Multiple Myeloma

7th Annual Living with Myeloma Conference
New Developments in Multiple Myeloma Treatment: A 25-year Review
Scottsdale, AZ
March 23, 2013
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Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Disclosures for Robert A. Kyle

Johnson & Johnson	Disease Monitoring Committee
Celgene	Disease Monitoring Committees
Novartis	Disease Monitoring Boards
Merck	Data Monitoring Committee
Bristol-Myers Squibb	Independent Monitoring Committee
Aeterna Zentaris (Keryx)	Data & Safety Monitoring Board
Onyx	Data Monitoring Committee
Binding Site	Honoraria

Multiple Myeloma
Criteria for Diagnosis

- M-protein in serum and/or urine
- Bone marrow clonal plasma cells or plasmacytoma
- End-organ damage: CRAB (hypercalcemia, renal insufficiency, anemia, bone lesions)

Brit J Haem 121:749, 2003

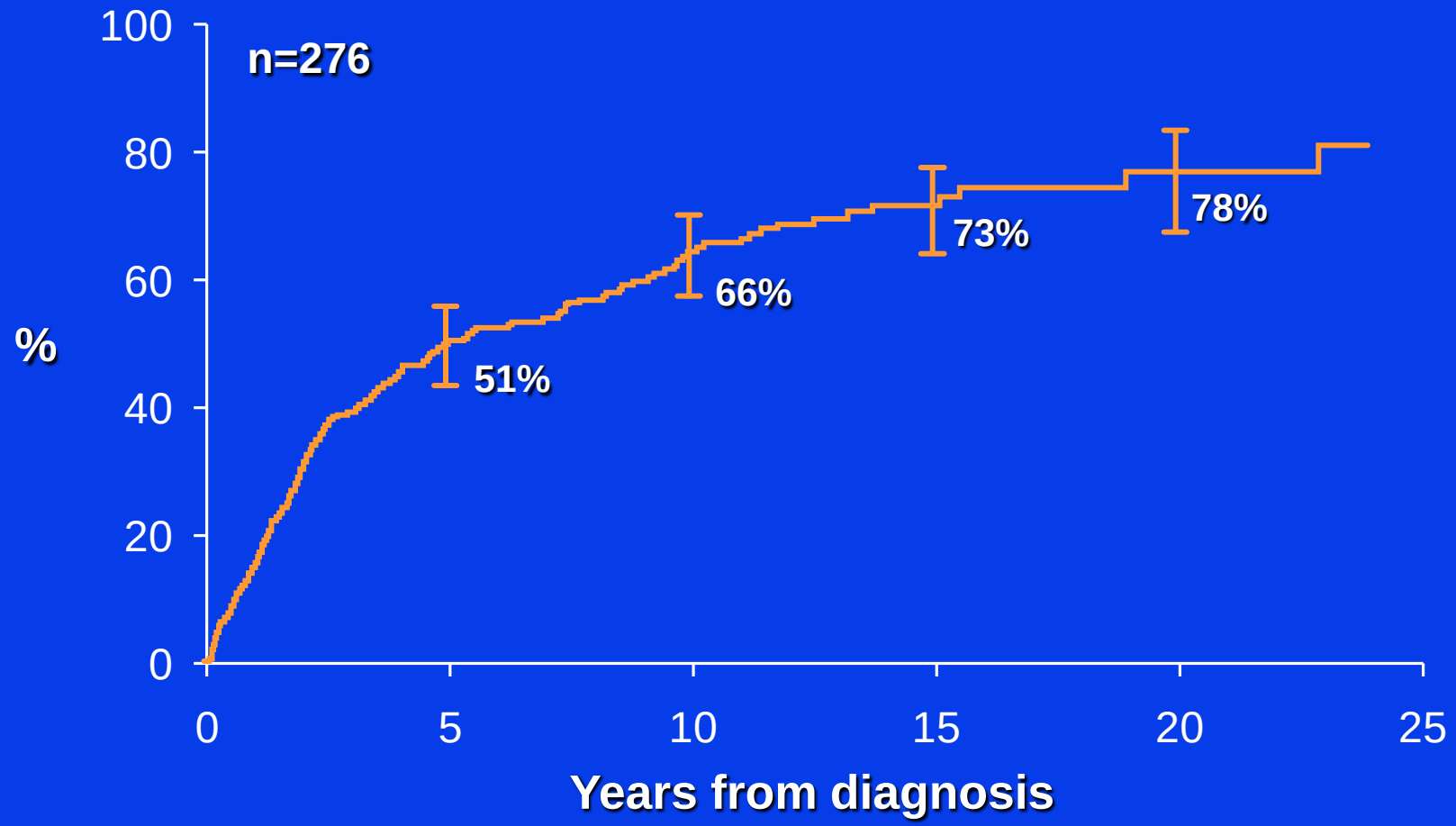
Smoldering Multiple Myeloma (SMM)

M-protein in serum and/or	≥3 g/dL
Plasma cells in marrow	≥10%
Anemia	None
Calcium	Normal
Creatinine	Normal
Lytic lesions	None

No end organ damage (CRAB)

Kyle and Greipp NEJM 302:147, 1980
Kyle et al NEJM 356:2582, 2007

Progression to Multiple Myeloma or Amyloid 1970-1995



Kyle et al: NEJM 356:2582, 2007

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URETHANE AND STILBAMIDINE IN MULTIPLE MYELOMA *

REPORT ON TWO CASES

NILS ALWALL
M.D. Lund
From the Medical Clinic, Lund University, Sweden

Lancet 2:388, 1947


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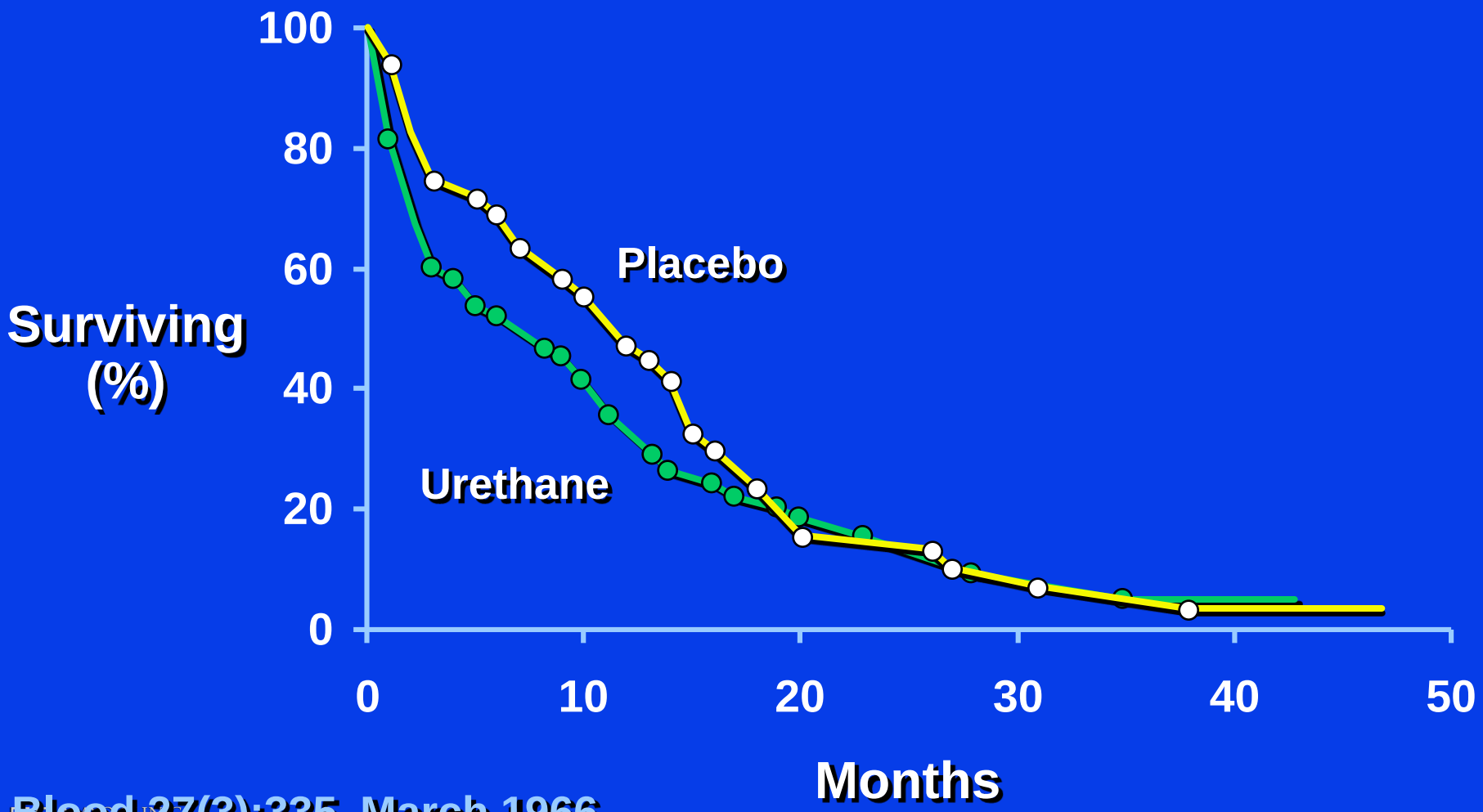
Survival from Onset of Treatment of Multiple Myeloma



Blood 27(3):335, March 1966

Treatment of Multiple Myeloma

L-sarcolysin (L-phenylalanine mustard) (Melphalan) (Alkeran)

Blokhin et al, 1958
Bergsagel et al, 1962

Multiple Myeloma
Single (M/P) vs Combination Chemotherapy (CCT)

n=4,930 (20 trials)

Therapy	Response (%)
M/P	53
CCT	60

P<0.00001

No difference in survival

No subsets with benefit

mSMART 2.0: Classification of Active MM

High-Risk

- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk*

- FISH
  - t(4;14)‡
- Cytogenetic Deletion 13 or hypodiploidy
- PCLI ≥3%

Standard-Risk*†

All others including:

- Hyperdiploid
- t(11;14)**
- t(6;14)

* Note that a subset of patients with these factors will be classified as high-risk by GEP
† LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis
‡ Prognosis is worse when associated with high beta-2 M and anemia
**t(11;14) may be associated with plasma cell leukemia

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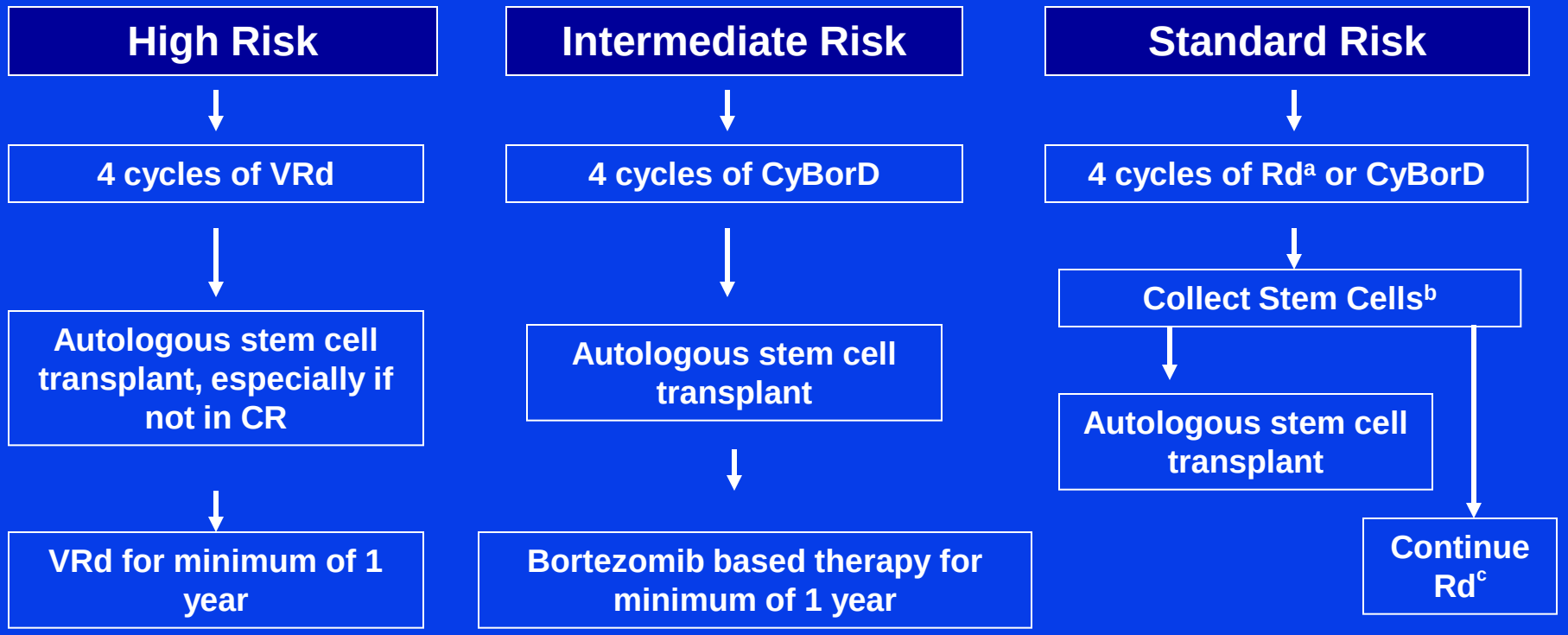
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110
v2 Revised and updated: Jun 2010

Multiple Myeloma
Autologous Transplant Eligibility

- Diagnosis of Multiple Myeloma with CRAB
- Age (physiologic) < 70
- Performance status (0-2)
- Bilirubin ≤ 2.0 mg/dL, creatinine ≤ 2.5 mg/dL & New York Heart Class I or II
- Adequate stem cells
- Concomitant diseases (heart, stroke, etc.)

mSMART – Non-Protocol

Transplant Eligible



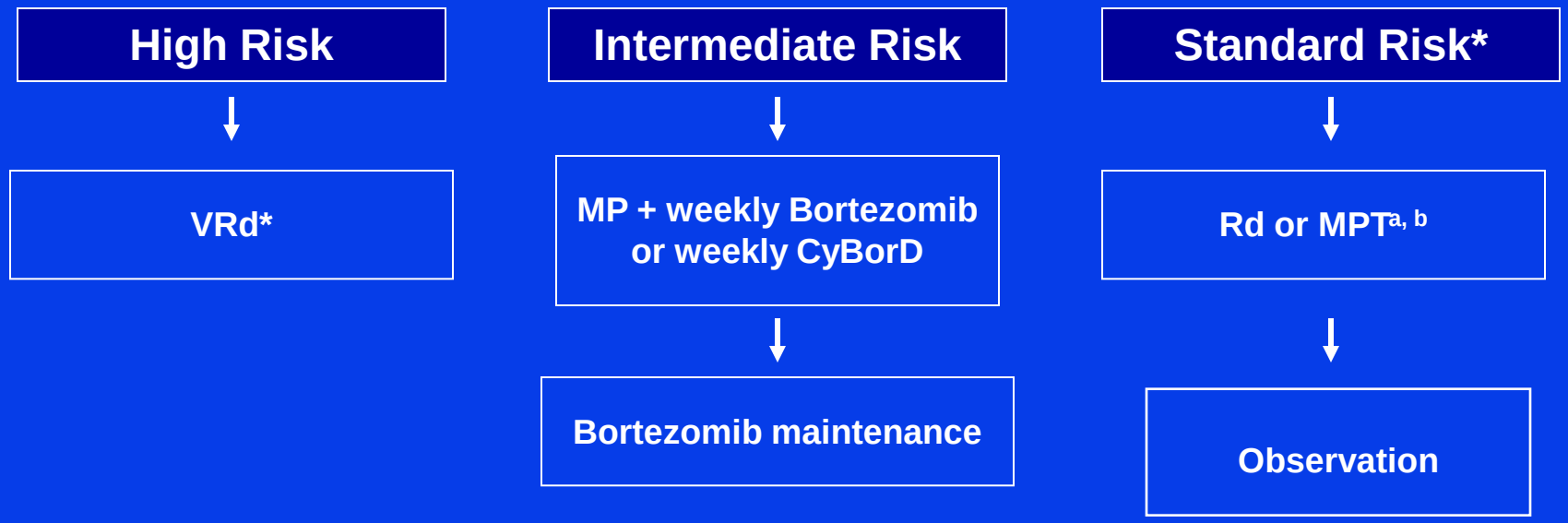
[a] *Bortezomib containing regimens preferred in renal failure or if rapid response needed*
[b] *If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor*
[c] *Continuing Rd is option for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year*

MAYO CLINIC

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110
v8 Revised and updated: Feb 2011

mSMART – Non-Protocol

Transplant Ineligible



[a] In patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; Dex is usually discontinued after first year

[b] Bortezomib containing regimens preferred in renal failure or if rapid response needed

**Clinical trials strongly recommended as the first option*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110

v8 Revised and updated: Feb 2011

Multiple Myeloma Untreated

Initial Therapy

Transplant eligible

Survival Rate

	N	Survival Probability	
		One-Year %	Two-Year %
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	223	87	75
vs.			
Lenalidomide 25 mg d 1-21 + Dexamethasone 40 mg d 1, 8, 15, 22	222	96	87

Rajkumar, et al., Lancet Oncology 11:29, 2010.

Multiple Myeloma

Untreated
N = 48

	Response	
Bortezomib 1.3 mg/M2		**%**
2/wk x 2 q3 wks	**CR/NCR**	**19**
+		
Dexamethasone 40 mg		
Day of and day after Bortezomib	**PR**	**71**
if no response		
	Total	**90**

Overall survival 67% at 4 years

Jagannath et al., Blood 108: 238a, 2006; Jagannath et al., Br. J Haem 146:619, 2009

Multiple Myeloma
Bortezomib Therapy

- Give at weekly intervals (3 of 4)
- May give subcutaneously

Multiple Myeloma Maintenance After Transplant N=614

	PFS MOS (med)	OS 4 yr %	Second Cancer/ 100 patient years
Lenalidomide 10-15 mg daily	41	73	3.1
vs			
Placebo	23	75	1.2

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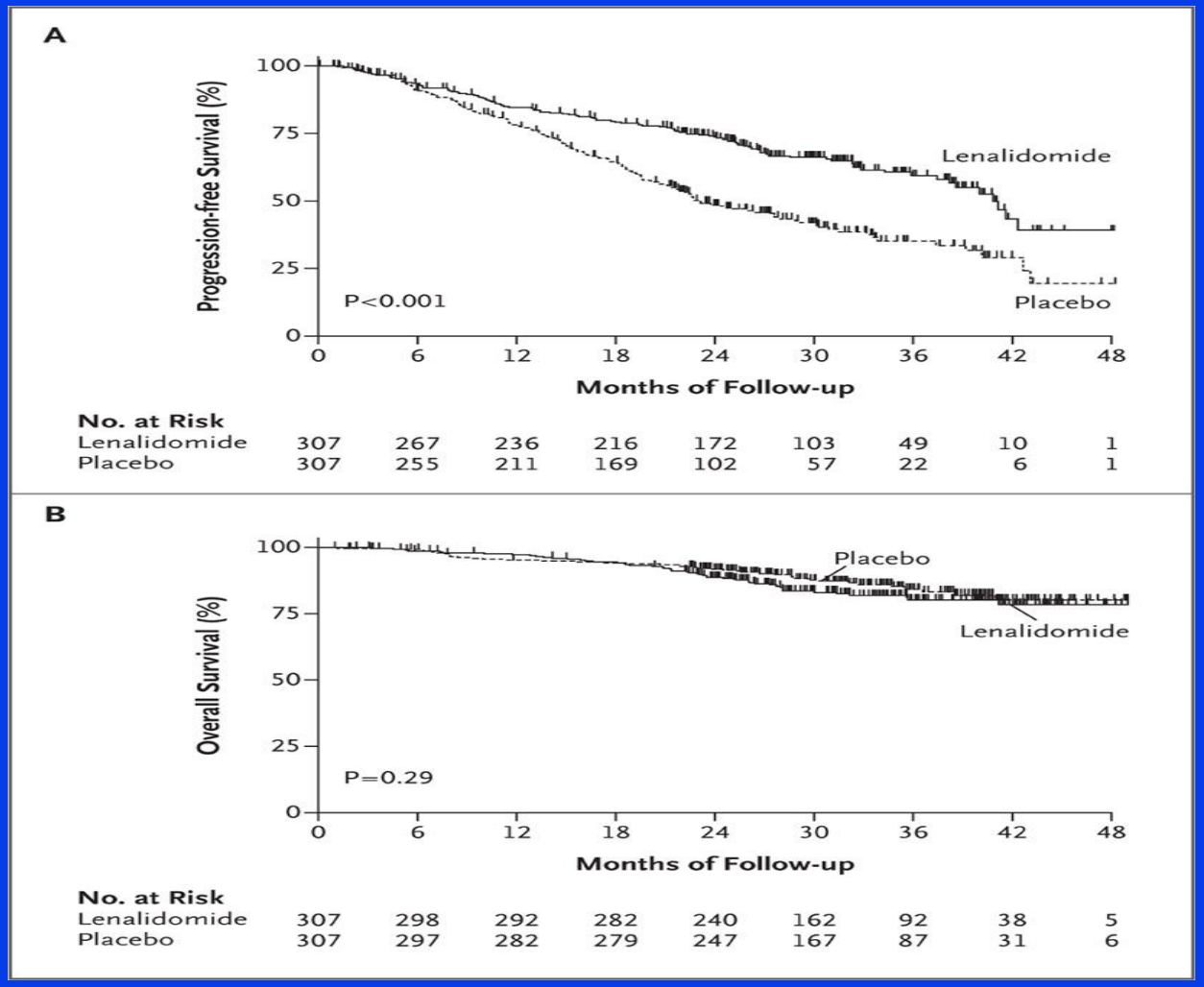
Attal et al., N. Engl. J Med 366:1782, 2012

Multiple Myeloma
Lenalidomide Maintenance after Stem-Cell Transplantation



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Attal M et al. N Engl J Med 2012;366:1782-1791.

Multiple Myeloma Maintenance After Transplant N=460

	PFS MOS (med)	OS 3 yr %	Second Cancers %
Lenalidomide 10-15 mg daily	39	88	7.8
vs			
Placebo	21	80	2.6

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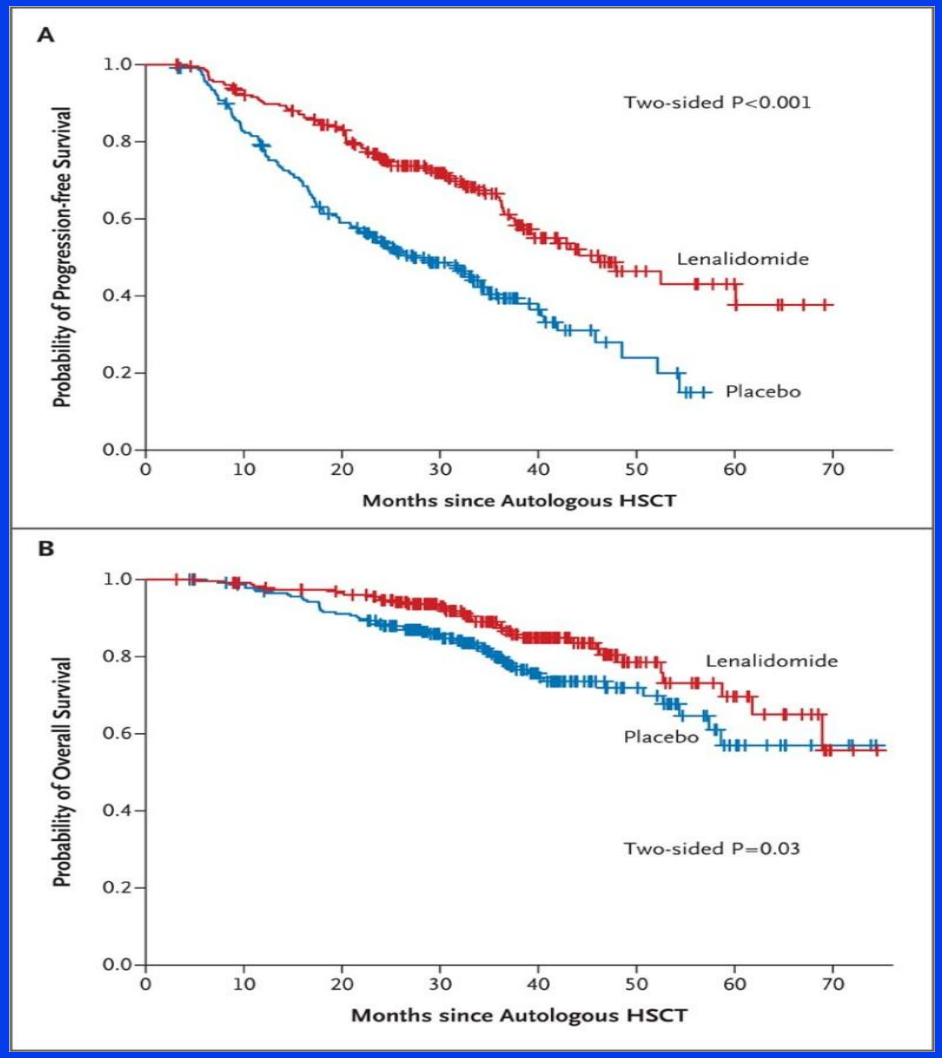
McCarthy et al., N. Engl. J Med 366:1770, 2012

Multiple Myeloma
Lenalidomide Maintenance



McCarthy PL et al. N Engl J Med 2012;366:1770-1781

Multiple Myeloma Transplant Ineligible Maintenance Therapy N=459

	PFS MOS	OS 3 yr %	Second Primary malignancies %
MPR-R	31	70	7
MPR	14	62	7
MP	13	66	3

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Palumbo et al., N. Engl. J Med 366:1759, 2012

Multiple Myeloma Maintenance Considerations

- Meaningful OS
- Risk of second cancers
- Unforeseen adverse effects
- Need for physician visits on maintenance
- Quality of life
- Resistance of residual myeloma?
- Cost ($100,000 per year)

Kyle RA, Mayo Clinic Proceed 86:419, 2011

Multiple Myeloma Untreated

Initial therapy

Transplant ineligible

Multiple Myeloma Relapsed/Refractory

009,010
N = 704

	Response CR/PR %	TTP Mos (Med)
Lenalidomide 25 mg d1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	60.5	11.2
vs.		
Placebo d. 1-21 + Dexamethasone 40 mg d 1-4, 9-12, 17-20	22	4.7

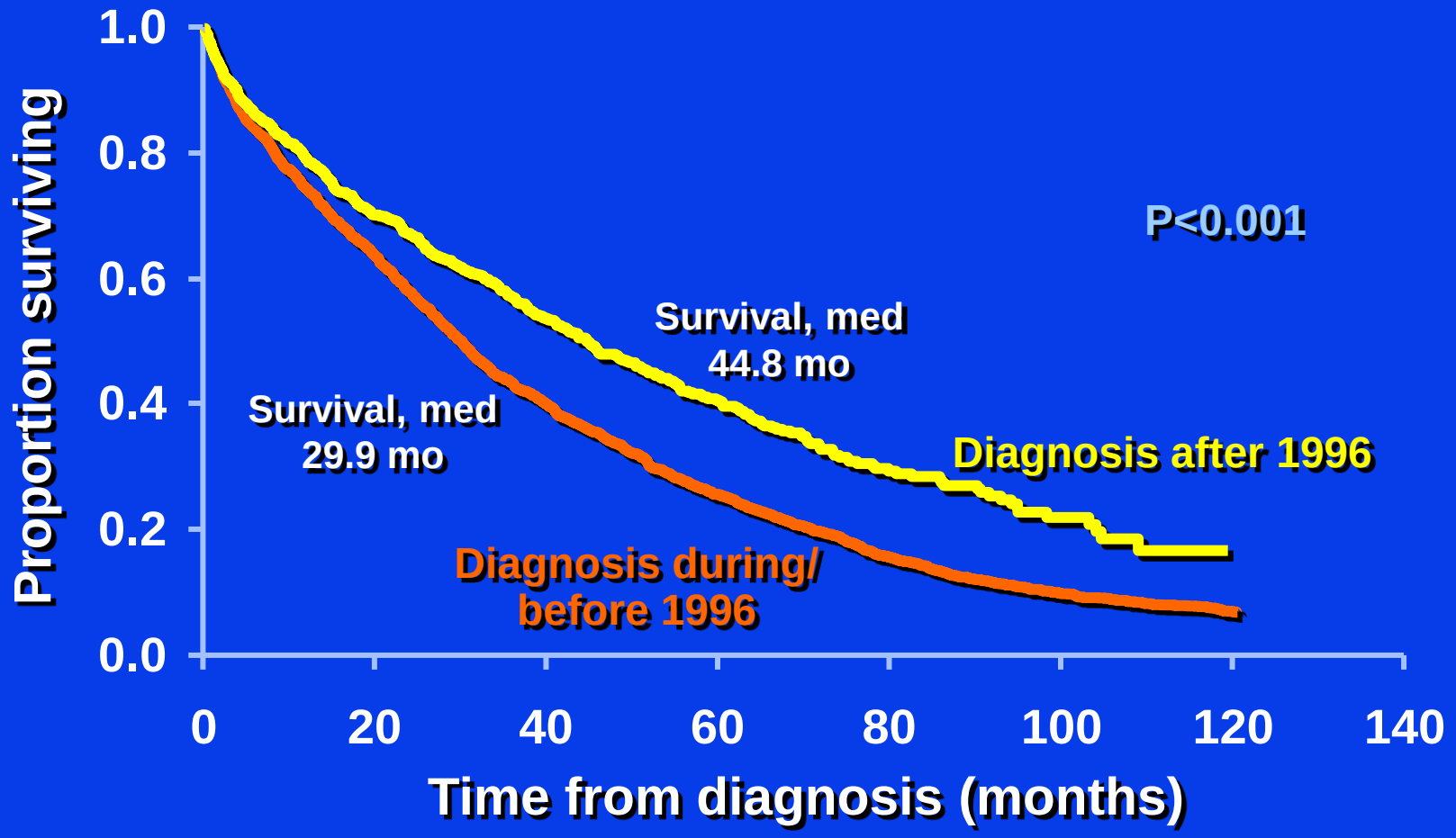
Weber, et al., NEJM, 2007, 357:2133; Dimopoulos, et al., NEJM, 2007, 357:2123

Multiple Myeloma Response to Treatment

	MPV N=337	MP N=331
CR (IF-)	30%	4%
PR ≥	71%	35%
Duration of Response (Med, Mos)	19.9	13.1

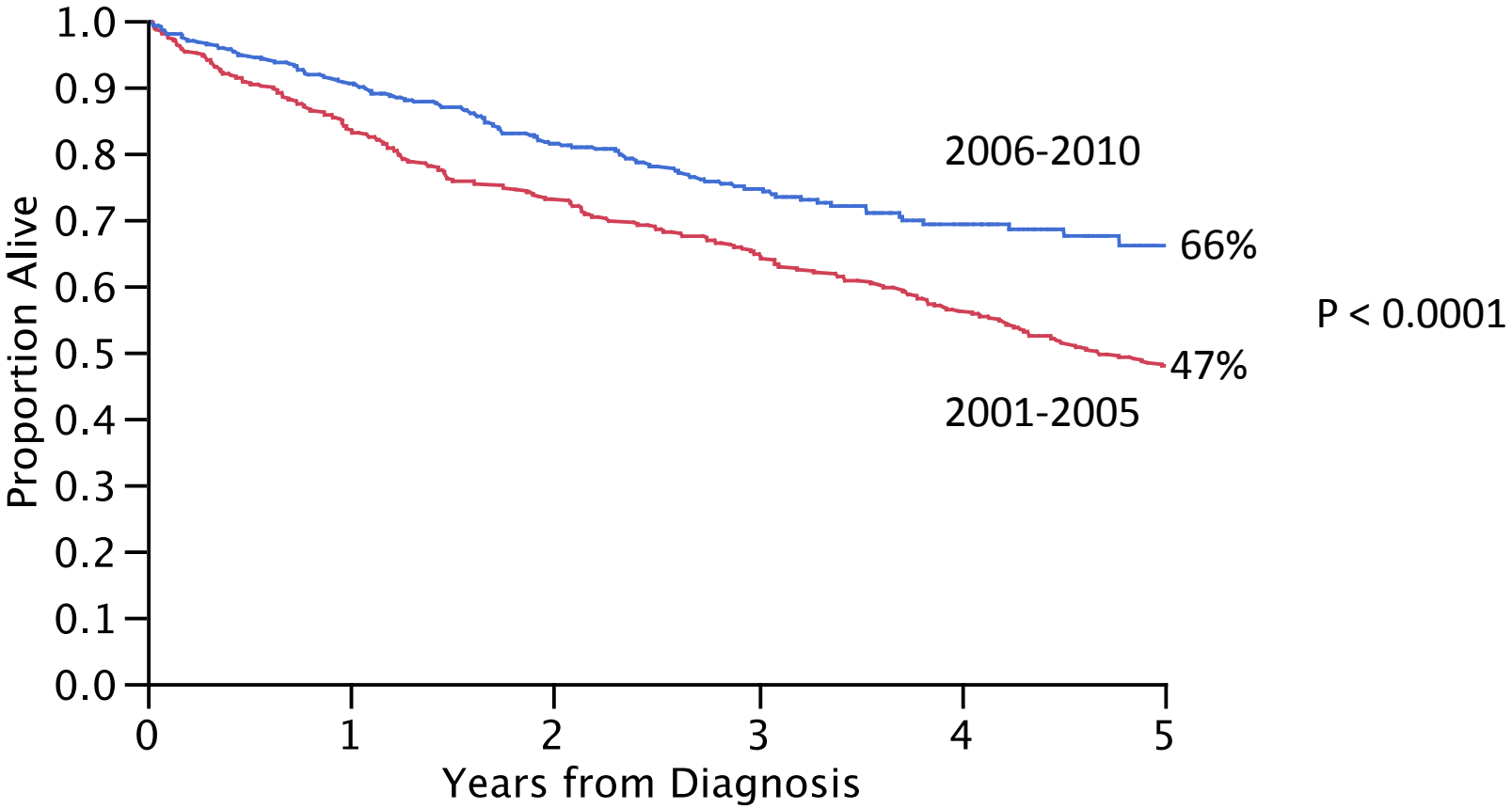
San Miguel, et al., NEJM 2008, 359:906

Multiple Myeloma 1971-2006
n=2,981



Kumar et al: Blood 111:2516, 2008

Multiple Myeloma
Mayo Patients



S. Kumar, 2012

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Multiple Myeloma
Novel Agents

Pomalidomide	CC-4047
Carfilzomib	PR-171
Proteosome inhibitor (oral/IV)	MLN-9708
Proteosome inhibitor (oral)	NPI-0052
Elotuzumab	
Bendamustine	
Histone deacetylase inhibitor	Vorinostat (SAHA)
Histone deacetylase inhibitor	Panobinostat

Patients Refractory to LEN, and LEN + BORT Best Overall Response Pomalidomide

	LEN and BORT refractory*	
	POM (n = 64)	POM + LoDEX (n = 69)
ORR (≥ PR) %	16	30
CR %	2	0
VGPR	2	6
PR %	14	30
Median time to response, months	2.0	1.8
Median duration of response, months	8.3	6.5

*Refractory defined as progression while on the last LEN- or BORT containing regimen, or within 60 days after the last dose of that therapy

Richardson et al., ASH 2011

Multiple Myeloma Relapsed/Refractory to both Lenalidomide and Bortezomib (N=35)

Pomalidomide	VgPR	PR	MR	ORR
2 mg daily				
+	9%	23%	14%	46%
Dexamethasone 40 mg d 1, 8, 15, 22				

Lacy et al JCO 28:573S (8002), 2010

Carfilzomib

- Selective and irreversible proteasome binding
- No neurotoxicity in animals

[1]Demo S et al. *Cancer Res*. 2007;67:6383. [2]Kirk C et al. *Blood*. 2008;112: 2765.

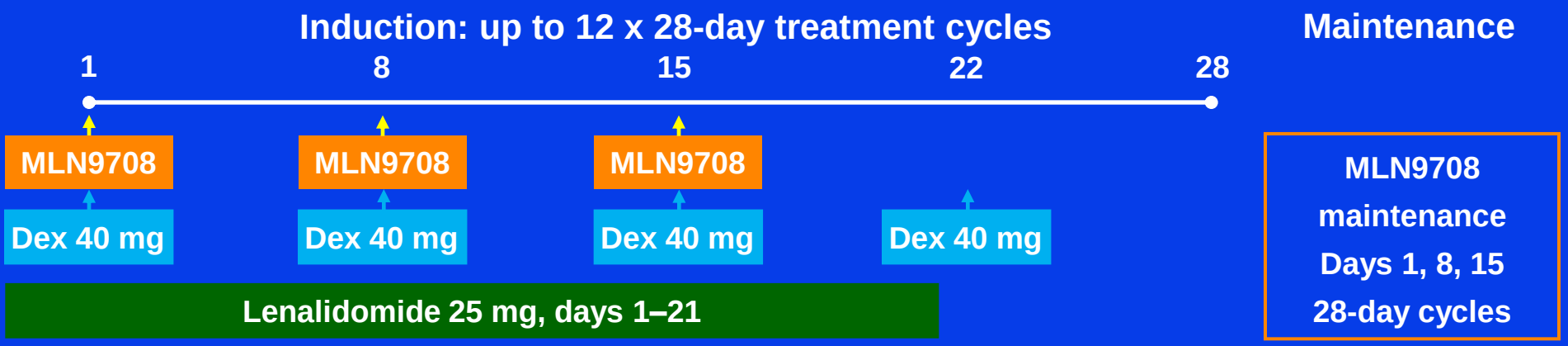
Single-agent Anti-tumor Activity *Bortezomib-naïve*

	Cohort 1 20 mg/m^2 (n=59)	Cohort 2 20/27 mg/m^2 *Bortezomib-naïve* (n=67)*
Best Response	%	%
CR	3	2
VGPR	14	27
PR	25	24
ORR (CR+VGPR+PR)	42	52
PD	12	16

**3 patients were not included as they did not have either baseline or post-baseline assessment.*

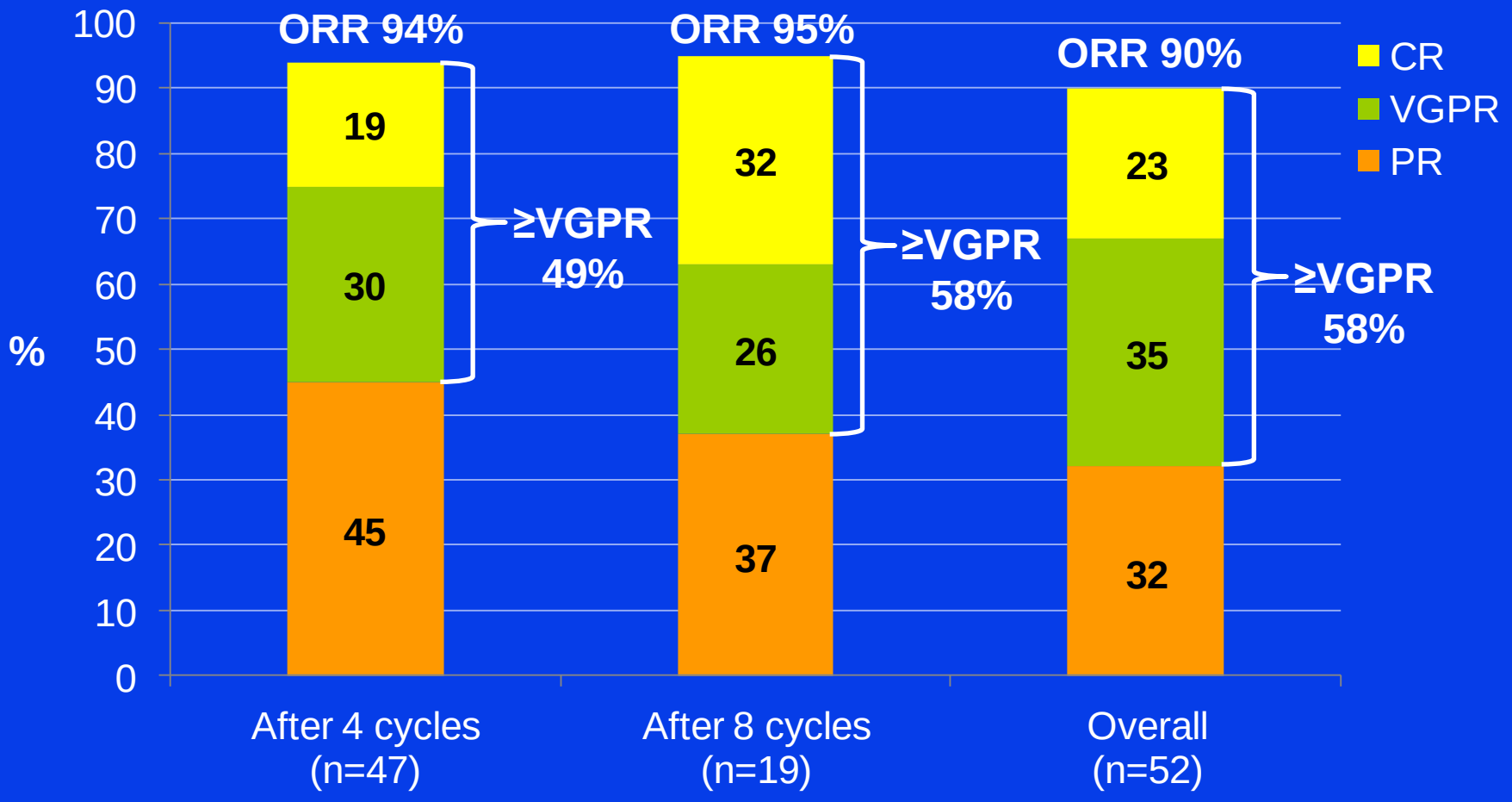
Vij et al., ASH 2011

Study design



- Phase 1: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- Phase 2: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Preliminary response data over course of treatment – patients treated at RP2D (2.23 mg/m^2 / 4.0 mg)



- Of 3 response-evaluable patients who completed 12 cycles, 2 achieved CR and 1 VGPR

Conclusions

- The all-oral combination of weekly MLN9708, lenalidomide, and dexamethasone appears to be generally well tolerated
  - To date, the incidence of PN has been limited with this triplet regimen
- The primary endpoint of the study was met, suggesting antitumor activity at the RP2D
  - At data cut-off, with a median drug exposure of 6 months, 92% of patients overall had achieved PR or better, including a ≥VGPR rate of 55% and a CR rate of 23%
  - Responses increased with number of cycles and deepened over time
  - 88% of patients achieving CR who were evaluable for MRD status were confirmed as MRD-negative
- A phase 3 trial of MLN9708 plus lenalidomide–dexamethasone versus placebo plus lenalidomide–dexamethasone in patients with relapsed and/or refractory MM is currently enrolling (NCT01564537)
  - A phase 3 trial of MLN9708 plus lenalidomide–dexamethasone in previously untreated MM is in the planning stages