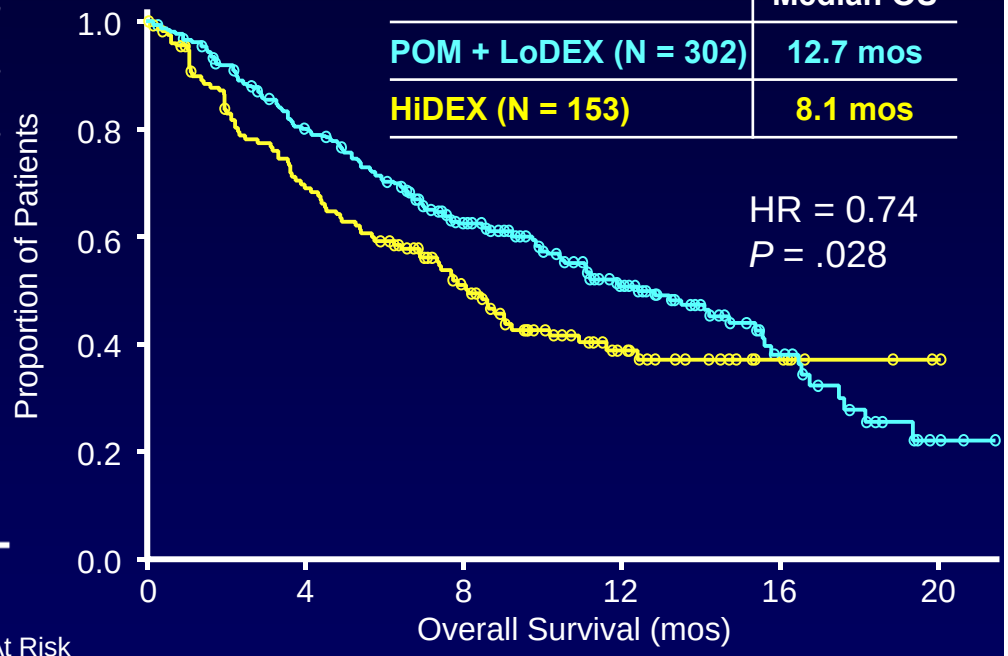
POM-Dex vs Dex in Relapsed MM
MM-003



	Median PFS[a]
POM + LoDEX (n = 302)	4.0 mos
HiDEX (n = 153)	1.9 mos

HR = 0.48
P < .001

At Risk (N)					
POM + LoDEX	302	140	63	15	1
HiDEX	153	29	9	0	0



	Median OS
POM + LoDEX (N = 302)	12.7 mos
HiDEX (N = 153)	8.1 mos

HR = 0.74
P = .028

At Risk						
POM + LoDEX	302	231	145	71	24	2
HiDEX	153	100	59	26	7	0

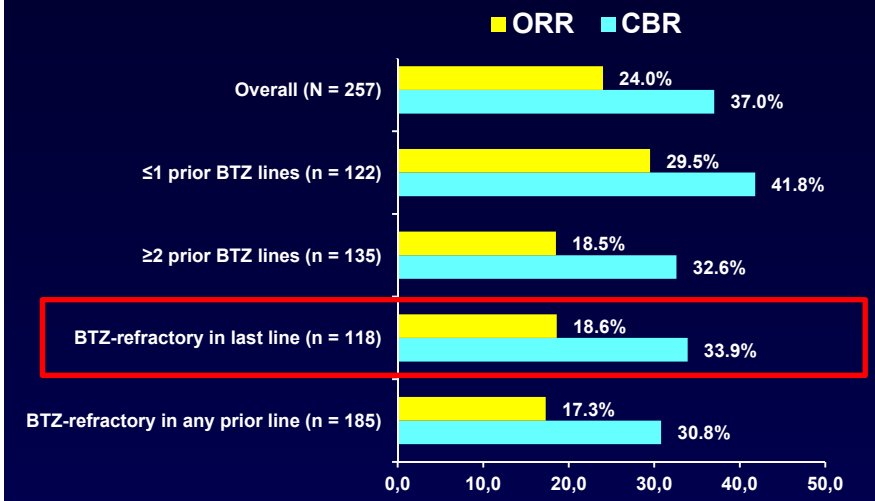
76 pts (50%) in the HiDEX arm received POM

[a] Based on IMWG criteria.

San-Miguel JF, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8510.

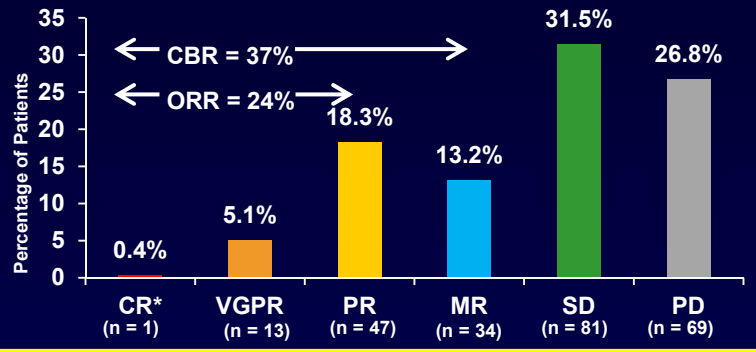
Carfilzomib in Bortezomib-Refractory MM Patients (PX-171-003-A1)

Response Rates



Response Rates

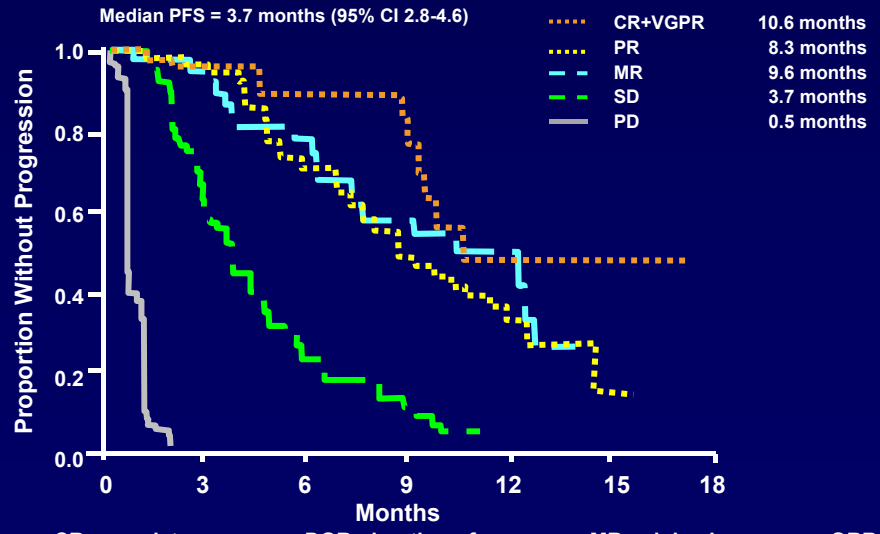
DOR: 7.8 months (≥PR) and 8.3 months (≥MR)



Subset analyses of higher-risk populations showed similar response rates
(eg, unfavorable cytogenetics, baseline peripheral neuropathy)

* CR IRC determined; 11 patients had unconfirmed response

PFS by Response



Treatment-Emergent AEs

N = 266	Grade 3-4, %
Hematologic	
Thrombocytopenia	29
Anemia	24
Neutropenia	11
Nonhematologic (>1.5%)	
Fatigue	7.5
Upper respiratory tract infection	4.5
Dyspnea	3.4
Blood creatinine increased	2.6
Other AEs of Interest (>1.5%)	
Peripheral neuropathy	1.1

CR, complete response; DOR, duration of response; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, sta… isease; VGPR, very good PR

Siegel DS, et al. *J Clin Oncol.* 2011; 29(15S): Abstract 8027.

Bendamustine in R/R MM

Study details	Results
+ Thal + Dex[1] (two doses of bendamustine: 60mg/m^2 vs 100mg/m^2)	• n=95 • B100TD stopped due to lack of tolerability • **B60TD: ≥ PR46%, median PFS 7.5 mos** • Grade 3/4: neutropenia 32%, thrombocytopenia 25%, anemia 14%
+ Bortezomib + Dex[2] (6 cycles + 6 cycles maintenance)	• n=73, median age 75.8 years • **≥ PR 69.8%, VGPR 16.5%, CR 13.6%** • **Median PFS 10.8 mos** • **Median OS 23 mos** • Grade 3/4: neutropenia: 19.1%, thrombocytopenia 10.9%, sepsis: 19.1%
+ Bortezomib + Dex[3] (up to 6 cycles + 12 mos consolidation)	• n=75, median age 68 • **≥ PR 71.5%, VGPR 18.5%, CR 16%** • **Prior bortezomib reduced ORR** • **Median TTP 16.5 mos, PFS 15.5 mos** • Severe AEs: thrombocytopenia (30.5%), neutropenia (18.5%), infections (12%)

1. Schey S, et al. *Blood.* 2013;120: Abstract 286; 2. Rodon G, et al. *Blood.* 2013;120: Abstract 1971; 3. Offidani M, et al. *Blood.* 2013;120: Abstract 1974

Management of Hematologic Toxicity

Neutropenia	Action
During the cycle < 500/µL ANC	Withhold until grade 1, reinitiate at lower dose
On the first day of next cycle > 1,500/µL ANC	

Thrombocytopenia	Action
During the cycle < 25-50,000/µL PLT	Withhold until grade 1, reinitiate at lower dose
On the first day of next cycle < 75,000/µL PLT	

ANC, absolute neutrophil count; PLT, platelet

Management of Non-Hematological Toxicity

Thromboembolism: risk factors	Action
No risk factors	Aspirin 100 mg/d
Previous TE, infection, immobilization, CVC Doxorubicin, high-dose dexamethasone (> 160 mg/mo),	Enoxaparin 40 mg/d (4 months) → Aspirin

Peripheral neuropathy symptoms	Action
Grade 1 (paresthesia)	No action
Grade 1 with pain or grade 2-3	Withhold until grade 1, reinitiate at lower dose

ADL, Activity of Daily Living; CVC, central venous catheter; TE, thromboembolism

Dose Reduction Strategies

Dexamethasone-Dose

Age	Action
≤ 65 years	40 mg/day - twice weekly
65–75 years	40 mg/day - weekly
≥ 75 years	10-20 mg/day - weekly

Lenalidomide-Dose

Renal function	Action
≥ 50ml/min CL_{Cr}	25 mg once daily
30-50 ml/min CL_{Cr}	10 mg once daily
< 30ml/min CL_{Cr}	5 mg once daily

CL_{Cr} , creatinine clearance

Dimopoulos MA, et al. *Leukemia.* 2011;25(5):749-760

Prophylactic Antibiotic

Infection	Action
At least for the first 3 cycles	Prophylactic antibiotic
Low blood counts	Immediate antibiotic treatment
Bortezomib, ASCT/allo-SCT	Prophylactic acyclovir
	Vaccination against influenza, Streptococcus pneumonia and Haemophilus influenzae

ASCT, autologous stem cell transplantation; allo-SCT, allogeneic stem cell transplantation

Pomalidomide + Low-Dose dexamethasone MM-008

A phase 1 study in patients with R/R MM and impaired renal function

Renal function	Action
≥ 60ml/min CL_{Cr}	POM 4 mg/day d 1-21/28
< 30ml/min CL_{Cr}	POM 2 mg/day escalating to 4 mg/day

Siegel DS, et al. *Blood.* 2013;120: Abstract 3185

Management of Adverse Events in MM Patients Treated With Novel Agents

Skin toxicity	Action
Grade 1	Steroids and antihistamines
Grade 1 with pain or grade 2-3	Steroids and antihistamines, withhold until grade 1, reinitiate at lower dose

Gastrointestinal toxicity	Action
Grade 1	Supportive therapy
Grade 1 with pain or grade 2-3	Supportive therapy, withhold until grade 1, reinitiate at lower dose

prIME Points™

- Evaluation of disease status
  - Early –Late relapse
  - Sensitive – Resistant disease
- Evaluation of patient status
  - Fit - Frail condition
- Prompt action on adverse event
  - withhold until grade 1
  - reinitiate at lower dose