Institute of Biomedical Research of Salamanca

University of Salamanca

Cancer Research Center

What a Difference a Generation Makes: The Evolution of Novel Agents

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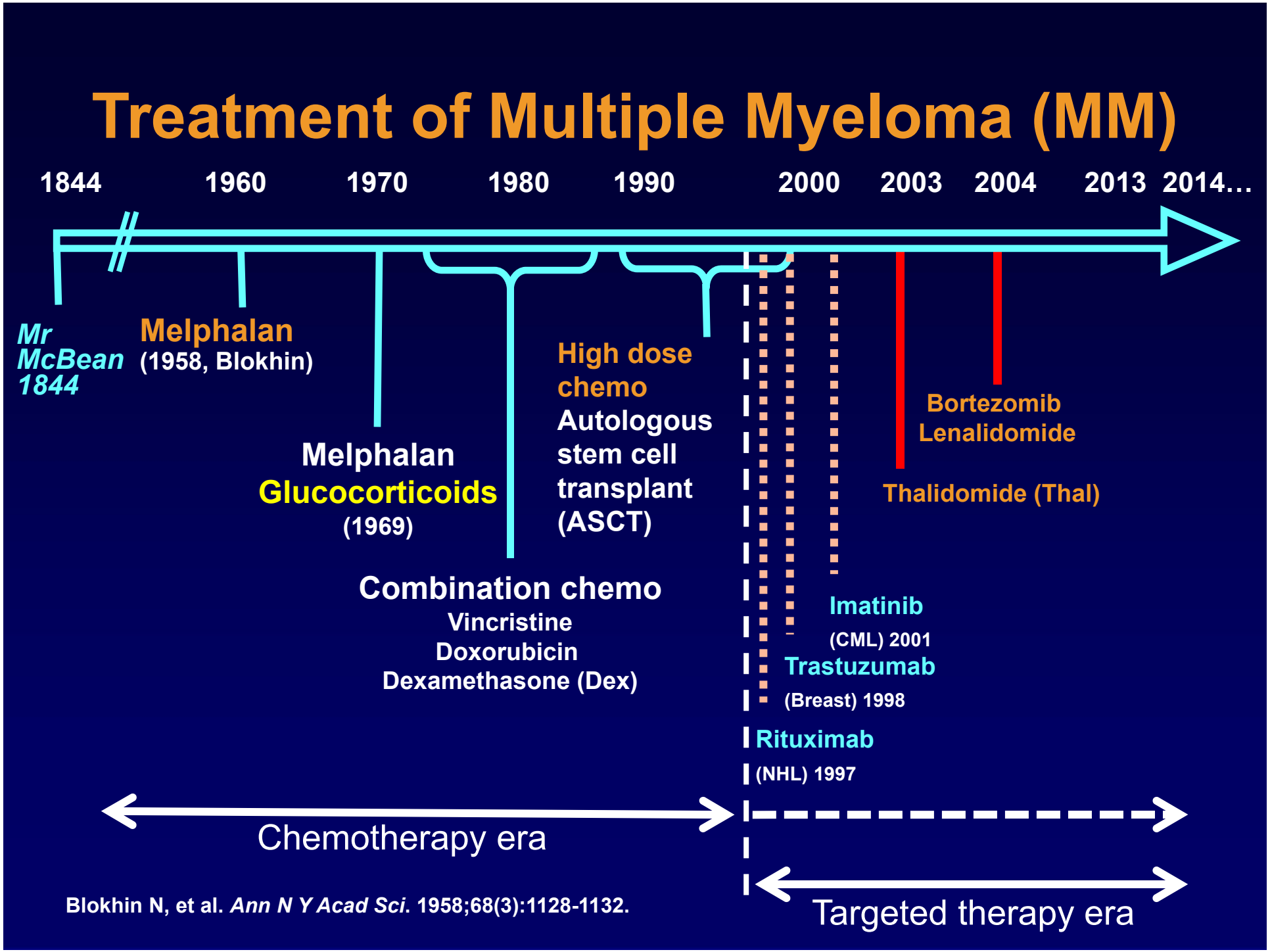
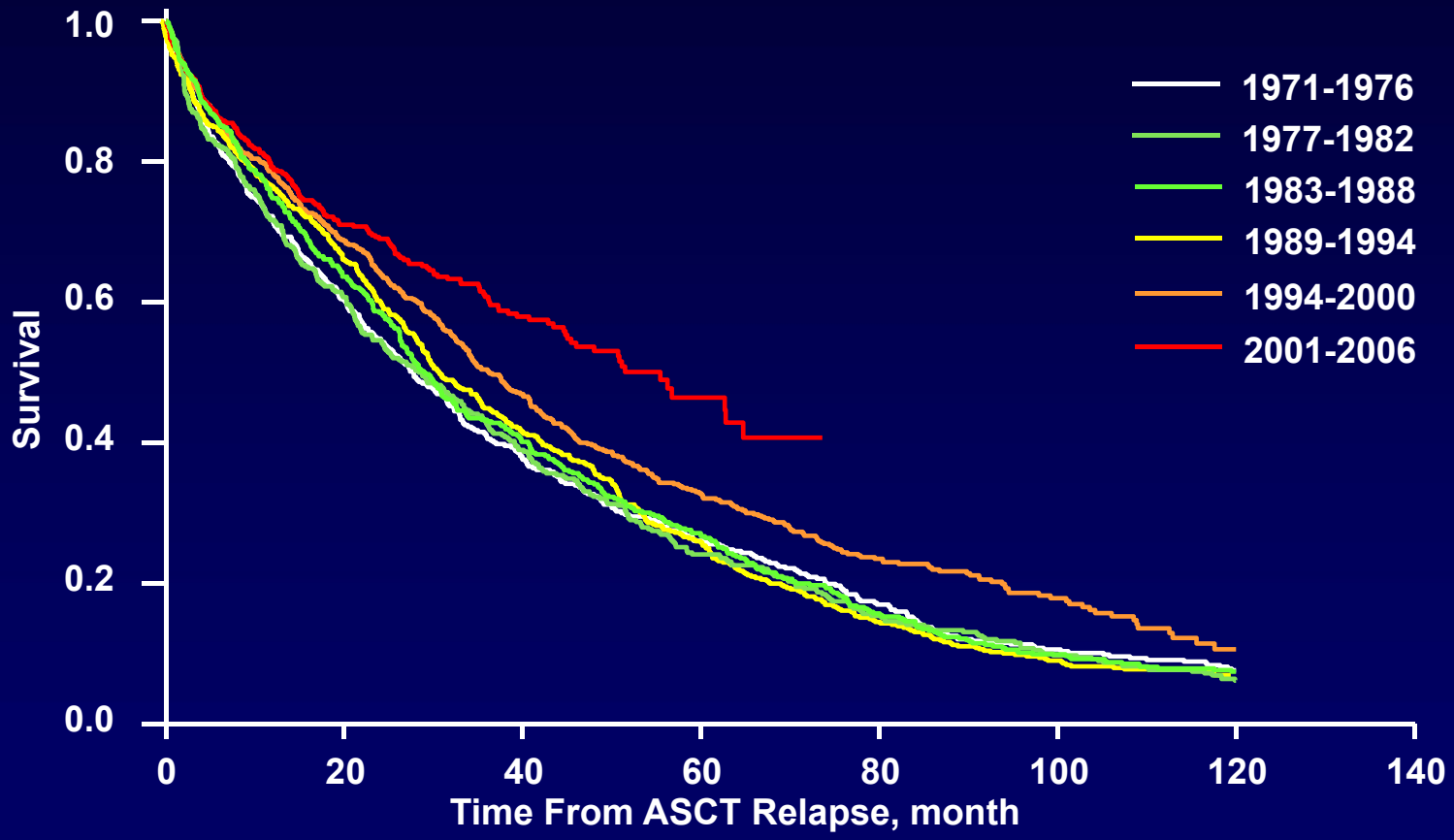
Treatment of Multiple Myeloma (MM)



Blokhin N, et al. *Ann N Y Acad Sci.* 1958;68(3):1128-1132.

Background: Changes in Overall Survival (OS) From 1970 to 2006

Despite the benefit observed with novel agents in recent years



Novel agents are necessary

Kumar SK, et al. *Blood*. 2008;111(5):2516-2520.

Emerging Agents: Novel Strategies

- **Proteasome inhibitors**
- **Immunomodulatory drugs**

Main Randomized Trials With Bortezomib for the Treatment of Relapsed/Refractory (R/R) Myeloma

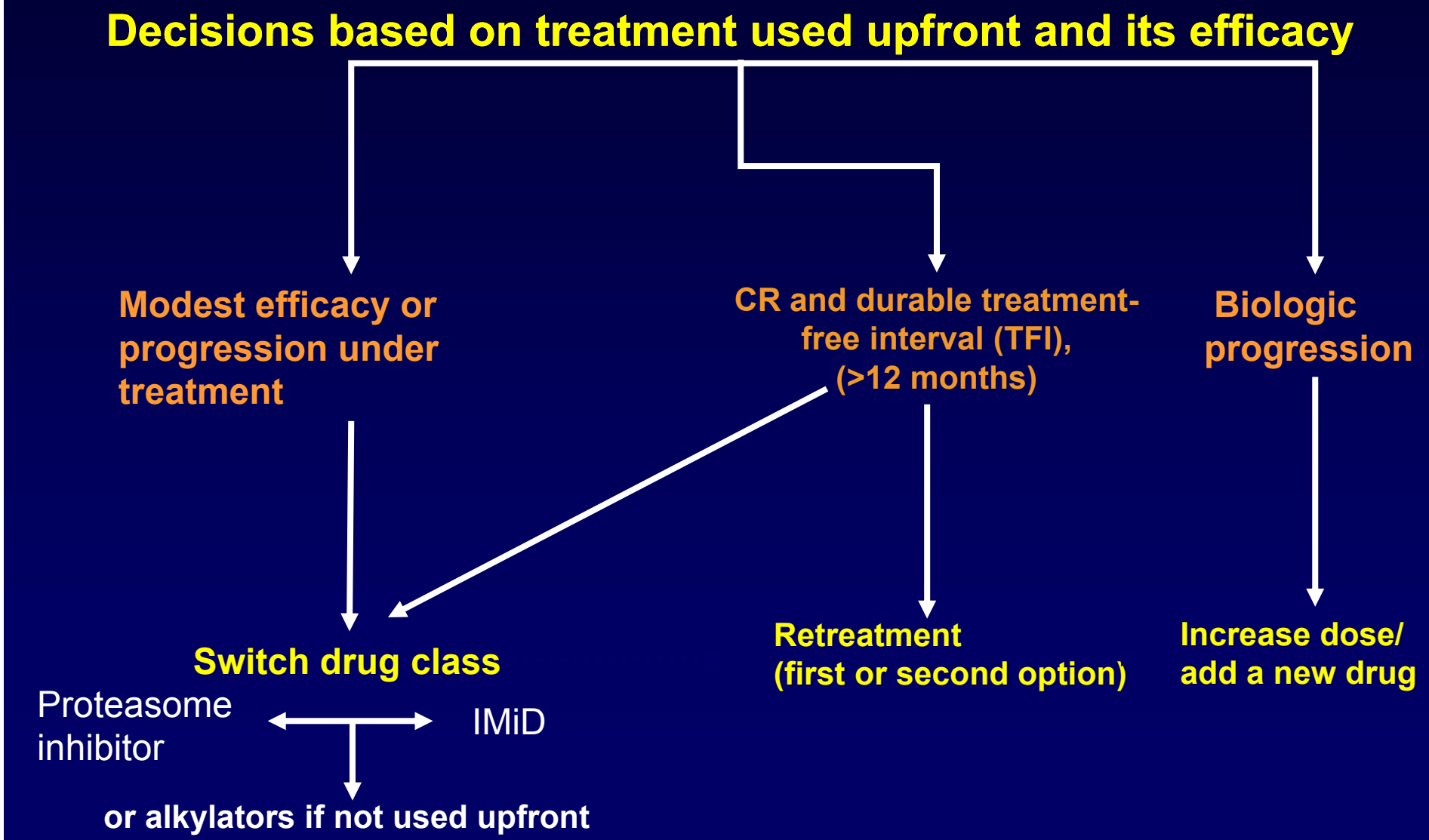
Regimen	ORR, %	CR, %	TTP, months	OS
Bortezomib vs Dex[1]	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% at 1 year
Bortezomib + PLD vs bortezomib[2]	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% at 15 months

- After its approval, bortezomib-based combinations emerged and were used for the treatment of relapsed/refractory multiple myeloma patients, but....
- Bortezomib was moved to be used as part of first-line therapy in transplant and nontransplant candidates
- What are the implications for the treatment at relapse?

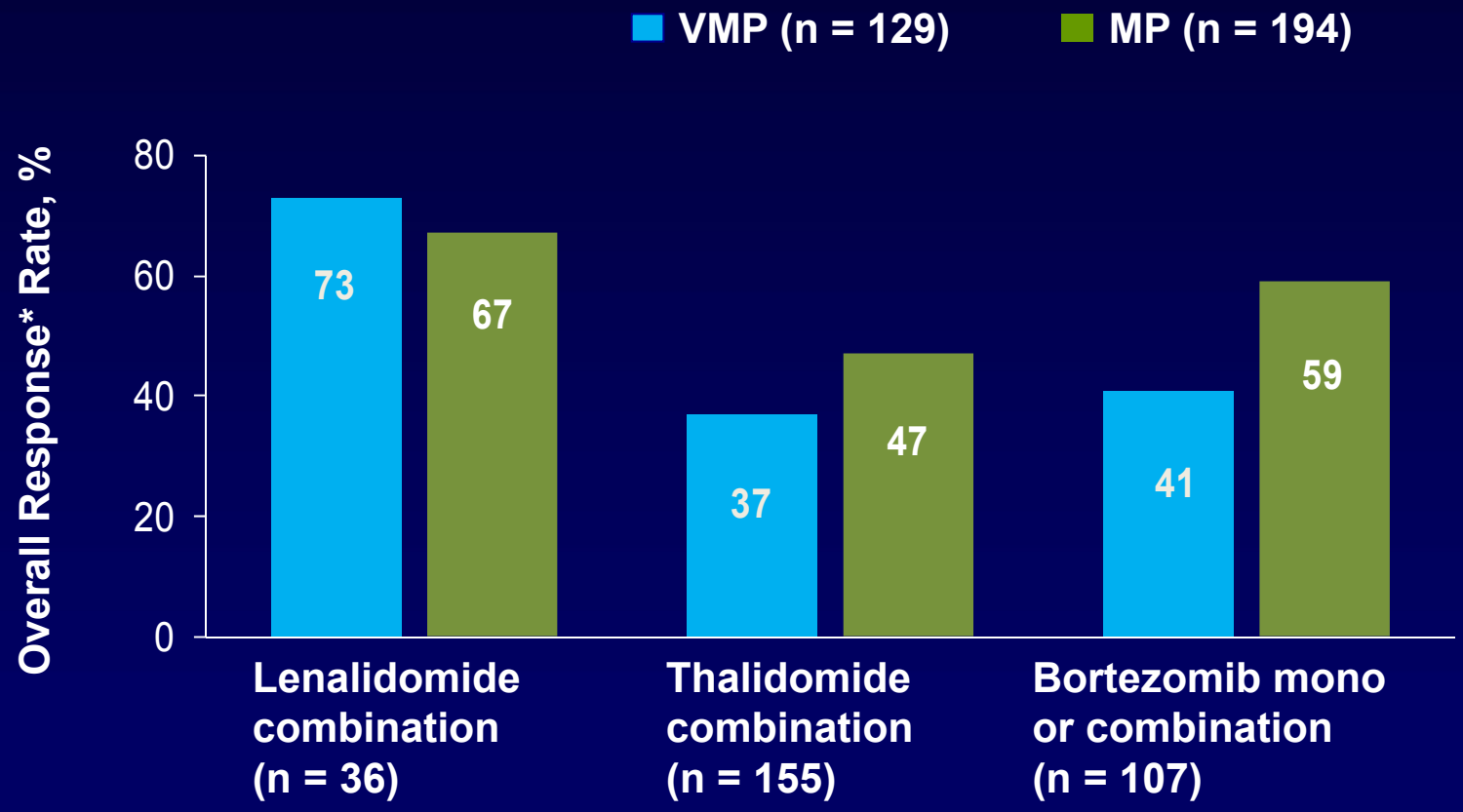
PLD, pegylated liposomal doxorubicin; ORR, overall response rate; CR, complete response; TTP, time to progression

1. Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498. 2. Orlowski RZ, et al. *J Clin Oncol.* 2007;25(25):3892-3901.

Is It Possible to Consider Retreatment With Bortezomib-Based Combination?



Second-Line Combinations After Bortezomib-Based Therapies: Data From the VISTA Trial



*Responses ≥partial response

VMP, bortezomib, melphalan, prednisone; MP, melphalan, prednisone

Mateos MV, et al. *J Clin Oncol.* 2010;28(13):2259-2266.

Phase II RETRIEVE Study: Results

Patients (n = 130)

- Up to eight cycles of bortezomib or bortezomib + Dex
- Median number of prior lines: 2
- Response to previous bortezomib: at least PR
- The TFI required to be retreated was 6 months

Results to retreatment (n = 124)	
CR + PR	40%
TTP	8.4 months
DOR	6.5 months

PN of all grades → 39%; 8.6% of grade 3

- 28% received single-agent bortezomib
- 72% received bortezomib + Dex

DOR, duration of response; PN, peripheral neuropathy

Petrucci MT, et al. *Br J Haematol.* 2013;160(5): 649-659.

Phase II RETRIEVE Study: Results

Results to retreatment (n = 124) by patient subgroup: ORR (≥PR)	
Bortezomib treatment	
• Single agent (28%)	32%
• Bortezomib-Dex (72%)	42%
Bortezomib dose	
• ≤1mg/m^2	35%
• 1.3mg/m^2	41%
Number of prior lines	
• 1	67%
• 2	39%
• 3 or 4	25%
Response to any prior bortezomib treatment	
• CR (n = 32)	60%
• PR (n = 94)	52%

Most patients respond rapidly, however, prolonged treatment results in improved response rate

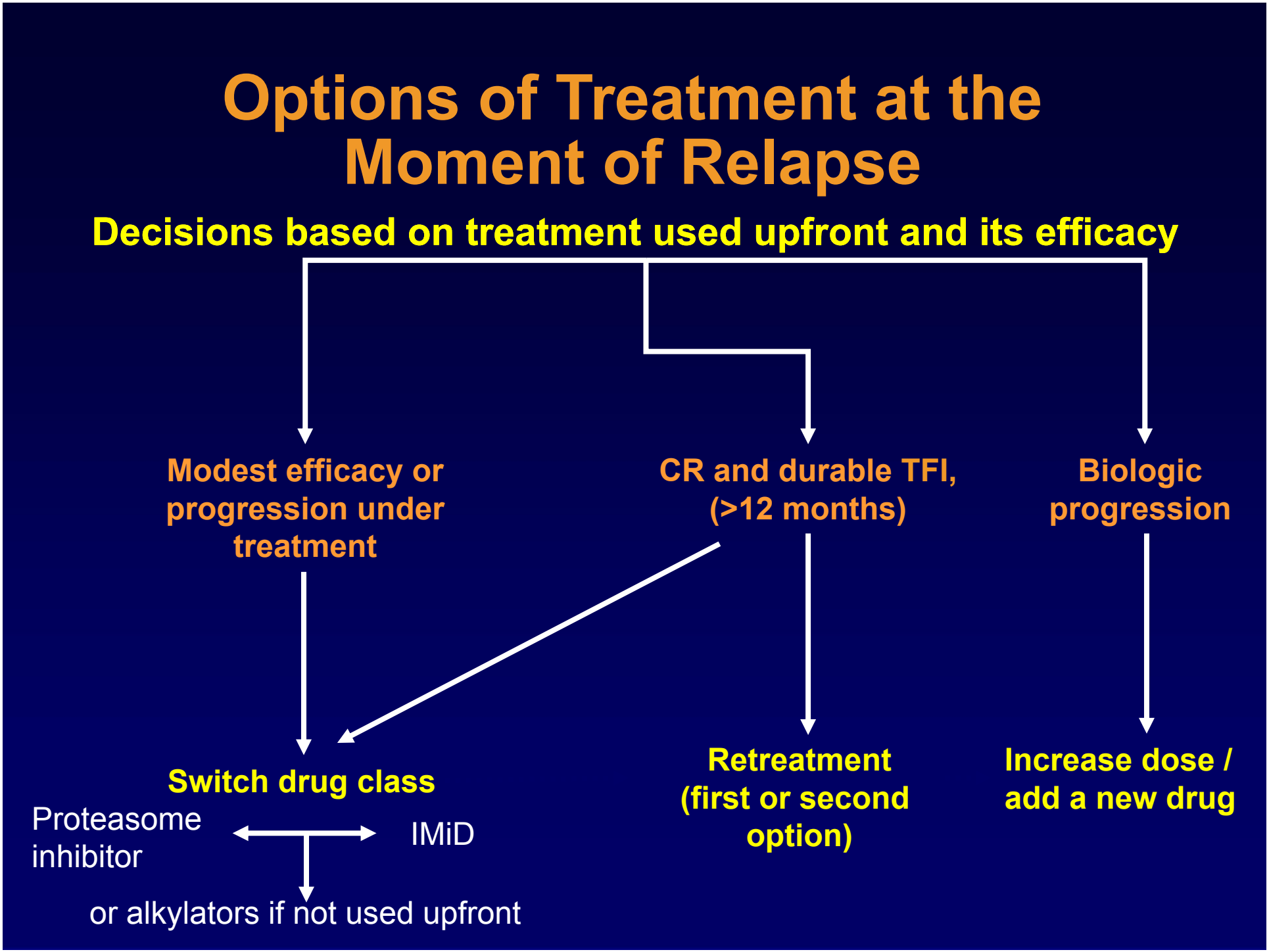
Petrucci MT, et al. *Br J Haematol.* 2013;160(5):649-659.

Phase II RETRIEVE Study: Conclusions

- Retreatment with bortezomib is feasible
- The most benefit of retreatment is observed in:
  - Patients who achieved CR/PR to prior bortezomib therapy
  - Patients who received full dose
  - Patients who received retreatment as first or second rescue treatment

Retreatment with bortezomib would be more attractive after the introduction of agents with different mode of action (MoA), such as histone deacetylase inhibitors monoclonal antibodies

Options of Treatment at the Moment of Relapse



Main Randomized Trials of Treatment for Relapsed/Refractory Myeloma

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Lenalidomide/Dex vs Dex[3]	61 vs 19.9	14.1 vs 0.6	11.1 vs 4.7	29.6 vs 20.2 months
Lenalidomide/Dex vs Dex[4]	60.2 vs 24	15.9 vs 3.4	11.3 vs 4.7	Not reached vs 20.6 months

- Lenalidomide is not used in first line in Europe now but...
- It will be used much more in the future and...

1. Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498. 2. Orlowski RZ, et al. *J Clin Oncol.* 2007;25(25):3892-3901. 3. Weber DM, et al. *N Engl J Med.* 2007;357(21):2133-2142. 4. Dimopoulos M, et al. *N Engl J Med.* 2007;357(21):2123-2132.

...But Thalidomide and Mainly Bortezomib Are Used in First-Line Therapy

- What are the implications for treatment at relapse?
  - How can relapse during treatment, such as maintenance treatment, be managed?
  - Is retreatment feasible?

Retreatment With IMiDs

Retrospective study

- Median of 2 treatments prior to IMiD-based salvage therapy
- Median time from diagnosis to repeat exposure to IMiD: 28 months

N = 140	Lenalidomide → lenalidomide N = 48	Lenalidomid → thalidomide N = 11	Thalidomide → lenalidomid N = 58	Thalidomide → thalidomide N = 23
ORR (≥PR) to repeat IMiD therapy	54%	20%	48%	30%
Median TTP from start of repeat IMiD therapy	16 months	3 months	9 months	6 months

- Repeat therapy with IMiDs is feasible
- Response rates with lenalidomide retreatment is higher than with repeat thalidomide administration

Madan S, et al. *Blood.* 2011;118(7):1763-1765.

Triple and Quadruple Lenalidomide and Bortezomib-Based Combinations in Relapsed/Refractory MM

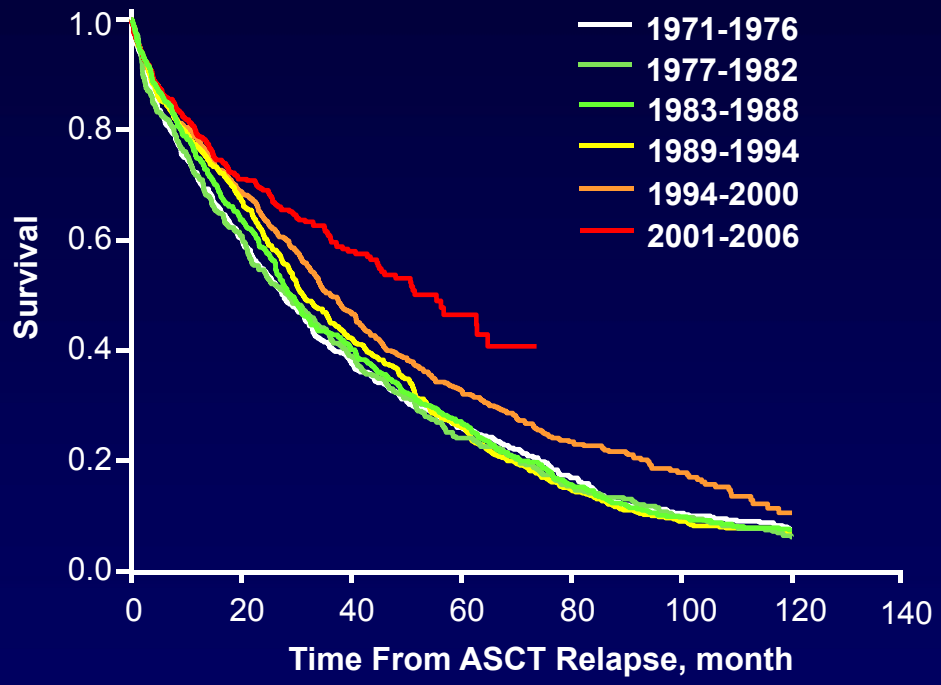
Regimen	N (evaluable)	Responses	Toxicities
VMPT[1]	30	23% PR 43% CR/VGPR	PN
VMDT[2]	62	66% ≥PR 40% CR/VGPR	Grade 3/4 myelosuppression, infections, PN
VCD[3]	50	82% ≥PR	Grade 3/4 myelosuppression, infections, PN
VMD[4]	53	23% CR/nCR 34% CR/nCR	Grade 3/4 thrombocytopenia, infections, neutropenia, PN
RVD[5]	62	64% ≥PR 25% nCR/CR	Grade 3/4 myelosuppression; DVT 2 patients Grade 3 PN 2 patients
RCD[6]	21	14% VGPR 5% CR	Neutropenia, DVT 3 patients
PAD[7]	64	25% VGPR 67% ≥PR	Grade 3/4 myelosuppression, infections, GI disturbances, PN

DVT, deep vein thrombosis; GI, gastrointestinal; nCR, near CR

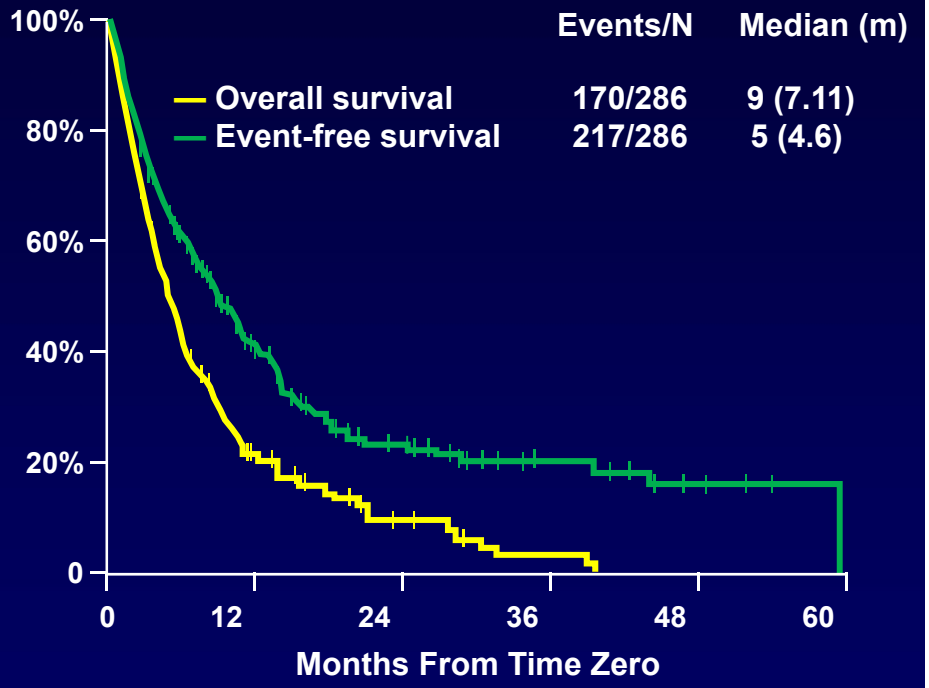
1. Palumbo A, et al. *Blood.* 2007;109(7):2767-2772. 2. Terpos E, et al. *Leukemia.* 2008;22(12):2247-2256. 3. Kropff M, et al. *Br J Haematol.* 2007;138(3):330-337. 4. Popat R, et al. *Br J Haematol.* 2009;144(6):887-894. 5. Richardson PG, et al. *Haematologica.* 2011;96(suppl 1): Abstract S105. 6. Morgan GJ, et al. *Br J Haematol.* 2007;137(3):268-269. 7. Palumbo A, et al. *Ann Oncol.* 2008;19(6):1160-1165.

Historical Evolution of MM Patients

Evolution of MM OS over the years



Outcome of patients refractory to bortezomib & IMIDs*



* 286 patients refractory to bortezomib and relapsed or refractory or ineligible to receive an IMiD

Novel agents are necessary for these refractory patients

Kumar SK, et al. *Blood.* 2008;111(5):2516-2520. Kumar SK, et al. *Leukemia.* 2012;26(1):149-157.

Bortezomib/Thalidomide-Lenalidomide: Background

- In spite of this significant benefit…
- Resistance to bortezomib-based therapy and lenalidomide can emerge over time
- Some toxicities can limit its use and its potential effectiveness
- We would need novel proteasome inhibitors and novel IMiDs

What Do We Ask of Novel Proteasome Inhibitors?

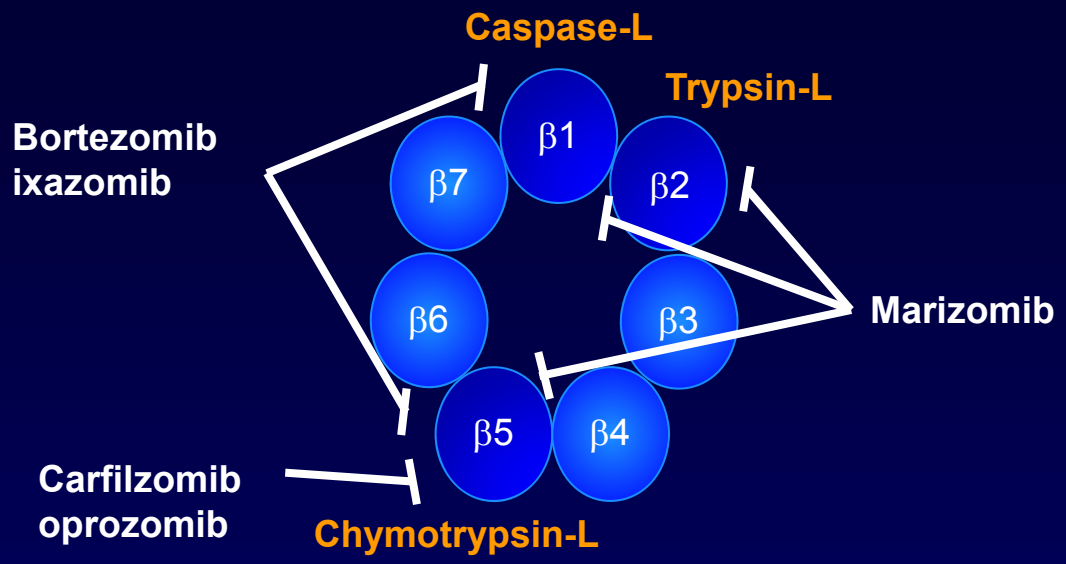
- Maintain or improve efficacy
- Overcome bortezomib resistance
- Improve toxicity profile
  - Peripheral neuropathy
- Convenience of administration
  - Oral / subcutaneous

Proteasome Inhibitors: MoA

β-subunit ring of the proteasome

Catalytic site

Three distinct N-terminal threonine protease active sites



	Type	Reversibility	PO/IV	Dosing	Phase
Bortezomib	Boronic	Reversible	IV	1, 4, 8, 11	Approved
Carfilzomib	Epoxi-ketone	Irreversible	IV	1-2, 8-9, 15-16	III
Ixazomib (MLN-9708)	Boronic	Reversible	PO	1, 4, 8, 11	III
Marizomib (NPI-0052)	Salinospore	Irreversible	IV	1, 4, 8, 11	I
Oprozomib (PR-047)	Epoxi-ketone	Irreversible	PO	BID	I

Carfilzomib and oprozomib no emergent or worsening PN; ixazomib some low grades (grade 1/2)

Carfilzomib Single Agent in Relapsed/Refractory MM: Summary Efficacy Data

PX-171-003 A0/A1[1]: Relapsed after bortezomib and lenalidomide/thalidomide + refractory to last regimen
PX-171-004[2,3]: Relapsed to 1 to 3 previous lines

Population	Study	N	Dose of carfilzomib	ORR (%)
Bortezomib-treated	003A0	46	20 mg/m^2	15.2
	003A1	266	20/27 mg/m^2	22.9
	004	35*	20 mg/m^2	17.1
Bortezomib-naïve	004	59	20 mg/m^2	42.4
	004	70	20/27 mg/m^2	50
Bortezomib-refractory	003A1	194	20/27 mg/m^2	16.5-18.3

*Subgroup of patients included in 004 study and bortezomib-exposed

Bortezomib (APEX) ≥PR 43%

1. Siegel D, et al. *Blood.* 2012;120(14):2817-2825. 2. Vij R, et al. *Blood.* 2012;119(24):5661-5670. 3. Vij R , et al. *Br J Haematol.* 2012;158(6):739-748.

Carfilzomib Single Agent in Relapsed/ Refractory MM: Summary Safety Data

Summary of 526 patients included in PX-171-003, PX-171-004, & PX-171-005

	All grades (>30% of patients)	≥ Grade 3 (>10% of patients)
Hematologic		
Anemia	47%	22%
Neutropenia		10%
Thrombocytopenia	36%	23%
Nonhematologic		
Fatigue	55%	
Nausea	45%	
Diarrhea	33%	
Dyspnea	35%	
Pneumonia		11%

PN: 14% overall (1.3% grade 3)

- Only 5 patients (1%) required dose modification or discontinuation.
- Only 13% of 378 patients that had baseline PN (grade ≤2), reported treatment-emergent symptoms during the study.

Singal S, et al. *Blood.* 2011;118: Abstract 1876.

Carfilzomib: Single Agent in Patients With Relapsed/Refractory MM

Phase III focus trial

Study population (n = 84)
- Measurable disease
- ≥3 previous lines of therapy
- Refractory to the last line
- Previous treatment with bortezomib and IMiDs drugs

1:1

Cycles 1-9 of 28 days
Carfilzomib 27 mg/m^2 IV
Days 1, 2, 8, 9, 15, 16
(20 mg/m^2 IV on days 1, 2 of cycle 1)

After cycle 10, carfilzomib given on days 1, 2, 15, 16

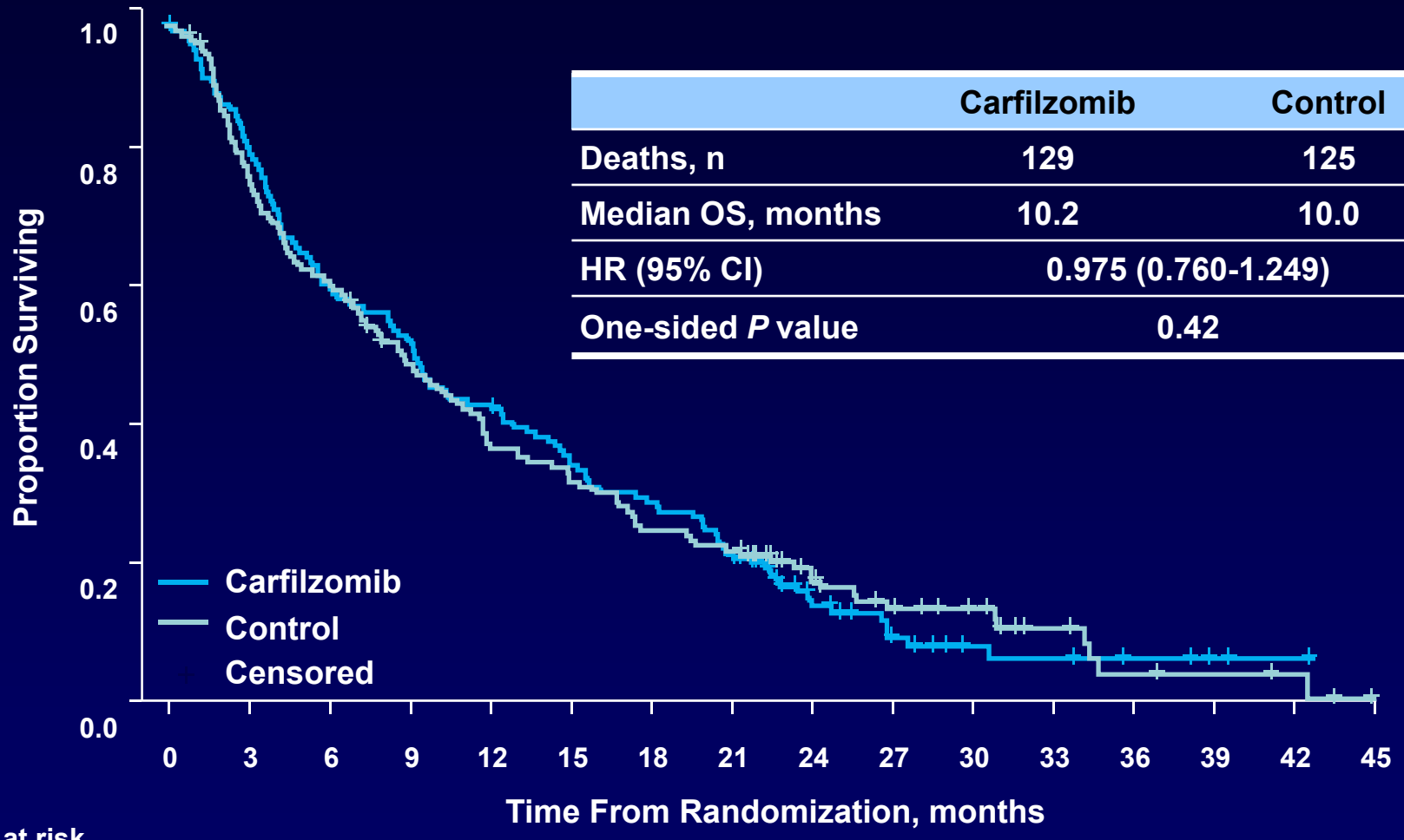
- Corticosteroid
- Optional cyclophosphamide (50 mg PO every day)

Primary endpoint: Overall survival

95% of patients received cyclophosphamide in the control arm

Ludwig H, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA28.

Primary Endpoint: Overall Survival



	Carfilzomib	Control
Deaths, n	129	125
Median OS, months	10.2	10.0
HR (95% CI)	0.975 (0.760-1.249)	
One-sided *P* value	0.42	

No. at risk																
Carfilzomib	157	129	101	89	75	61	53	42	21	13	8	7	5	3	1	0
Control	158	121	100	79	62	55	45	41	26	19	15	9	5	4	3	0

Ludwig H, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA28.

Combinations of Carfilzomib in Relapsed/Refractory MM

- **Carfilzomib + Len + Dex*** *PX-171-006*

  Phase I[1] 40 R/R patients ……*ORR 62%* *PFS: 10.2 months*

  Phase I/II[2] 84 R/R patients ……*ORR 69%* *PFS: 101.8 months*

- **Carfilzomib + pomalidomide (POM) + Dex[3]**

  72 R/R patients - prior regimens 6 (2-15) ……*ORR 64% (1 CR, 18 VGPR, 24 PR)*

  PFS: 12 months

  OS 16.3 months

  87% prior bortezomib all Len refractory

- **Carfilzomib + filanesib[4]**

  n = 20 patients - median lines 4 (2-10) ……ORR 37% *(1 nCR, 6 uPR/PR, 4 minor response [MR])*

  All previous bortezomib refractory / intolerant

- **Carfilzomib + panobinostat[5]**

  n = 44 - prior therapies 3 (1-6) ……ORR 64% (31% ≥VGPR, 30% PR)

  PFS @ 6 & 12 months: 63% & 41%

  Prior bortezomib in 89% with 36% bortezomib refractory…… ORR 67%

  OS 83% @ 12 months

*Basis for the phase III randomized trial in R/R patients (ASPIRE) Len-Dex +/- carfilzomib[6]

1. Niesvitzky R, et al. *Clin Cancer Res*. 2013;19(8):2248-2256. 2. Wang M, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 8529. 3. Shah JJ, et al. *Blood*. 2013;120: Abstract 690. 4. Shah JJ, et al. *Blood*. 2013;120: Abstract 1982. 5. Berdeja J, et al. *Blood*. 2013;120: Abstract 1937. 6. Moreau P, et al. *J Clin Oncol*. 2011;29(15S): Abstract TPS225.

Carfilzomib-Len-Dex (CRd) in Relapsed MM

Phase III ASPIRE trial

Study population (N = 700)

- Measurable disease
- Relapsed progressive MM after 1-3 prior therapies
- ECOG PS 0-2

Stratification:

- Prior bortezomib
- Prior lenalidomide
- β-microglobulin levels

1:1

CRd

Carfilzomid 27mg/m^2 IV
Day 1, 2, 8, 9, 15, 16 (20 mg/m^2 on days 1 and 2 of cycle only)

Lenalidomide 25 mg
Days 1-21

Dexamethasone 40 mg
Once weekly days 1, 8, 15, and 22

After cycle 12, CFZ given on days 1, 2, 15, 16
After cycle 18, CFZ to be discontinued

Rd

Lenalidomide 25 mg
Days 1-21

Dexamethasone 40 mg
Once weekly days 1, 8, 15, and 22

Primary endpoint: PFS

Both arms to receive 28 day cycles until progression

Preliminary reports from Amgen have revealed that PFS for CRd was 26.3 months, a statistically significant improvement over 17.6 months for Rd. Trend towards improvement in OS

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT01080391. Accessed: October 28, 2014.

Activity of Ixazomib (MLN9708)

- **Relapsed/refractory**
  - **Weekly** (n = 60, 85% received prior bortezomib)… ≥PR: 18%
  - Maximum tolerated dose (MTD) was 2.97 mg/m^2
  - Median number of prior lines: 4
  - Fatigue (37%), thombocytopenia (43%), nausea (38%), diarrhea (38%), rash (18%), PN (20%)

  - **Biweekly** (n = 60, 88% received prior bortezomib) …….≥PR: 15%
  - MTD was 2 mg/m^2
  - Median number of prior lines: 4
  - Fatigue (40%), thombocytopenia (42%), nausea (42%), diarrhea (23%), rash (40%), PN (12%)

Kumar S, et al. *Blood.* 2014; 124(7): 1047-1055. Richardson PG, et al. *Blood.* 2014; 124(7): 1038-1046.

Activity of Ixazomib in Combinations (Ongoing)

- Relapsed/refractory……MLN + Len-Dex
- Not refractory to bortezomib ……..MLN + Dex

- Newly diagnosed…….MLN + MP (bw/w)/ Len+ LoDex +/- MLN9708
- Maintenance……MLN + Len
- Smoldering……...MLN + Dex

MLN, ixazomib; MP, melphalan plus prednisone; LoDex, low-dose Dex

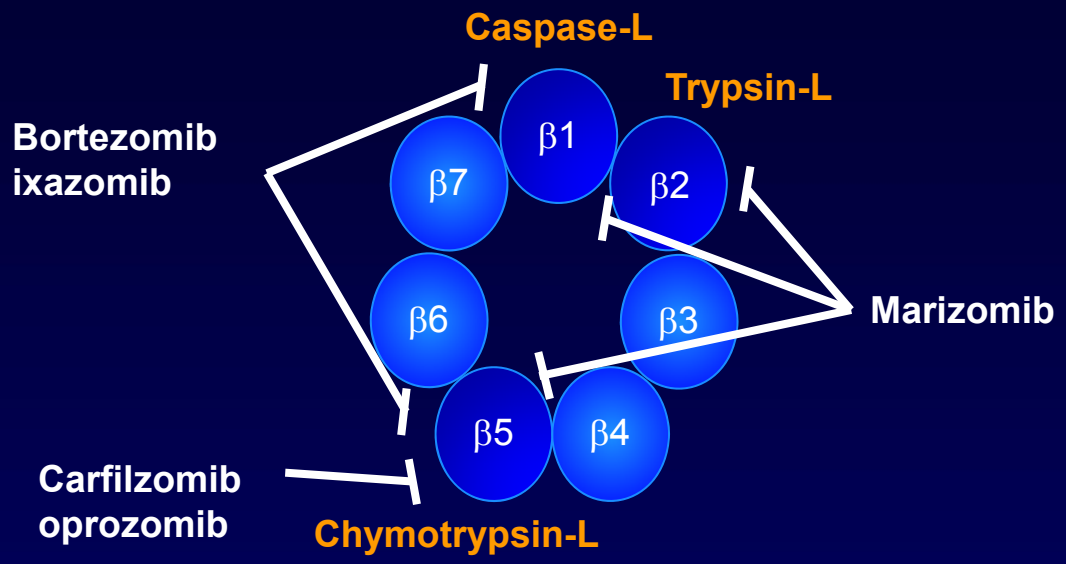
1. Kumar S, et al. *Blood.* 2012;120(21): Abstract 332. 2. Richardson PG, et al. *Haematologica.* 2012;97: Abstract O1144. 3. San Miguel J, et al. *Haematologica.* 2012;97: Abstract P0293.

Proteasome Inhibitors: MoA

β-subunit ring of the proteasome

Catalytic site

Three distinct N-terminal threonine protease active sites



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Carfilzomib and oprozomib no emergent or worsening PN; ixazomib some low grades (grade 1/2)

Second Generation PI for R/R MM Patients

- Maintain or improve efficacy: YES
- Overcome bortezomib resistance: YES
- Improve toxicity profile: YES
  - Peripheral neuropathy
- Convenience of administration: ??
  - Carfilzomib is given on days 1,2-8,9 and 15-16 IV in 10'-30' infusion
  - (Weekly administration is being tried in trials)
  - MLN9708 is oral and weekly
  - Marizomib is of IV administration
  - Oprozomib is of oral administration

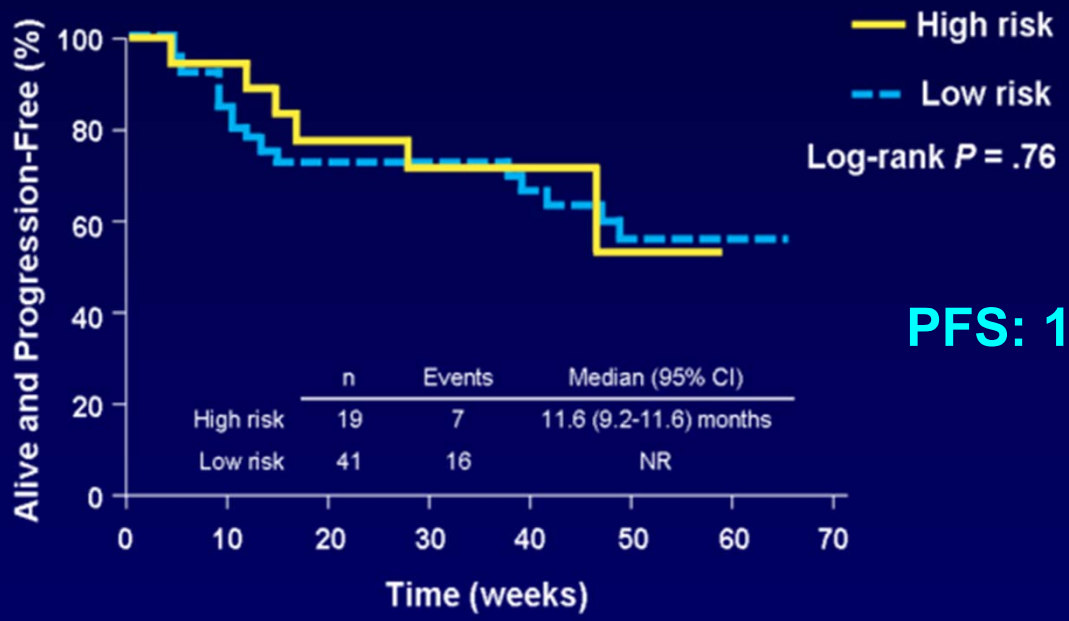
What Do We Ask of Novel IMiDs?

- Maintain or improve efficacy
- Overcome Len resistance
- Improve toxicity profile
- Convenience of administration

Pomalidomide + LoDex in R/R MM Patients With 1-3 Prior Therapies

N = 60 R/R patients **35% previous Len and 47% previous Thal**

ORR 63%: 5% CR + 28% VGPR + 30% PR



PFS: 11.6 months

Updated at ASH 2012: ORR 65%; PFS: 13 months; OS 40 months

POM: 2 mg (1-28)[1] + LoDex: 40 mg (1, 8, 15, 22) **Len + Dex[2,3] ≥PR: 60% (15% CR)** **TTP: 11.2 months**

1. Lacy MQ, et al. *J Clin Oncol.* 2009;27(30):5008-5014. Lacy MQ, et al. *Blood*. 2012;119: Abstract 201. 2. Weber DM, et al. *N Engl J Med*. 2007;357(21): 2133-2142. 3. Dimopoulos M, et al. *N Engl J Med*. 2007;357(21):2123-2132.

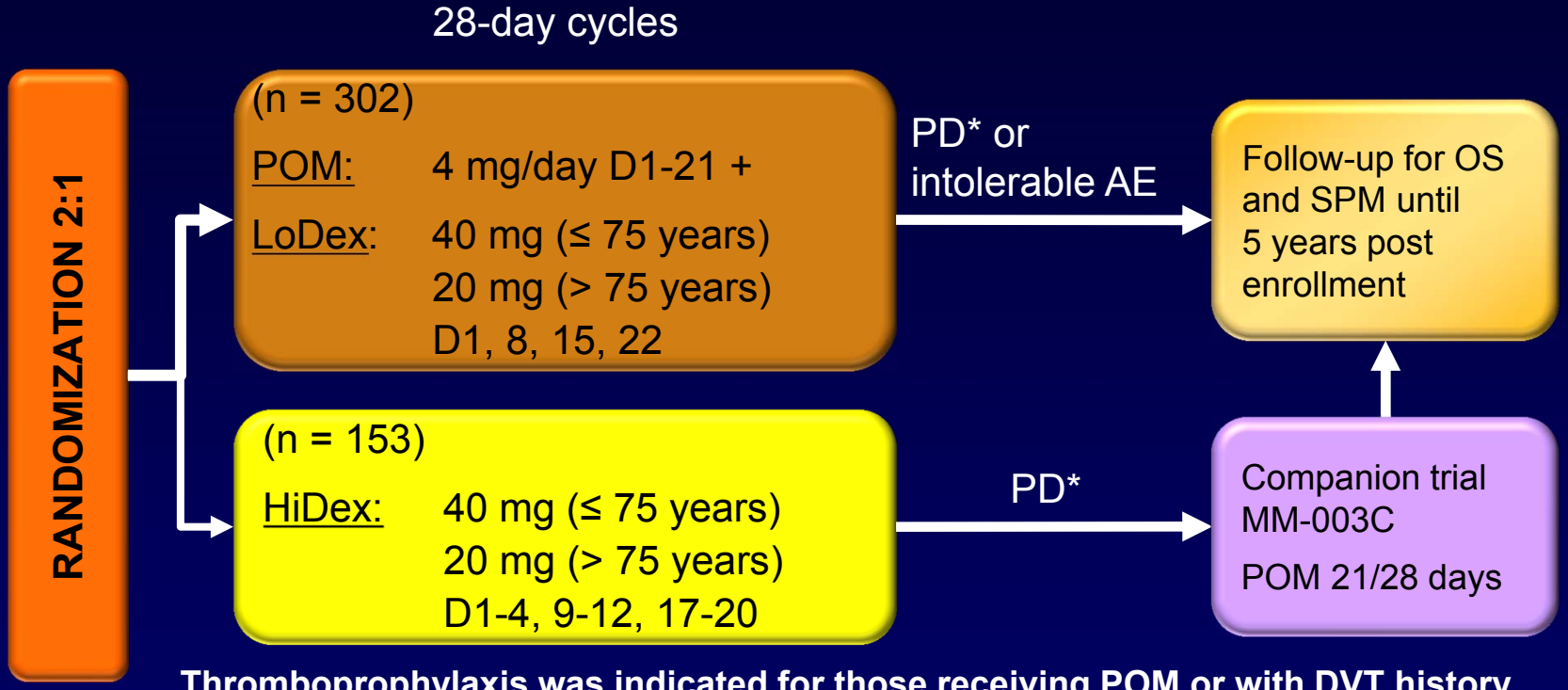
Activity of Pomalidomide + Dex in Lenalidomide Refractory Patients

	n	Population	Dose	≥*PR*	PFS/TTP/DOR
Lacy[1,2]	34	Len refractory	2 mg (1-28)	32 %	PFS 4.7 months
Lacy[2]	60	Len refractory	4 mg (1-28)	38%	PFS 7.9 months
Leleu[3]	84	Len & bortezomib refractory	4 mg (1-21)	35 %	PFS 5.4 months
			4 mg (1-28)	34 %	PFS 3.7 months
Lacy[2,4]	70	Len & bortezomib refractory	2 mg (1-28)	26 %	PFS 6.5 months
			4 mg (1-28)	29 %	PFS 3.3 months

1. Lacy MQ, et al. *Leukemia.* 2010;24(11):1934-1939. 2. Lacy MQ, et al. *Blood.* 2012;119: Abstract 201.
3. Leleu X, et al. *Blood.* 121(11):1968-1975. 4. Lacy MQ, et al. *Blood.* 2011;118(11):2970-2975.

MM-003 Design: POM + LoDex vs HiDex

455 patients refractory MM patients who have failed bortezomib and Len



Thromboprophylaxis was indicated for those receiving POM or with DVT history

Stratification

- **Age (≤75 vs >75 years)**
- **Number of prior treatments (2 vs >2)**
- **Disease population**

- **Len: Prior (100%); refractory (93%)**
- **Bortezomib: Prior (100%); refractory (78%)**

HiDex, high dose Dex; AE, adverse events

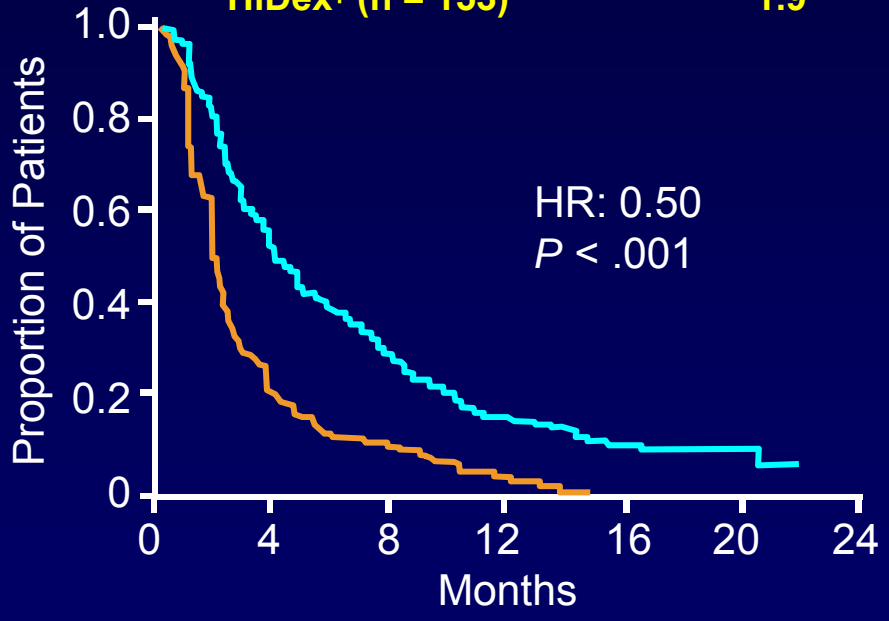
San Miguel et al. *Lancet Oncol.* 2013;14(11):1055-1066.

MM-003 Final Analysis: Pomalidomide/ LoDex vs HiDex: PFS and OS

ORR (≥PR): 31% vs 3%; (≥MR): 39% vs 16%

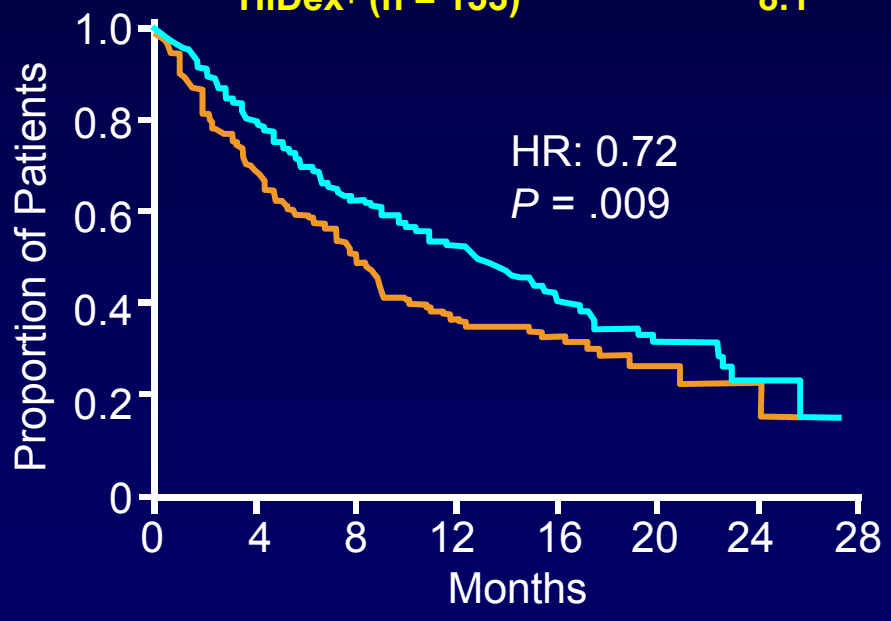
Median PFS*, months

POM + LoDex (n = 302)	4.0
HiDex† (n = 153)	1.9



Median OS, months

POM + LoDex (n = 302)	13.1
HiDex† (n = 153)	8.1

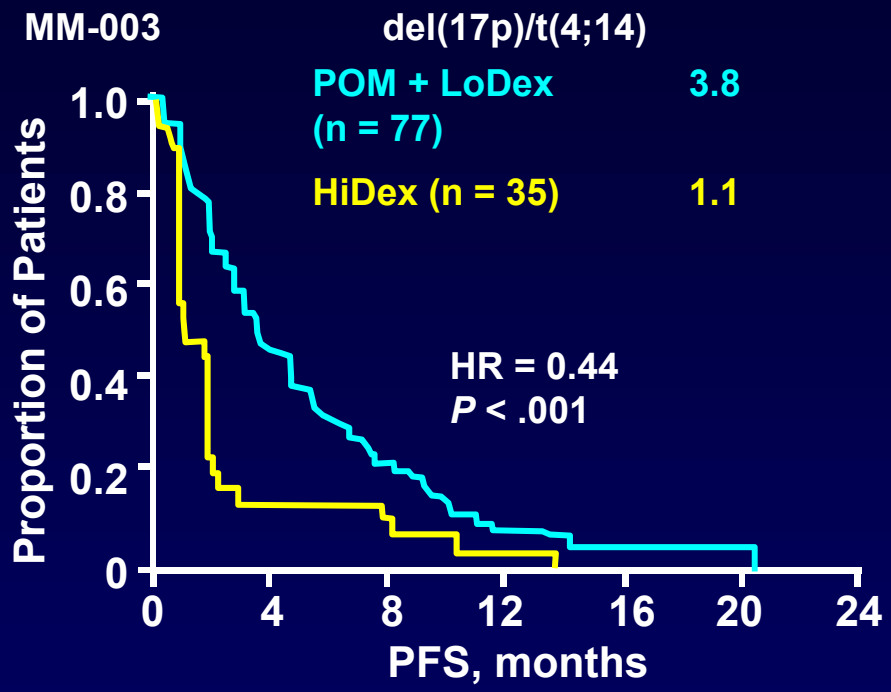


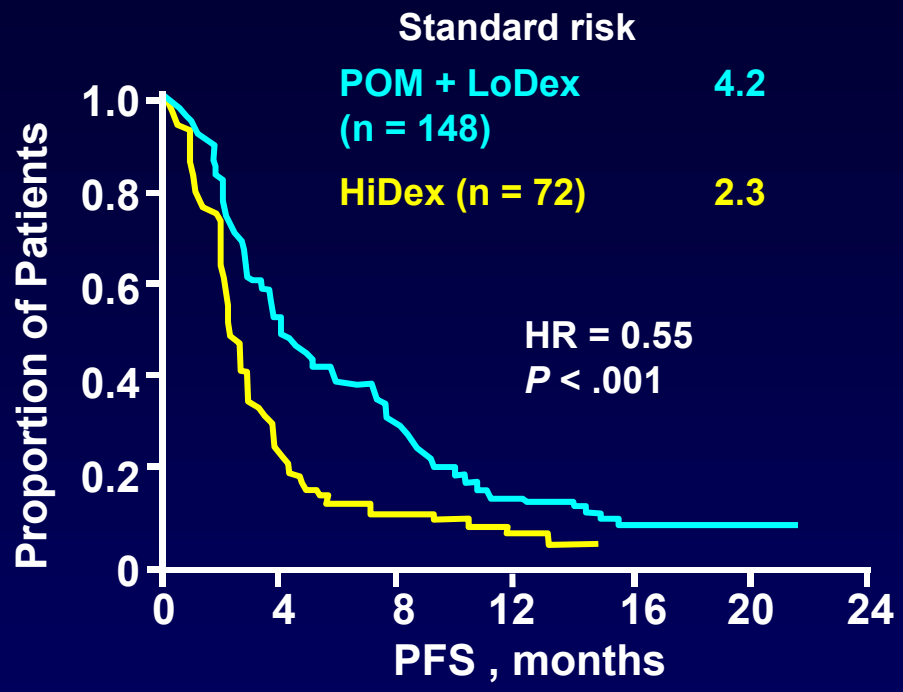
*Primary endpoint

†85 patients (56%) on the HiDex arm received subsequent POM

Dimopoulos MA, et al. *Blood.* 2013;122: Abstract 408.

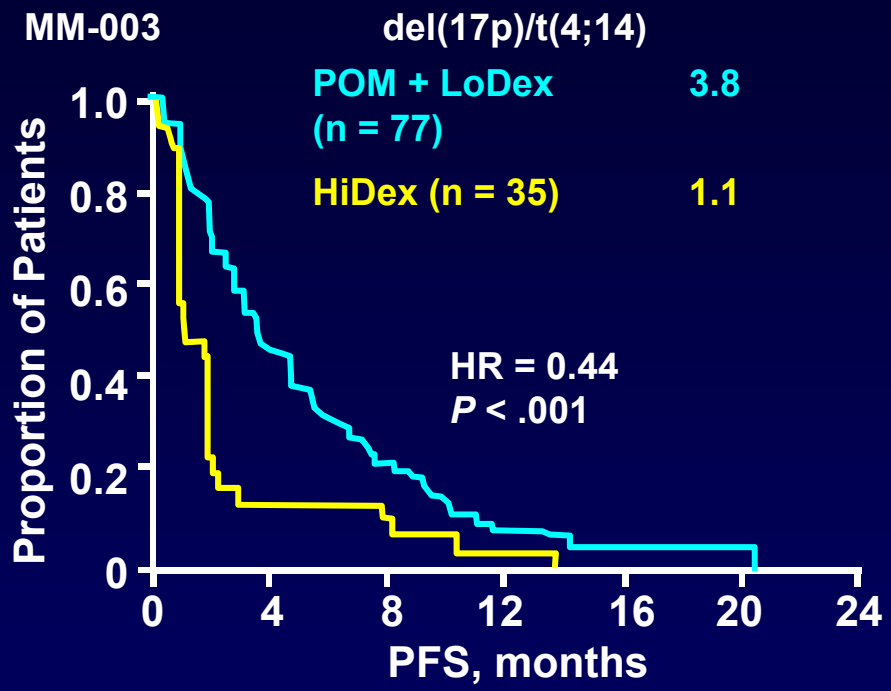
Pomalidomide Overcomes High Risk Cytogenetics

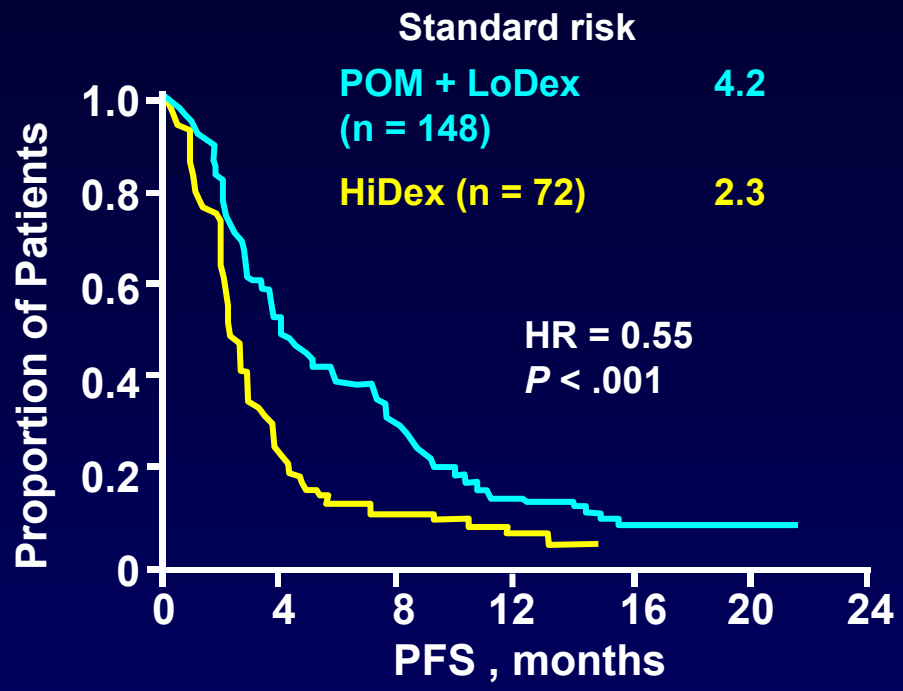




Dimopoulos MA, et al. *Blood.* 2013;122: Abstract 408.

Pomalidomide Overcomes High Risk Cytogenetics





Dimopoulos MA, et al. *Blood.* 2013;122: Abstract 408.

Pomalidomide in patients with relapsed/refractory MM with del(17p) and/or t(4;14)

n = 50
17p (22 patients)
t(4;14) (32 patients)
Median follow-up 8.2 months

	ORR	TTP, months	OS, months
All pts (n = 50)	22%	2.9	12
del(17p) (n = 22)	32%	7.3	12
t(4;14) (n = 32)	16%	2.8	9.2

Leleu X, et al. *Blood.* 2013;121(11):1968-1975.

MM-003: Safety Profile

	POM + LoDex (N = 300)	HiDex[a] (N = 150)
Grade 3/4 hematologic AEs (%)		
Neutropenia	49	17
Febrile neutropenia	9	0
Anemia	33	39
Thrombocytopenia	22	26
Grade 3/4 nonhematologic AEs (%)		
Infections	33	25
Pneumonia	14	8
Bone pain	7	5
Fatigue	5	6
Asthenia	4	7
Glucose intolerance	4	7
Discontinuation due to AEs (%)	9	10

[a]Patients may have received POM + LoDex following crossover

San Miguel JF, et al. *Blood*. 2013;122: Abstract 686.

MM-003: Safety Profile
Additional AEs of Interest

AEs of interest (%)	POM + LoDex (N = 300)		HiDex[a] (N = 150)	
	Any	Grade 3/4	Any	Grade 3/4
Rash	8	1	1	0
DVT / pulmonary embolism	3	1	1	0
Peripheral neuropathy[b]	17	1	12	1

- Approximately 50% of patients with treatment-emergent neuropathy had baseline neuropathy

[a] Patients may have received POM + LoDex following crossover
[b] Peripheral neuropathy includes the preferred terms hyperesthesia, neuropathy peripheral, peripheral sensory neuoropathy, paraesthesia, hypoesthesia, and polyneuropathy

San Miguel JF, et al. *Blood*. 2013;122: Abstract 686.

Combinations of Pomalidomide in R/R MM

- ***POM + Cycl + Pred[1] (n = 55) …….ORR 75% (19% ≥VGPR)***

  x 6 cycles + maintenance POM/Dex ***(47% PR in Len refractory)***

  AE grade 3: 13% neutropenia, 6% rash, 8% infections

- ***POM + Clar + Dex[2] (n = 100) ……ORR 54% (4.1%sCR) PFS: 8.2 months***

  (64% Len & bortezomib refractory)

- ***POM + bortezomib + Dex[3] (n = 22) ……ORR 75% (30% ≥VGPR)***

- ***POM + carfilzomib + Dex[4] (n = 72) …….ORR 64%***

  PFS: 12 months

  OS: 16.3 months

- ***POM + PLD + Dex[5] (n = 27) ……ORR 39%***

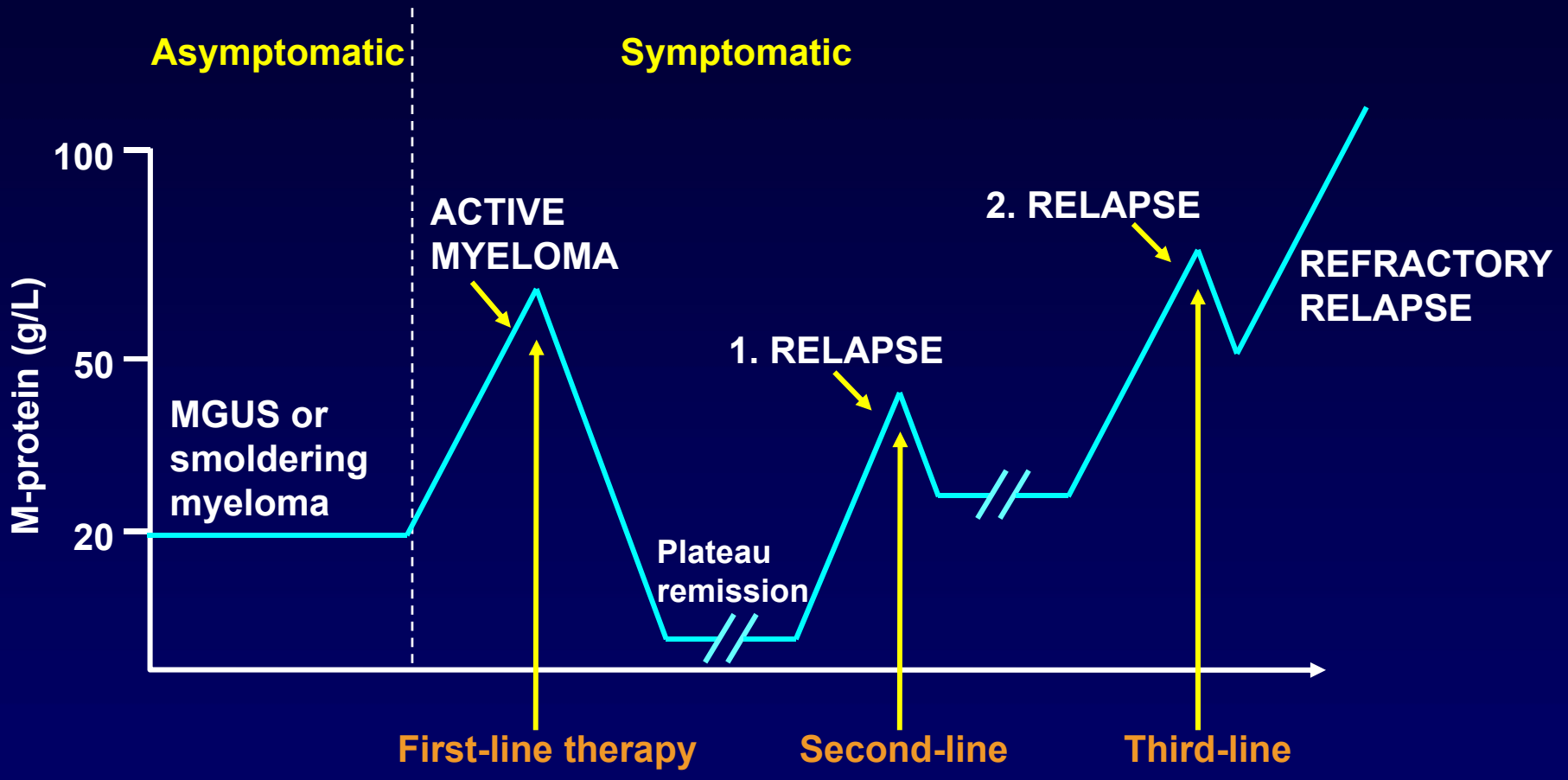
Cycl, cyclophosphamide; Pred, prednisone; Clar, clarithromycin

1. Palumbo A, et al. *Blood.* 2012:119: Abstract 446. 2. Mark TM, et al. *Blood.* 2012;119: Abstract 77. 3. Richardson PG, et al. *Blood.* 2013;122(21): Abstract 1969. 4. Shah JJ, et al. *Blood.* 2013;122(21): Abstract 690. 5. Hilger JD, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8598.

Second Generation IMiDs for R/R MM

- Maintain or improve efficacy: YES
- Overcome Len resistance: YES
- Improve toxicity profile: similar
  - Less myelosuppressive effect than lenalidomide
  - More PN than lenalidomide
- Convenience of administration: Oral

Natural History of MM



……other drugs are still needed for relapsed/refractory patients

MGUS, monoclonal gammopathy of undetermined significance