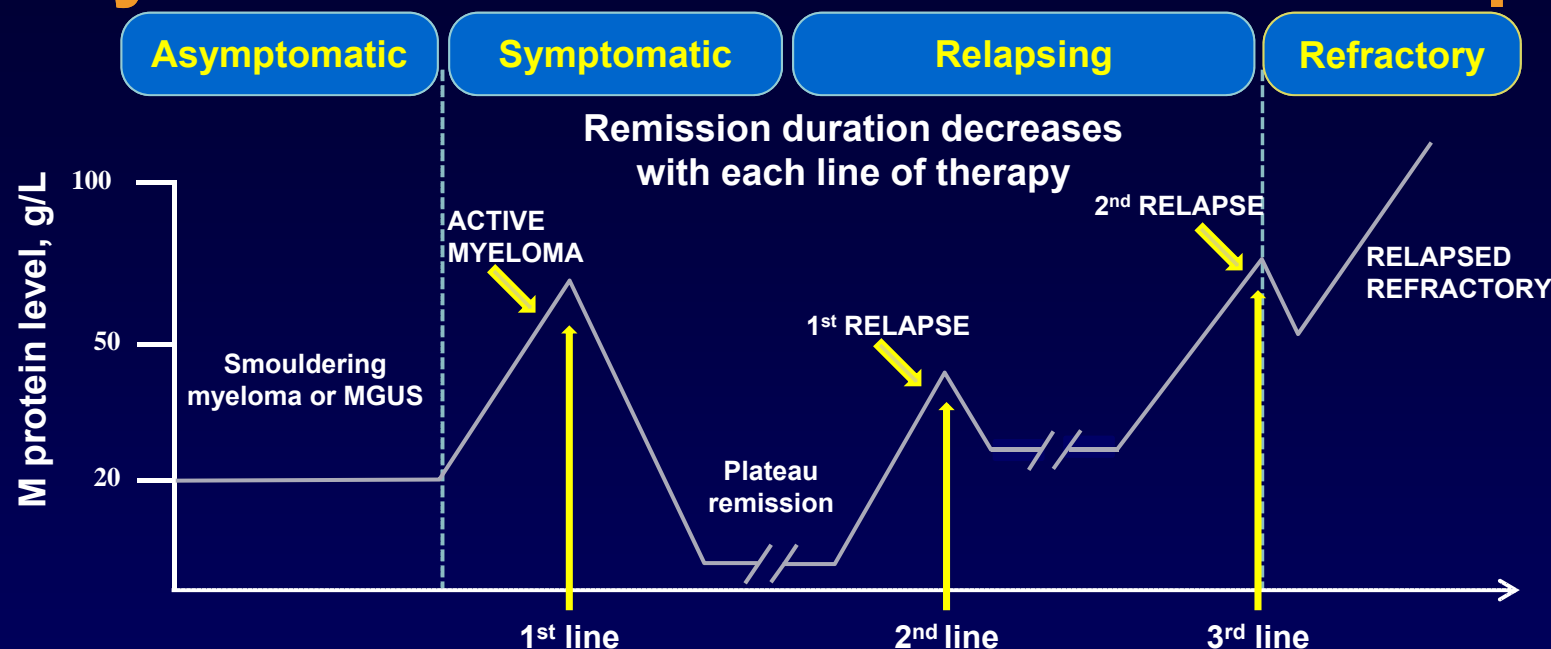


First do no Harm (*Primum non nocere*): Balancing Quality of Life With Quantity of Life

Antonia Palumbo, MD
University of Torino
Torino, Italy

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



	1 st line	2 nd line	>3 rd 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, dexamethasone; 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 \rightarrow lenalidomide combination
 - Switch lenalidomide \rightarrow bortezomib combination
 - Introduce pomalidomide combination
 - Introduce carfilzomib combination

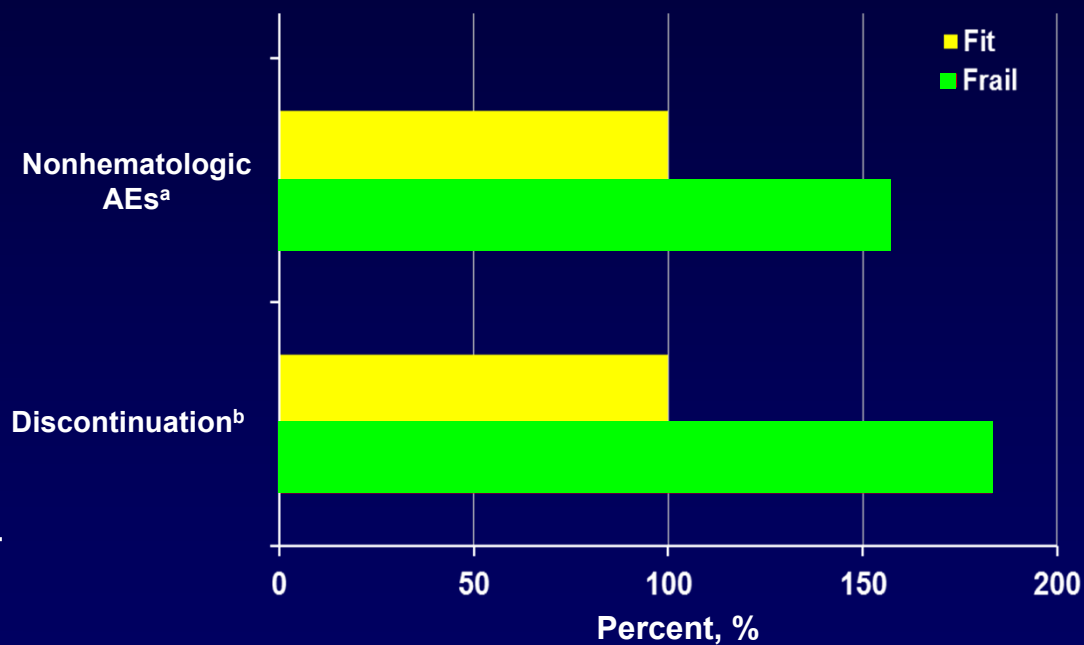
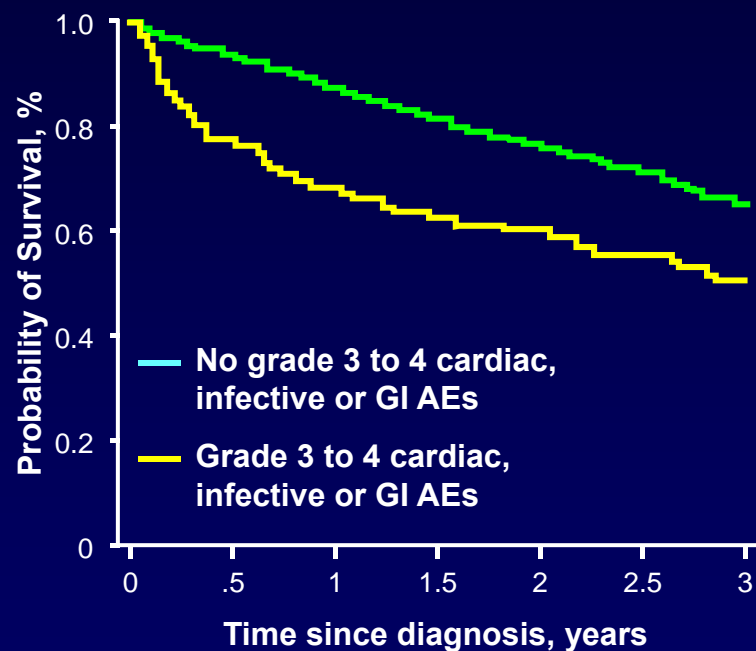
When to Start Treatment: Switch or Rechallenge

- 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

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



^aat least one adverse event; ^bDue to AEs, withdrawal of consent, patient compliance, unknown; progressive disease was excluded.

GI, gastrointestinal; AE, adverse event

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

New Treatment Algorithm for Elderly MM

Patient Status Assessment

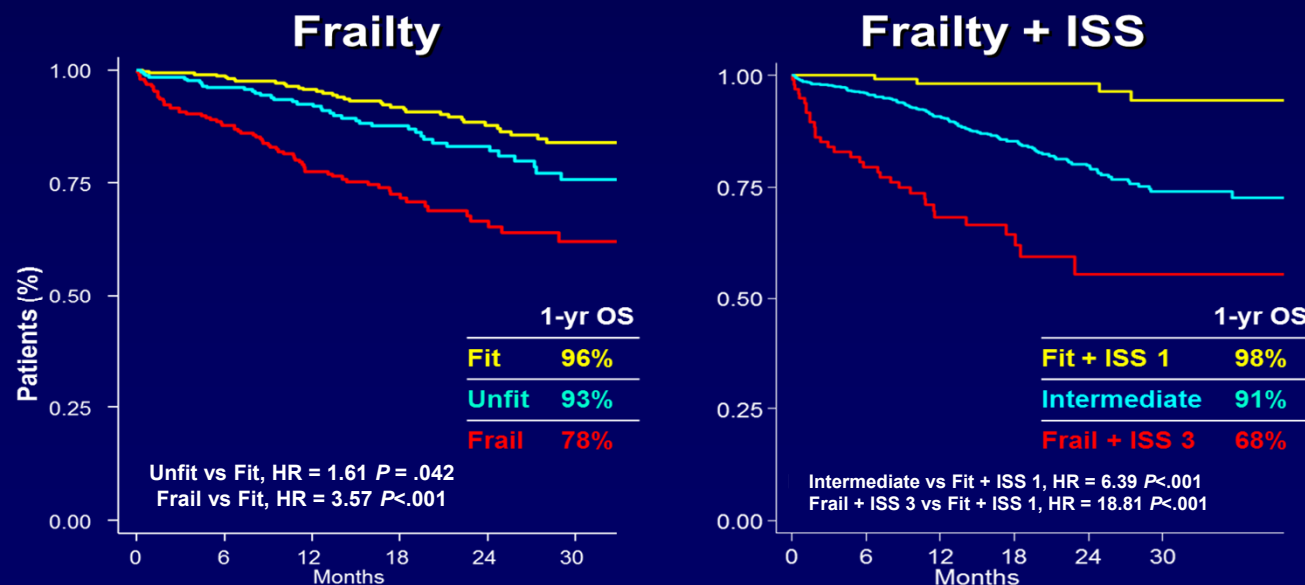
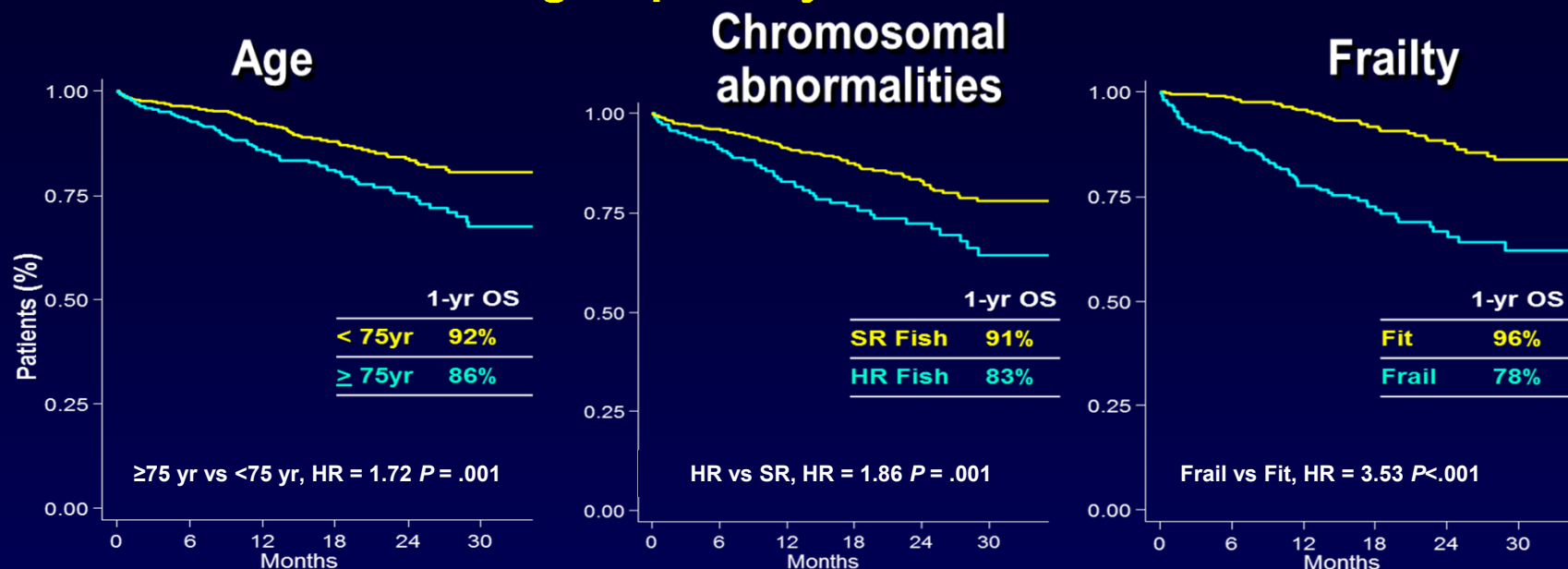
- Age
- ADL
- IADL
- Charlson comorbidity score

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

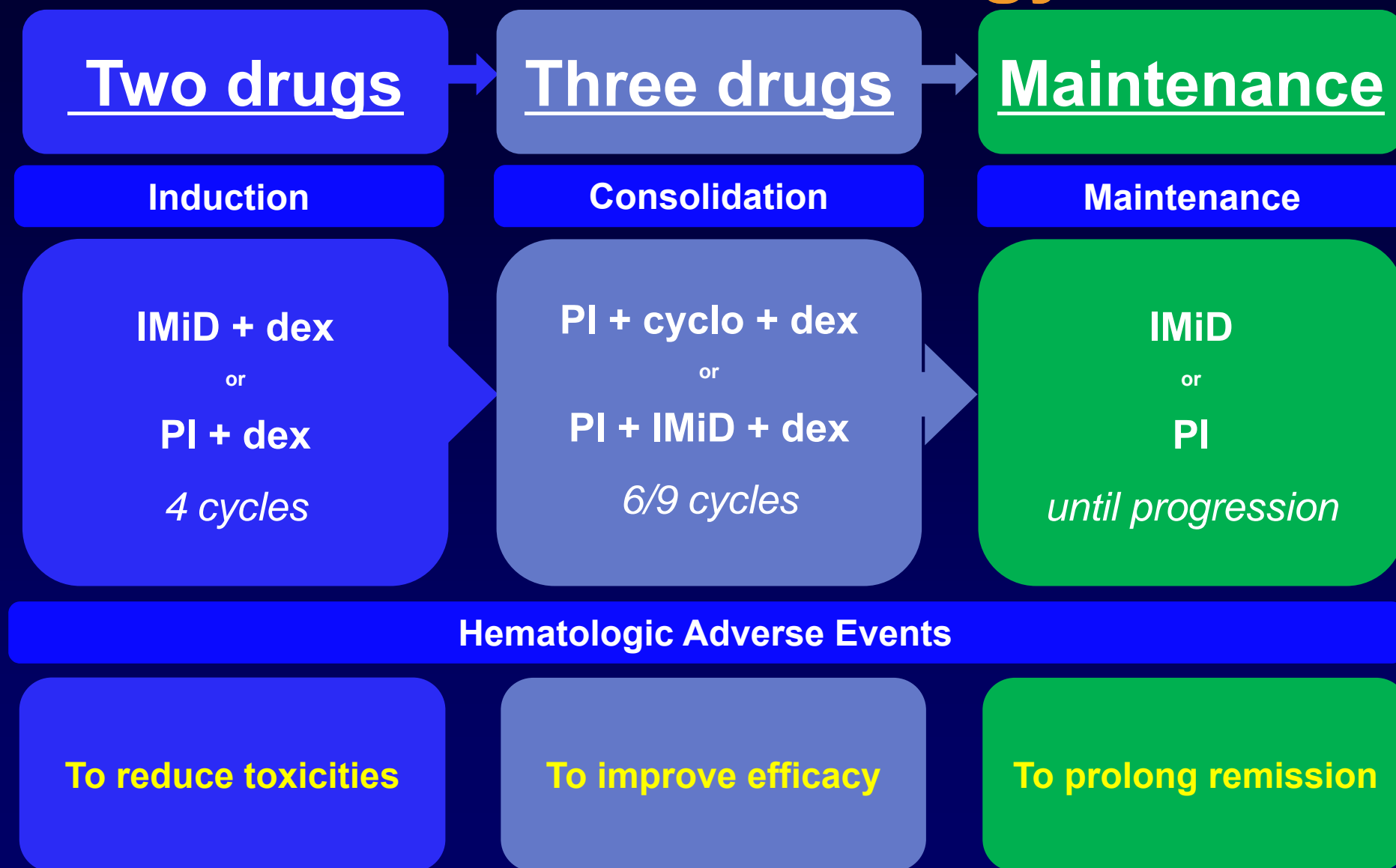
Subgroup Analysis in All Patients



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.

Therapeutic Algorithm

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ASCT, autologous stem cell transplant; BTZ, bortezomib; CFZ, carfilzomib; CYC, cyclophosphamide; DEX, dexamethasone; 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

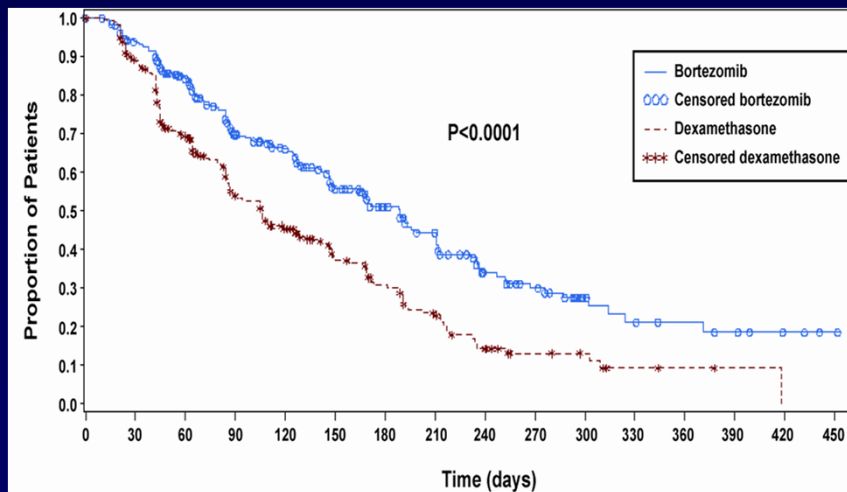
Symptomatic Progressive Disease

Switch -- Rechallenge

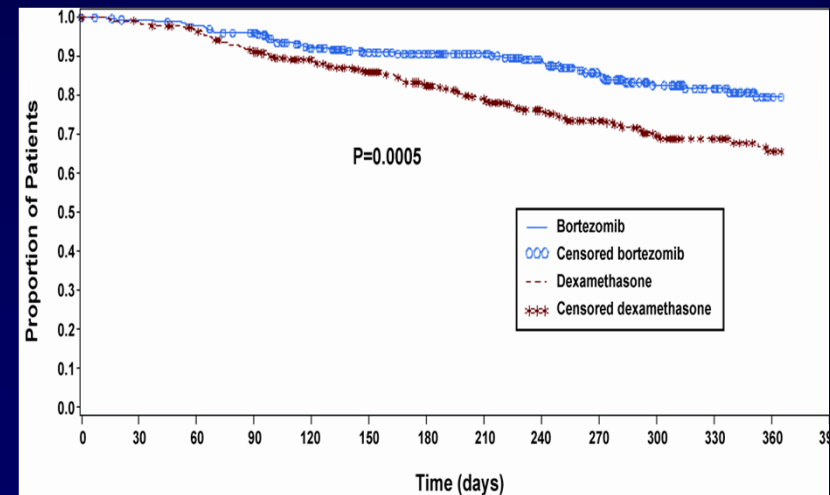
Bortezomib vs Dexamethasone in Relapsed MM

Bortezomib 1.3 mg/m² 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)



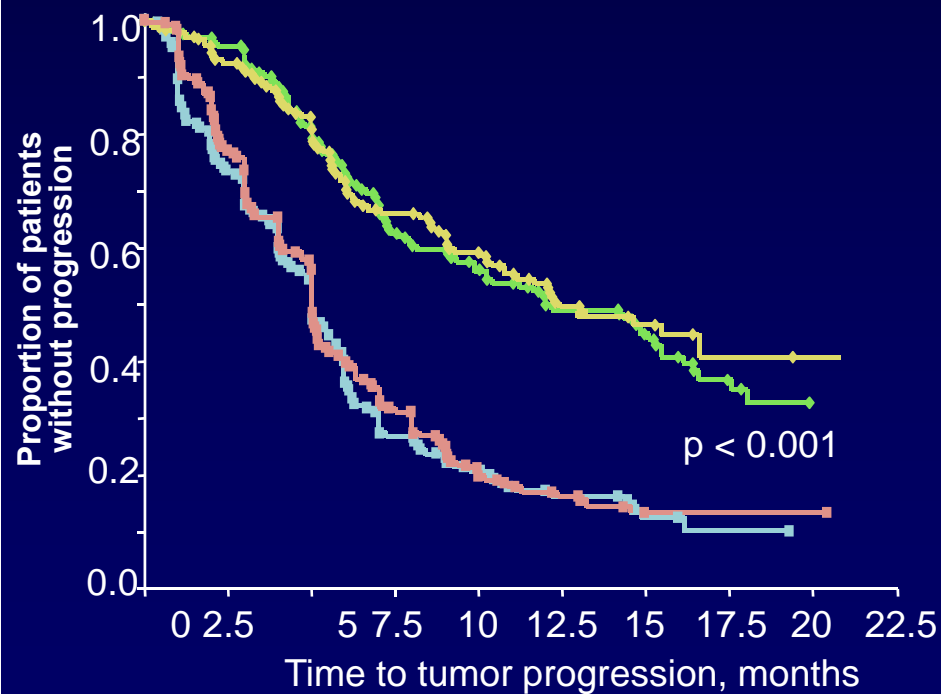
Len/Dex vs Dex in Relapsed MM (MM09-MM010)

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

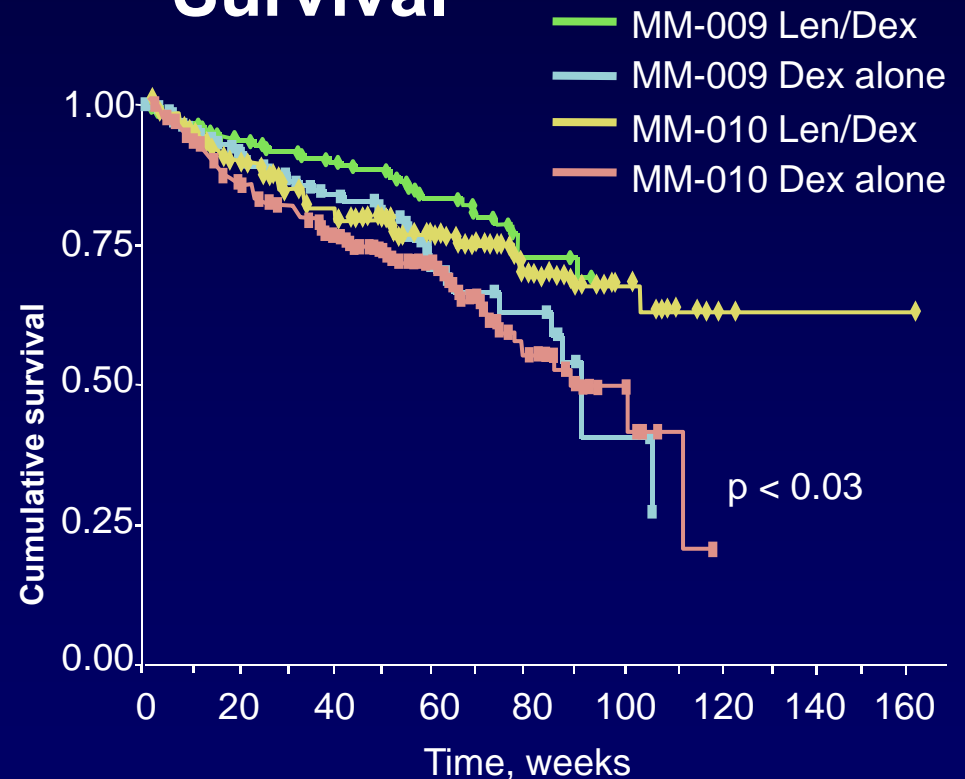
vs

Dex 40 mg d 1–4, 9–12, 17–20

TTP



Survival



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-Cyclophosphamide-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/m ² 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-Cyclophosphamide-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

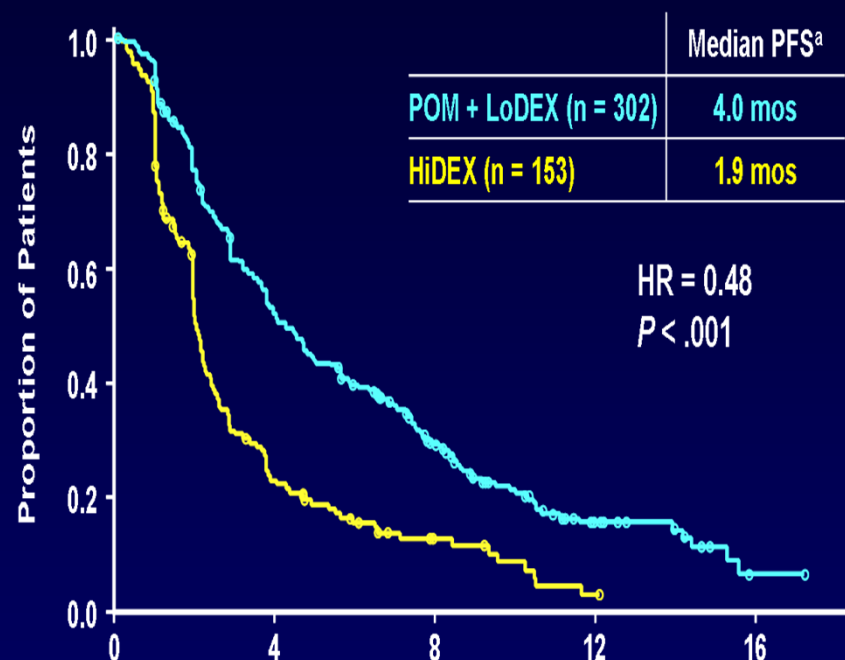
¹Harousseau JL, et al. J Clin Oncol. 2010;28(30):4621-4629; ²Khan ML, et al. Br J Haematol. 2012;156(3):326-333;

³Sonneveld P, et al. J Clin Oncol. 2012;30(24):2946-5295; ⁴Cavo M, et al. Lancet. 2010;376(9758):2075-2085;

⁵Richardson PG, et al. Blood 2010; 116(5):679-686.

POM-Dex vs Dex in Relapsed MM

MM-003



At Risk (N)

POM + LoDEX

302

140

63

15

1

HiDEX

153

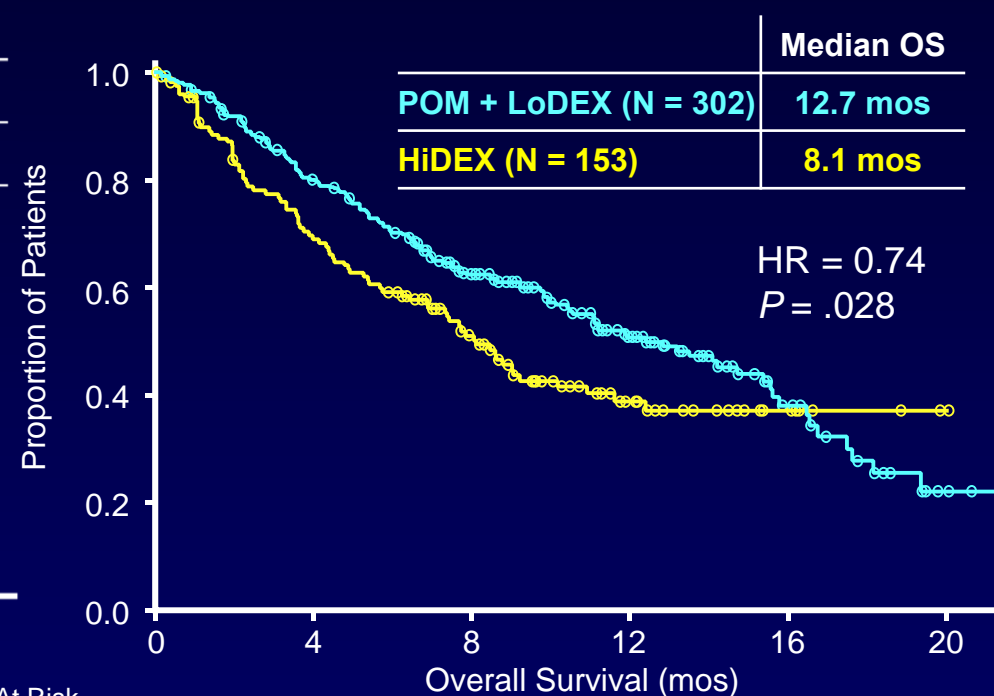
29

9

0

0

Progression-Free Survival (mos)



At Risk

POM + LoDEX

302

231

145

71

24

2

HiDEX

153

100

59

26

7

0

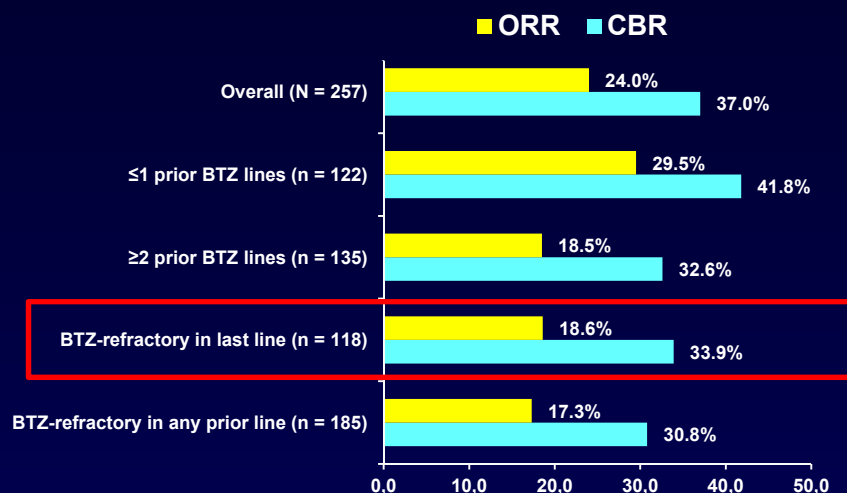
76 pts (50%) in the HiDEX arm received POM

^a Based on IMWG criteria.

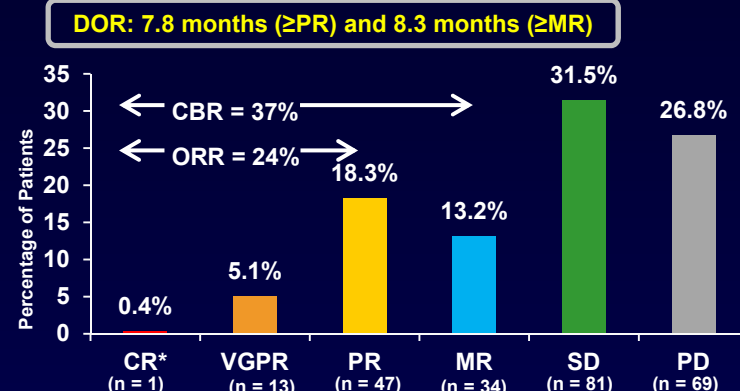
San-Miguel JF, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 8510.

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

Response Rates



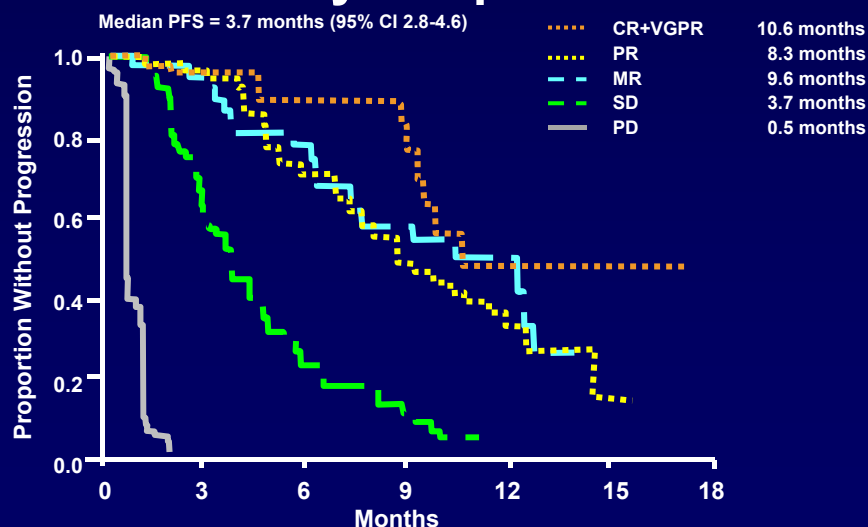
Response Rates



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



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

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

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

Bendamustine in R/R MM

Study details	Results
+ Thal + Dex ¹ (two doses of bendamustine: 60mg/m ² vs 100mg/m ²)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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/ μ L ANC

Withhold until grade 1,

reinitiate at lower dose

On the first day of next cycle

> 1,500/ μ L ANC

Thrombocytopenia

Action

During the cycle

< 25-50,000/ μ L PLT

Withhold until grade 1,

reinitiate at lower dose

On the first day of next cycle

< 75,000/ μ L 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

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
$\geq 60\text{ml/min CL}_{\text{Cr}}$	POM 4 mg/day d 1-21/28
$< 30\text{ml/min CL}_{\text{Cr}}$	POM 2 mg/day escalating to 4 mg/day

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