THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Evolving Management of Multiple Myeloma: 2015

Todd M. Zimmerman, M.D.

Associate Professor of Medicine

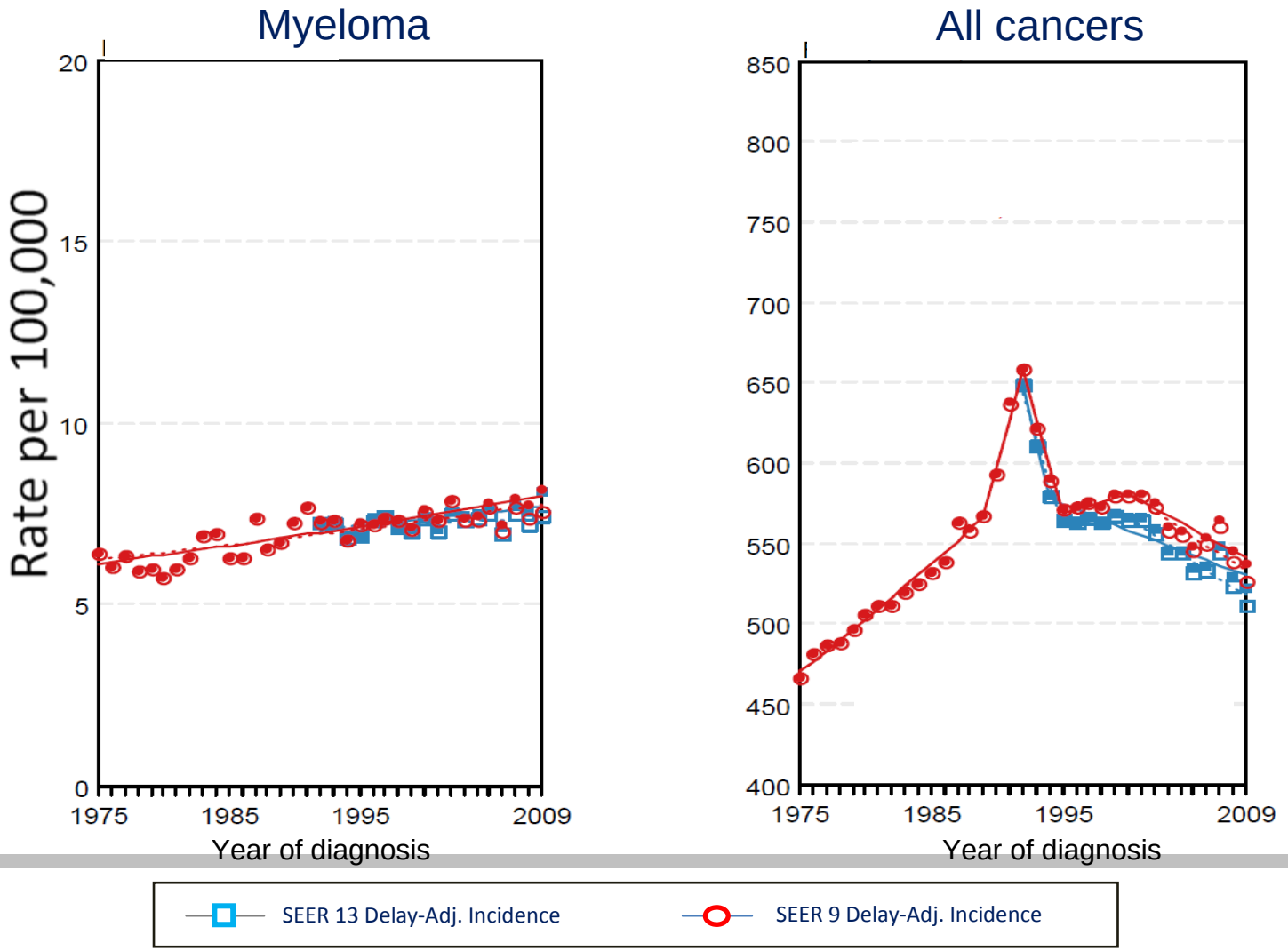
Section of Hematology/Oncology

MULTIPLE MYELOMA

- Estimated 24,050 cases and 11,090 deaths in 2014[1]
- Median age at diagnosis: 69 yrs[2]
- 5-yr survival has improved substantially (45% in 2004-2010 vs 28% in 1987-1989[2]) due to novel agents
- Sensitive to treatment, but not curable

1. American Cancer Society. Cancer facts & figures. 2014. 2. SEER stat fact sheet: myeloma. 2013.`

Incidence over time of multiple myeloma vs overall cancer incidence in the US



National Cancer Institute. Surveillance Epidemiology and End Results. www.seer.cancer.gov. Accessed March 4, 2013.

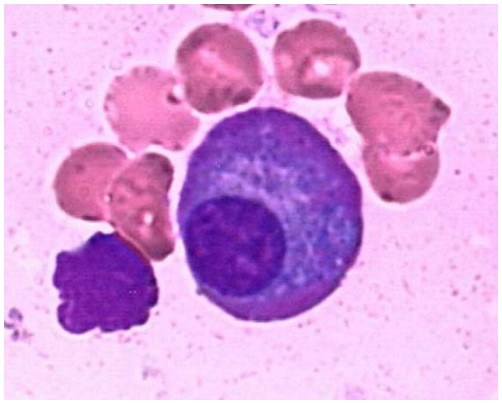
Etiology of multiple myeloma has not been clearly defined

Accepted risk factors	Possible risk factors
Increasing age	Obesity
Male sex	Low fish/green vegetable consumption
African/ African-American race	AIDS
Family history	Herpes zoster/shingles
MGUS	
Inconsistent data on risk	**Do not appear to be risk factors**
Hair dye use	Smoking
Farming occupation	Alcohol
Wood dust exposure	Pesticides
Chronic immune stimulation conditions	Organic solvents
Autoimmune diseases	Radiation
	Asbestos
	Allergic conditions

Alexander DD et al. Int J Cancer. 2007;120(suppl 12):40-61.

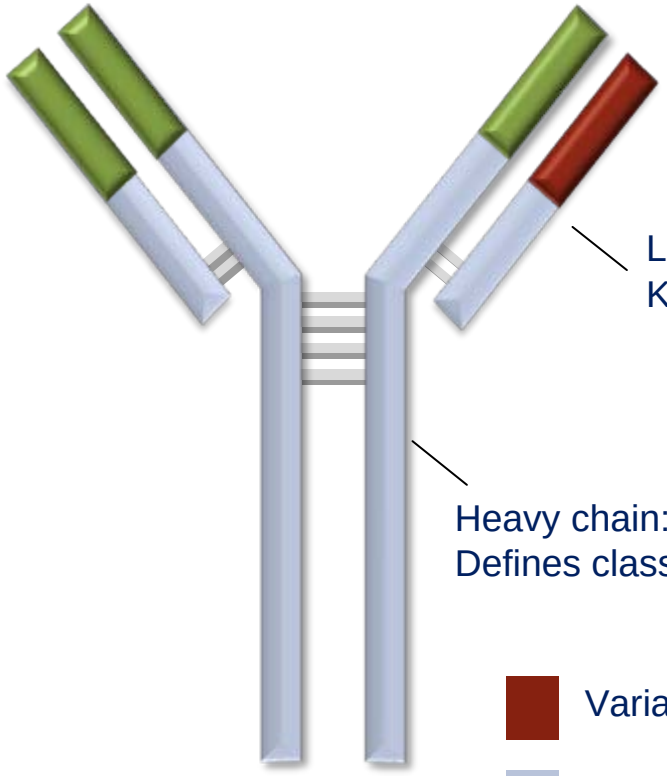
Description of multiple myeloma

- **Multiple myeloma is a B-cell malignancy derived from antibody-producing plasma cells in the bone marrow.**
- **The proliferation of myeloma cells leads to excessive production of a monoclonal antibody (M-protein), as well as adverse events in various organ systems.**



Myeloma plasma cell

Basic antibody structure and components



Light chain:
Kappa (κ) or lambda (λ)

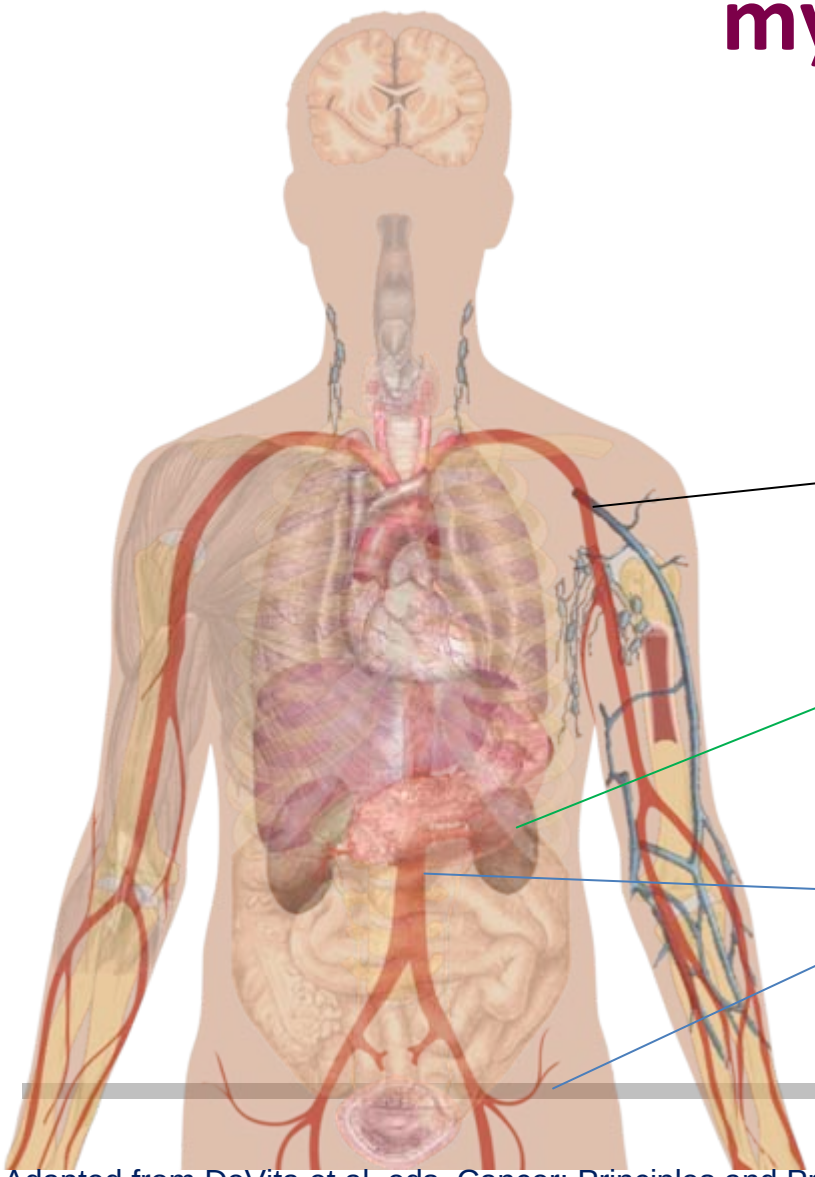
Heavy chain:
Defines class – IgG, IgD, IgA, IgM, or IgE

Variable (antigen-binding) region

Constant region

Plasma cell image was originally published in ASH Image Bank. Peter Maslak. Multiple Myeloma - 6. ASH Image Bank. 2011; 2011-1515. © The American Society of Hematology.

Common symptoms of multiple myeloma



Bone pain is the most common symptom, occurring in approximately 70% of patients2

System affected	Symptoms[1]	Common cause(s)[1]
Blood	Fatigue	• Anemia, therapy
	Recurrent infections	• Low uninvolved Ig, therapy
Kidneys	Nausea and vomiting	• Renal failure, hypercalcemia
	Confusion and CNS symptoms	• Renal failure, hypercalcemia
Bone/ spine	Bone pain	• Pathologic fracture, cord compression
	Peripheral neuropathy	• Nerve compression, amyloidosis, POEMS*, immune-mediated effects, therapy

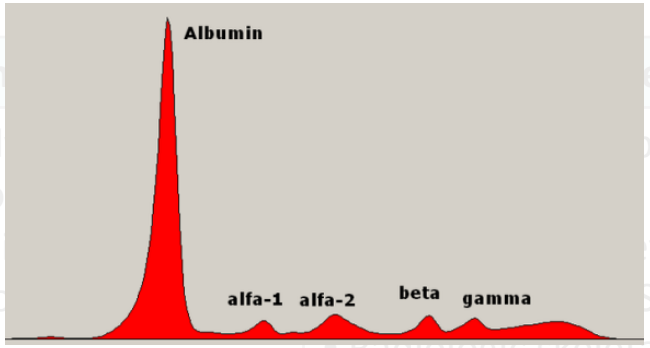
*POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

1. Adapted from DeVita et al, eds. Cancer: Principles and Practice of Oncology, 9th Ed.
2. Durie BGM. *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. International Myeloma Foundation. 2011/2012.

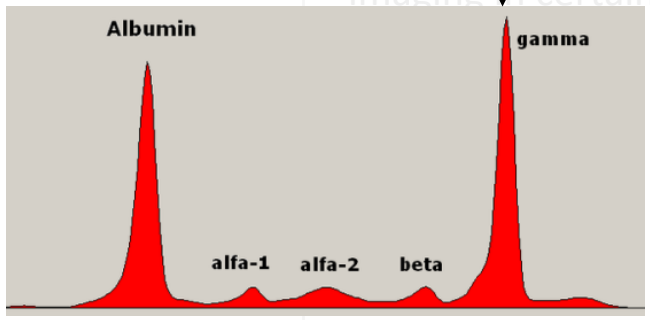
Recommended workup

Blood specimen

- Chemistry screen, including calcium and creatinine
- Serum β_2-microglobulin, albumin, and lactate dehydrogenase
- Serum protein electrophoresis (SPEP), immunofixation
- Measurement of serum-free light chains
- Nephelometric quantification of serum immunoglobulins



Normal SPEP



Abnormal SPEP showing M-spike of myeloma (arrow)

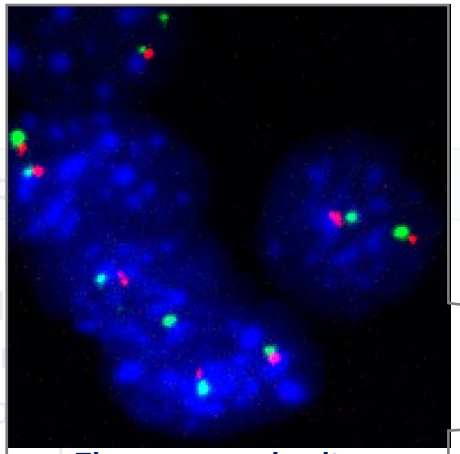
Adapted from Dimopoulos M et al. *Blood*. 2011;117:4701-4705.
Image: Steven Fruitsmaak

Recommended workup (cont'd)

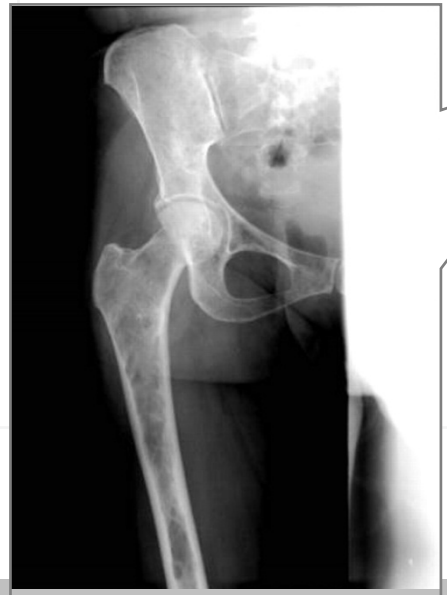
Blood specimen	Urine specimen	Bone (marrow) specimen
• Chemistry screen, including calcium and creatinine • Serum β_2-microglobulin, albumin, and lactate dehydrogenase • Serum protein electrophoresis (SPEP), immunofixation • Measurement of serum-free light chains • Nephelometric quantification of serum immunoglobulins	• Routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation	• Bone marrow aspirate and/or biopsy • Cytogenetics (metaphase karyotype and FISH) • Radiologic skeletal bone survey; magnetic resonance imaging in certain circumstances

Adapted from Dimopoulos M et al. *Blood*. 2011;117:4701-4705.

Recommended workup (cont'd)



Fluorescence in situ hybridization (FISH)



Skeletal survey

Bone (marrow) specimen

- Bone marrow aspirate and/or biopsy
- Cytogenetics (metaphase karyotype and FISH)
- Radiologic skeletal bone survey; magnetic resonance imaging in certain circumstances

Skeletal survey image was originally published in ASH Image Bank. Peter Maslak. Multiple Myeloma - 1. ASH Image Bank. 2011; 2011-1510. © The American Society of Hematology

Adapted from Dimopoulos M et al. *Blood*. 2011;117:4701-4705.

Differential diagnosis

	Monoclonal gammopathy of undetermined significance (MGUS)	Asymptomatic (smoldering) myeloma	Symptomatic myeloma
Serum monoclonal protein	<3 g/dL	≥3 g/dL	Presence of serum and/or urinary monoclonal protein
		And/or	
Clonal BM plasma cells	<10%	≥10%	≥10%
End-organ damage	Absent	Absent	Present; Can be attributed to the underlying plasma cell proliferative disorder (CRAB symptoms)

C: Serum Calcium ≥11.5 mg/dL
R: Renal insufficiency: serum creatinine >2 mg/dL
A: Anemia: Hb <10 g/dL or 2 g/dL below normal
B: Bone lesions: lytic or osteopenic, or pathologic fractures

Adapted from Dimopoulos M et al. *Blood*. 2011;117:4701-4705.

Durie-Salmon Staging System for MM

Stage	Criteria	Myeloma Cell Mass ($x10^{12}$ cells/m^2)
I	All of the following: Hemoglobin >10 g/dL; normal serum calcium or <10.5 mg/dL; normal bone/solitary plasmacytoma; low M protein (lgG <5 g/dL; IGA <3 g/dL; Bence-Jones protein <4 g/24 h)	<0.6 (low)
II	Not fitting stage I or III	0.6-1.2 (intermediate)
III	Any of the following: Hemoglobin <8.5 g/dL; serum calcium >12 mg/dL; multiple lytic bone lesions; high M protein (lgG >7 g/dL; IgA >5 g/dL; Bence-Jones protein >12 g/24 h)	>1.2 (high)
Subclassification Criterion		
A	Normal renal function (serum creatinine level <2.0 mg/dL)	
B	Abnormal renal function (serum creatinine level ≥2.0 mg/dL	

M = monoclonal

New MM Staging

New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β_2-microglobulin ≥5.5 mg/L	29

*There are two categories for stage II: serum β_2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β_2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

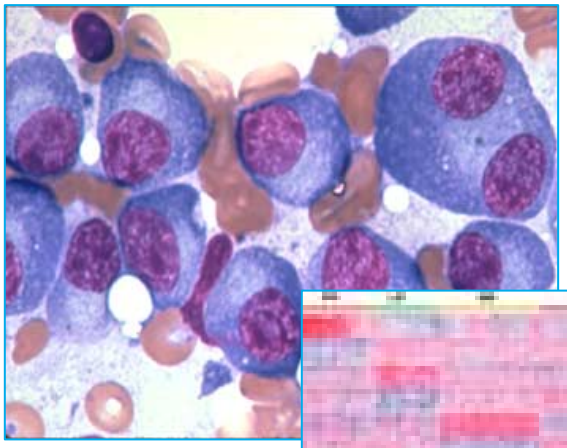
Greipp PR et al. *J Clin Oncol*. 2005;23:3412-3420.

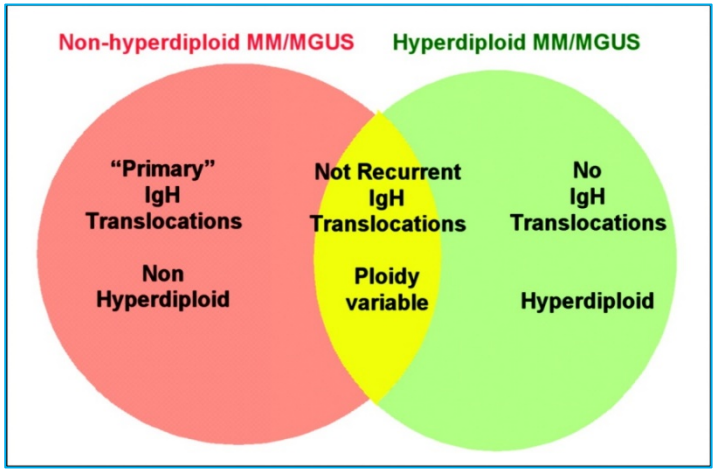
mSMART 2.0: Classification of Active MM

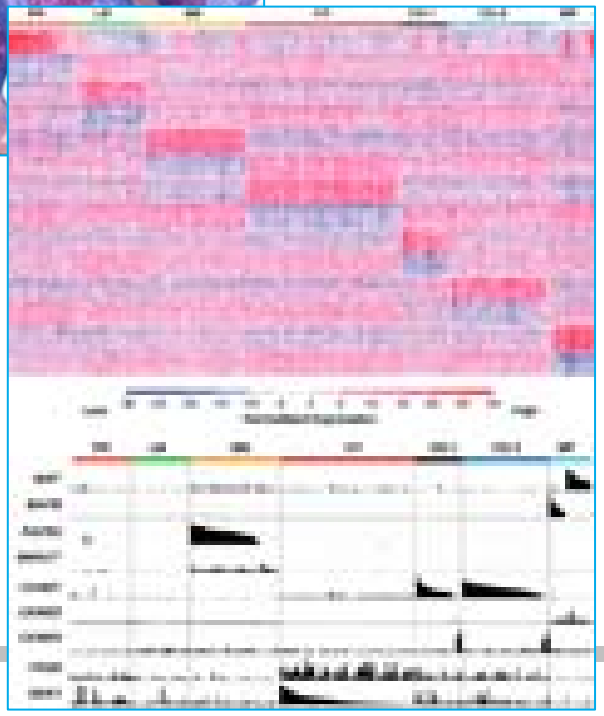
High-risk 20%	Intermediate-risk 20%	Standard-risk 60%
▪ FISH ▪ Del 17p ▪ t(14;16) ▪ t(14;20) ▪ GEP ▪ High-risk signature	▪ **FISH** ▪ **t(4;14)*** ▪ **Cytogenetic deletion 13 or hypodiploidy** ▪ **PCLI ≥3%**	All others including: ▪ Hyperdiploid ▪ t(11;14) ▪ t(6;14)
3 years	4-5 years	8-10 years

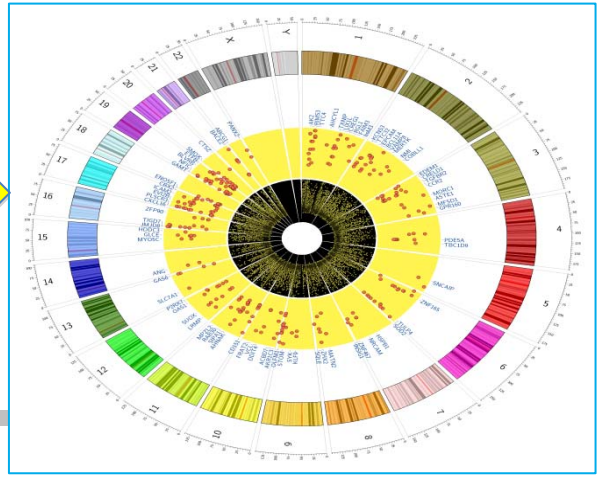
Mikhael J, et al. Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013. *Mayo Clin Proc*. 2013;88:360-376.

MM Classification Over Time

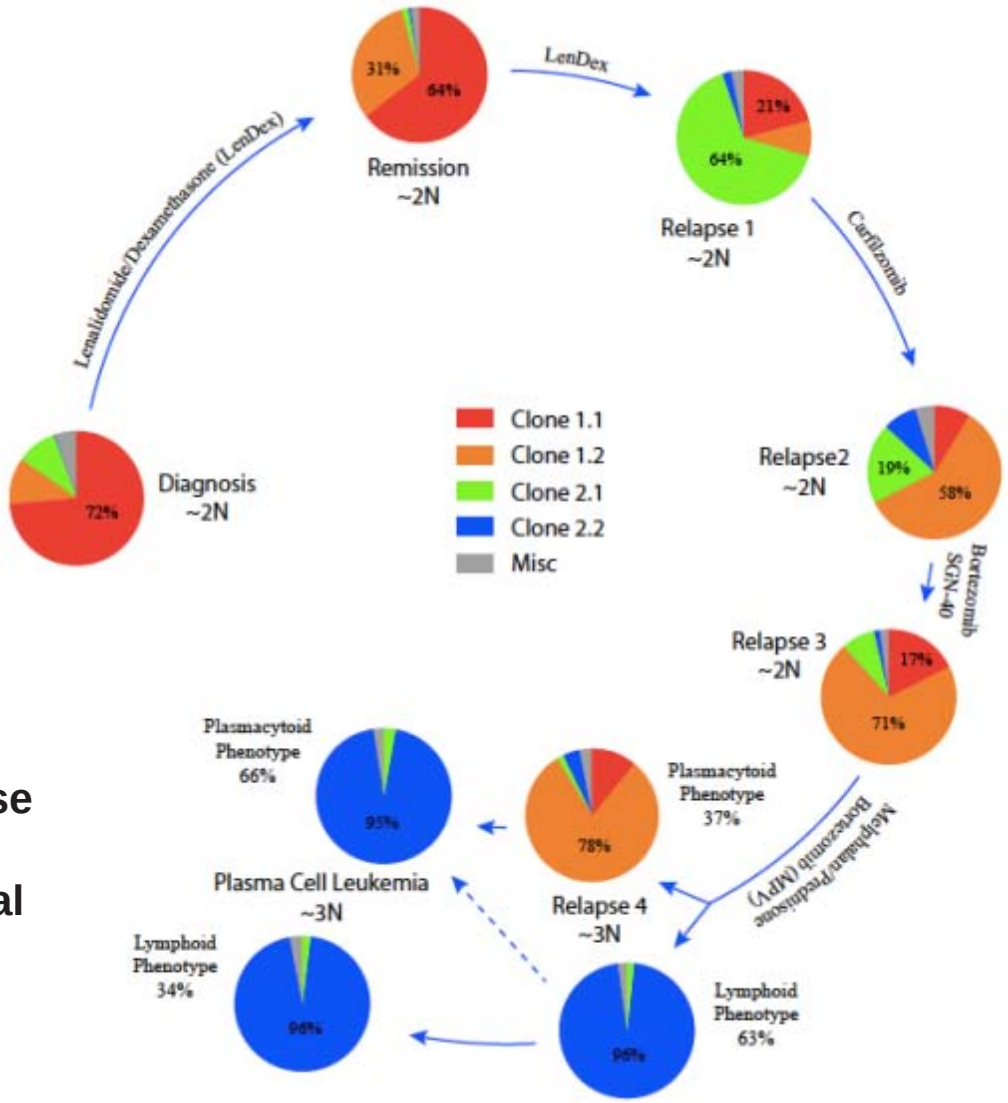








Clonal Tides Define Myeloma



6 unique clones at diagnosis

Variable chemotherapy response

Minor drug-resistant clone lethal

Implications

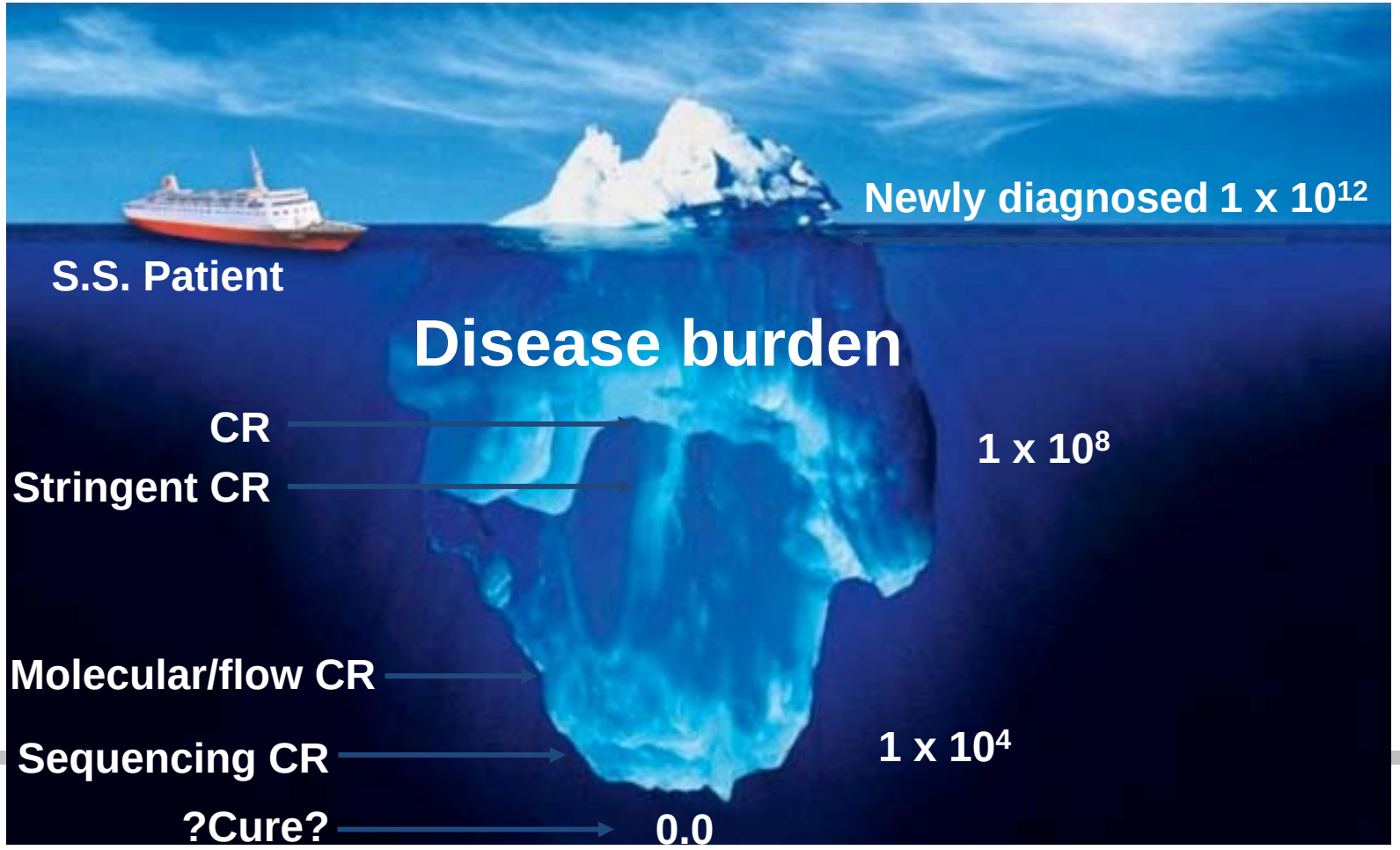
1 **Multiple clones with variable drug sensitivity**
(Combination chemotherapy a necessity and continuous therapy logical)

2 **Re-emergence of drug-sensitive clones**
(Once resistant not always resistant)

3 **Minor clone is lethal** (CR is a goal)

–

Minimal Residual Disease: New Definitions for CR



Redefining Symptomatic Myeloma

Smoldering Myeloma

- No symptoms; no related organ/tissue impairment
- 10% to 20% of newly diagnosed myeloma[1]
- Can remain indolent for yrs
- Progression rate: ~ 50% at 5 yrs[2]
  - Progression rate in high-risk subgroup: 50% at 2 yrs[3]
- Current question: *Who* should be treated?[4]

1. Kyle RA. ASCO Con**nection**. 2012. 2. Kyle RA, et al. Br J Haematol. 2007;139:730-743.
3. Mateos MV, et al. N Engl J Med. 2013;369:438-447. 4. Mateos MV, et al. Curr Hematol Malig Rep. 2013;8:270-276.

Smoldering Myeloma

Prognostic Models

Mayo Clinic (N = 273)

Risk Factors, n	Patients, n (%)	Progression at 5 Yrs, %
1	81 (28)	25
2	114 (42)	51
3	78 (30)	76

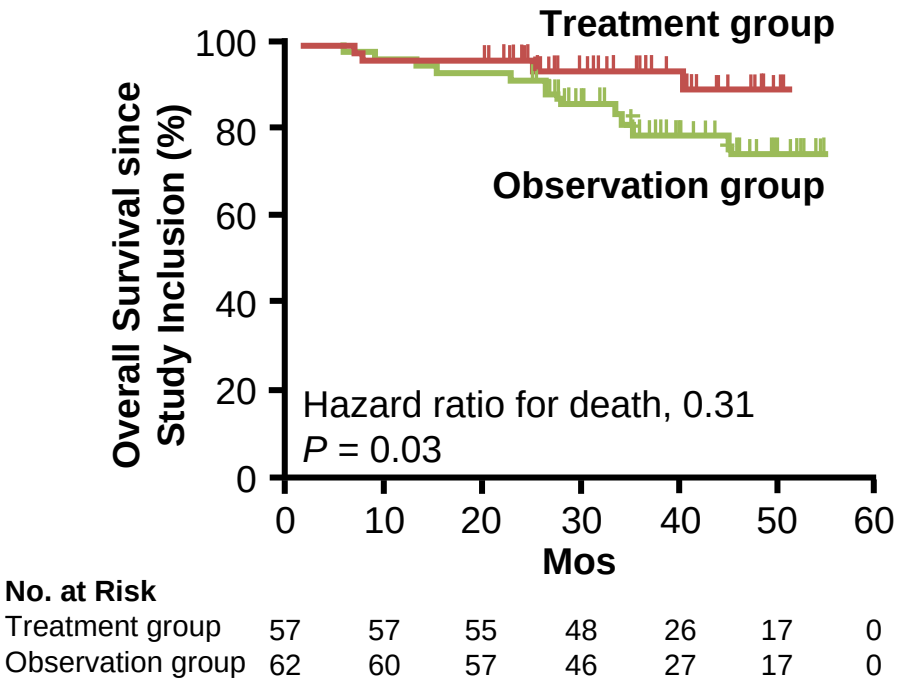
PETHEMA Study Group (N = 89)

Risk Factors, n	Patients, n (%)	Progression at 5 Yrs, %
0	28 (31)	4
1	22 (25)	46
2	39 (44)	72

- Risk factors
  - Mayo Clinic[1]
    - BMPCs ≥ 10%
    - M-protein ≥ 3 g/dL
    - FLC ratio < 0.125 or > 8
  - PETHEMA[2]
    - ≥ 95% abnormal plasma cells
    - Immunoparesis
  - University of Salamanca[3]
    - BMPCs ≥ 10%
    - High M-protein: IgG ≥ 3 g/dL, IgA ≥ 2 g/dL, or Bence-Jones > 1 g/24 hrs

1. Dispenzieri A, et al. Blood. 2008;111:785-789. 2. Pérez-Persona E, et al. Blood. 2007;110:2586-2592.
3. Mateos MV, et al. N Engl J Med. 2013;369:438-437.

PETHEMA Phase III Trial: Len/Dex vs Observation in High-Risk SM



- Study limitation in assessing OS: patients received treatment off-protocol at the time of disease progression to symptomatic myeloma
  - 53% treated with either bortezomib-based regimens
  - 28% treated with induction therapy followed by autologous stem-cell transplantation
  - 19% treatment not reported

Mateos MV, et al. N Engl J Med. 2013;369:438-447.

Active Myeloma

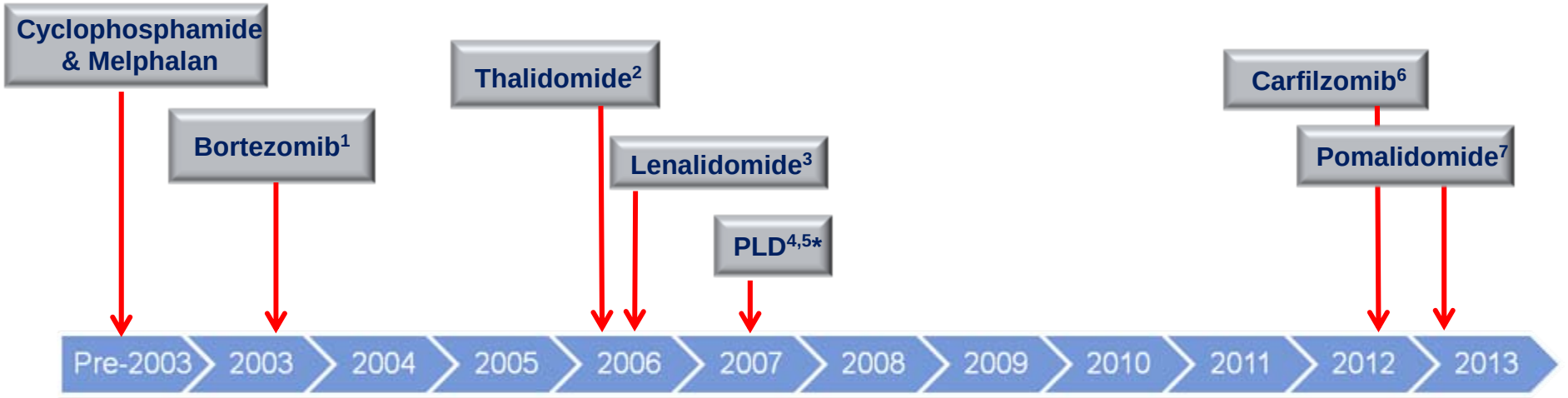
Not CRAB but now SLiM CRAB

- S (60% Plasmacytosis)
- Li (Light chains I/U >100)
- M (MRI 1 or more focal lesion)
- C (Calcium elevation)
- R (Renal insufficiency)
- A (Anemia)
- B (Bone disease)

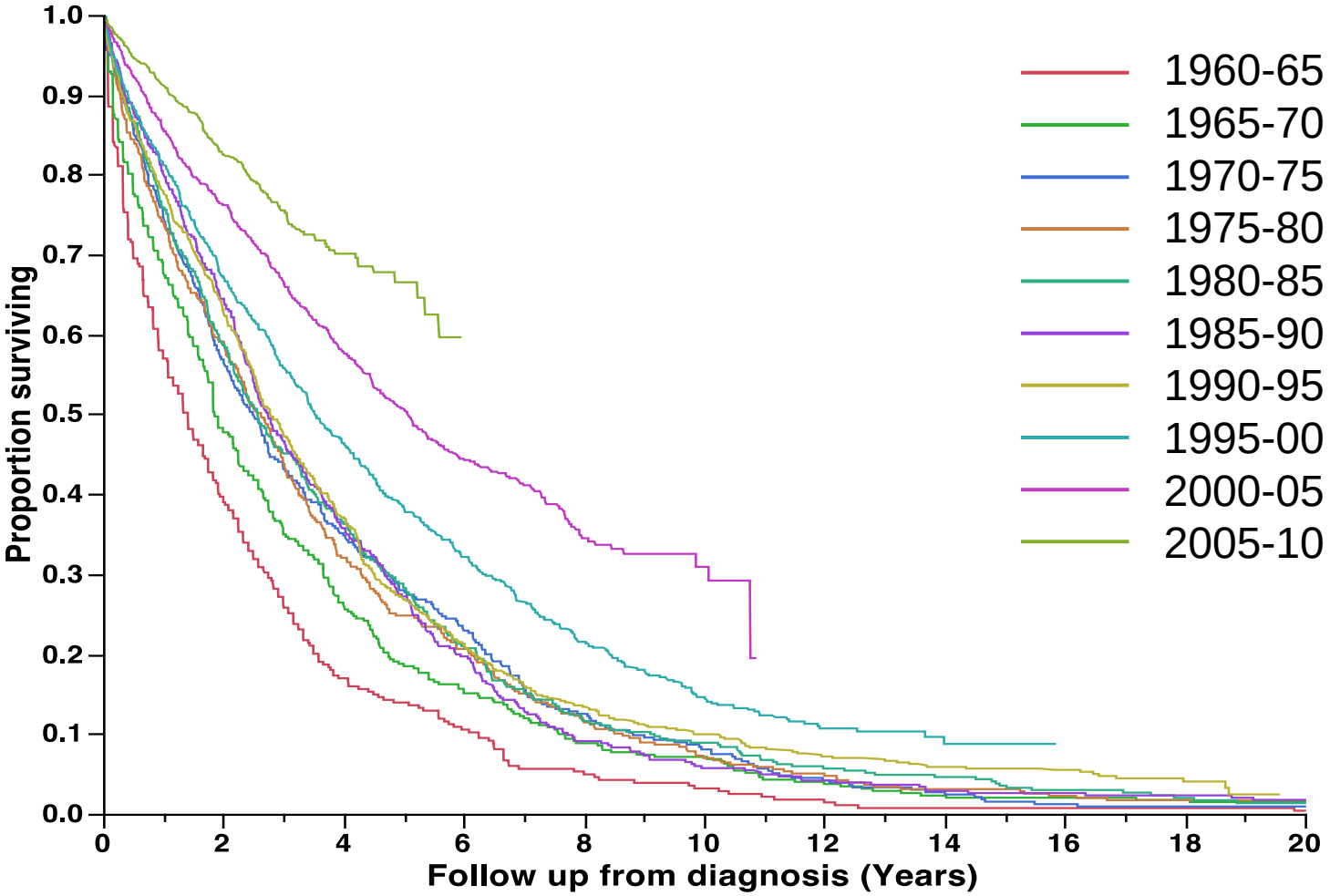
Rajkumar et al. IMWG updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538-e548

Untreated Active Multiple Myeloma

Approved agents in multiple myeloma

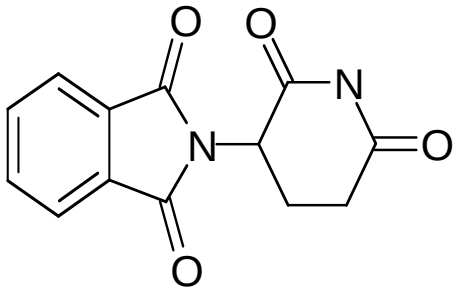


Improving Survival in MM



MAYO CLINIC

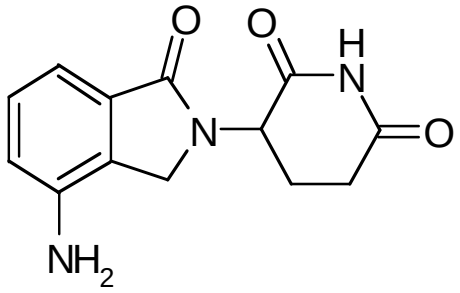
Chemical Structure of Thalidomide, Lenalidomide, and Pomalidomide



Thalidomide

100–200 mg/d

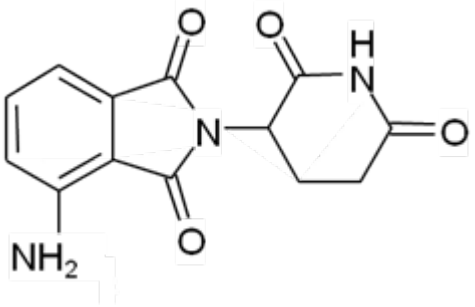
Neuropathy
Constipation
Sedation
DVT



Lenalidomide

15–25 mg/d

Myelosuppression
Skin rash
DVT



Pomalidomide

2–4 mg/d

Myelosuppression

Proteasome Inhibitors

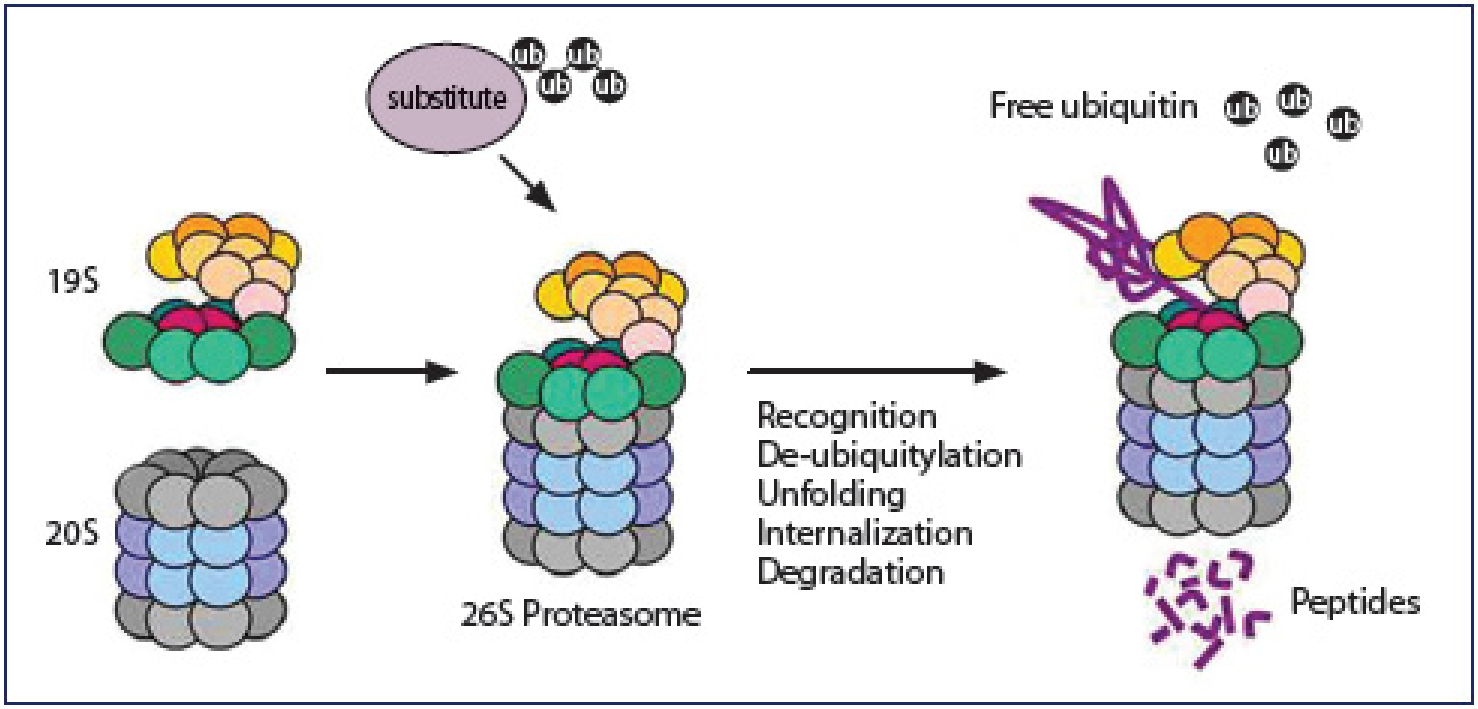
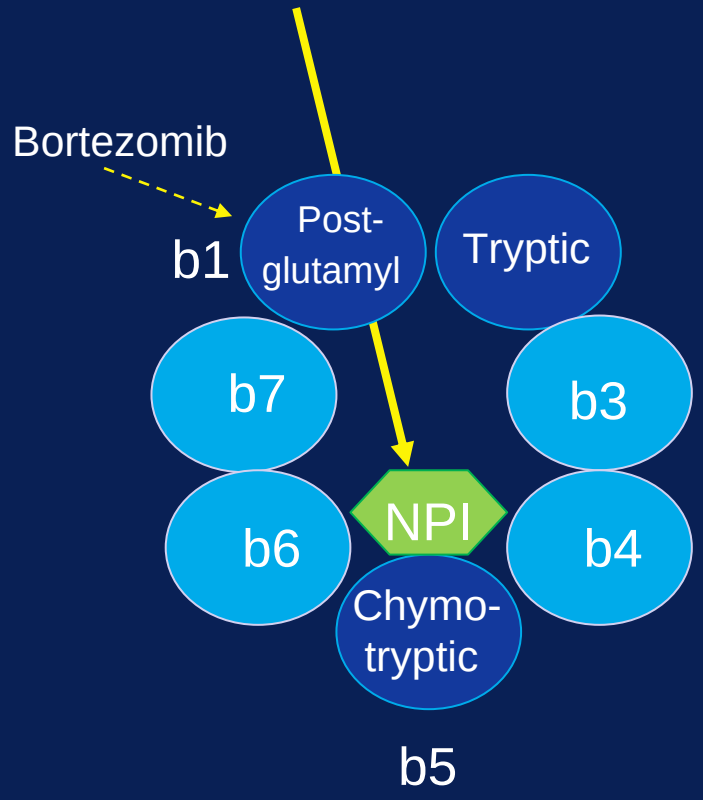


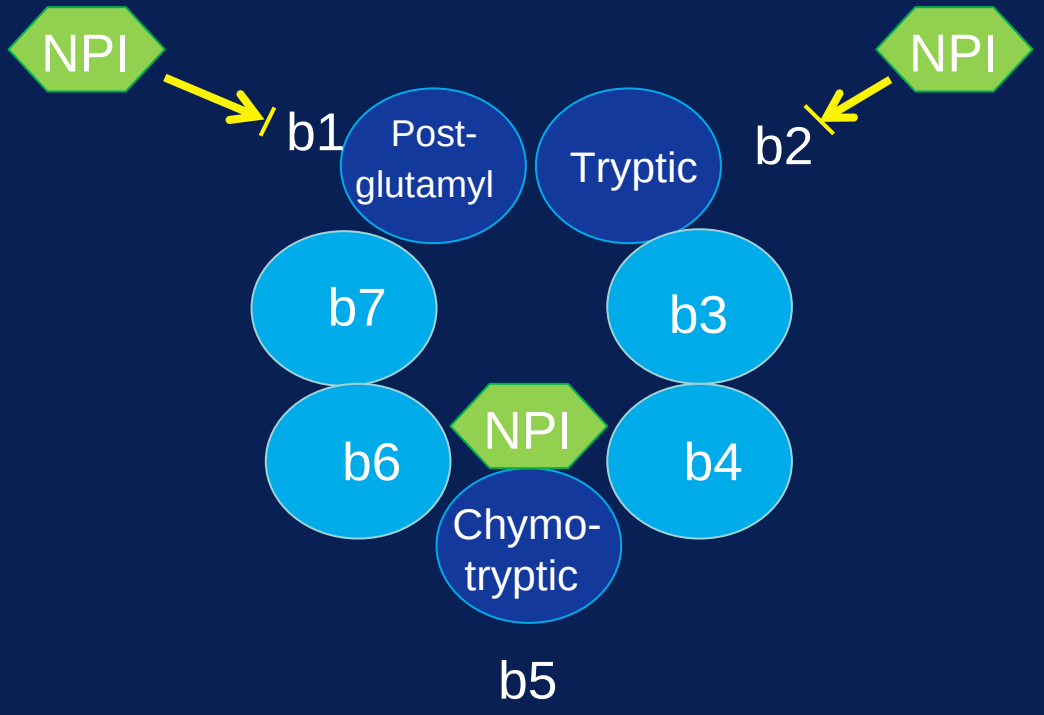
Figure 1: Structure of the 26S Proteasome—Adapted from Marteijn JA et al. Leukemia. 2006.[42] © 2006. Reprinted by permission from Macmillan Publishers Ltd.

Comparison of Proteasome Inhibitors

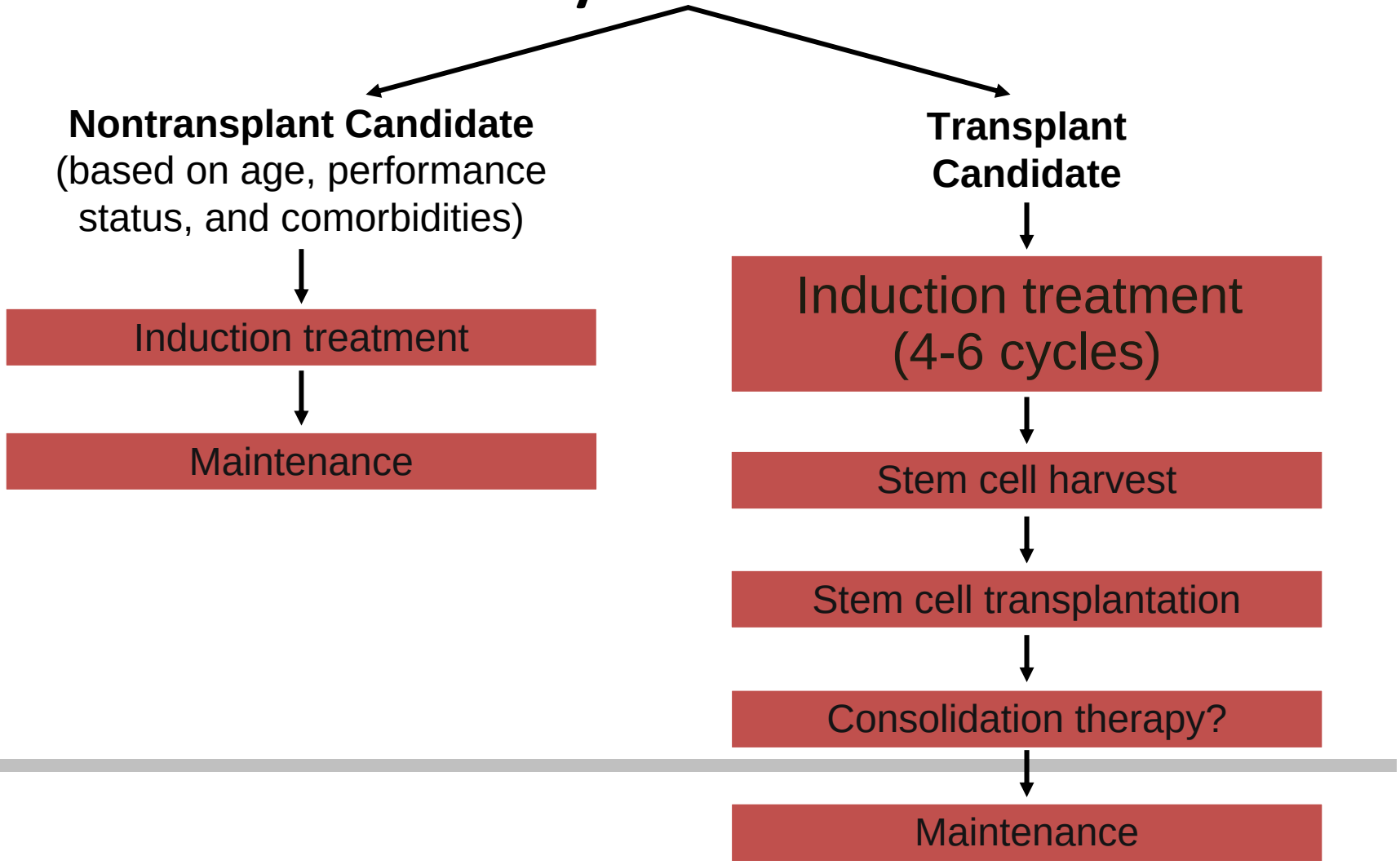
Bortezomib (reversible)
Carfilzomib (irreversible)
CEP 18770 (reversible)



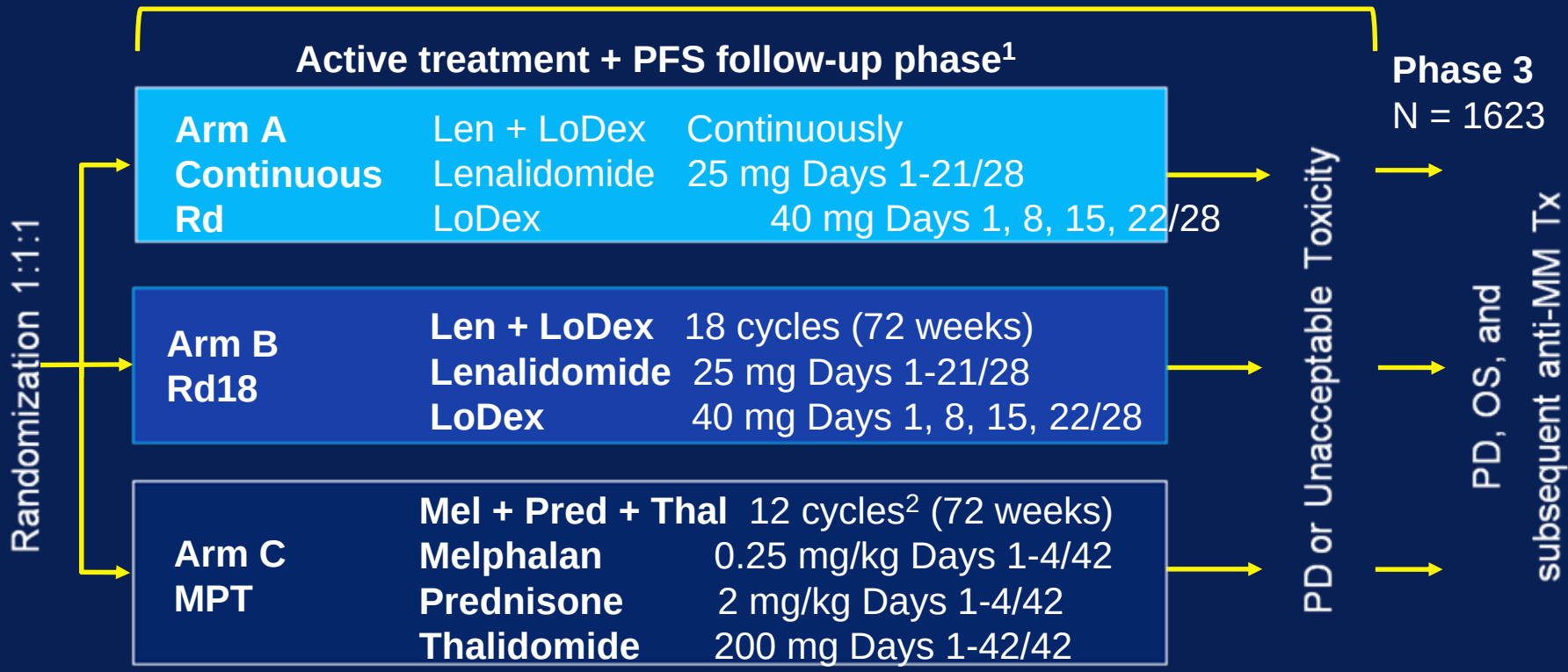
MLN9708 (reversible)
NPI-0052 (irreversible)



Initial Approach to Treatment of Myeloma



FIRST: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Patients

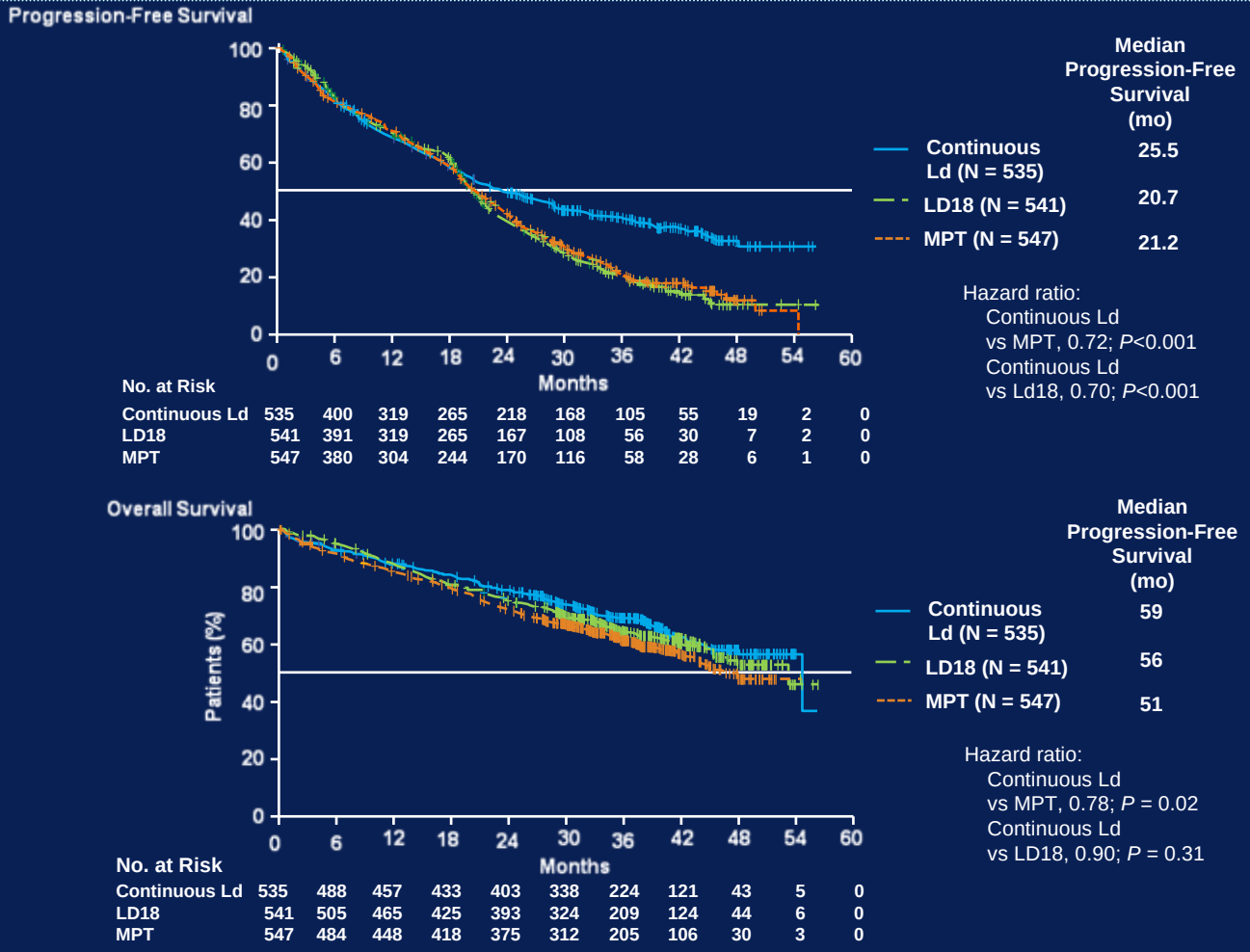


Patients >75 years: LoDex 20 mg Days 1, 8, 15, 22/28; Thal[3] 100 mg Days 1-42/42; Mel[3] 0.2 mg/kg Days 1-4
Stratification: age, country, and ISS stage

NDMM = newly diagnosed MM; SCT = stem cell transplant.

1. Facon T et al. ASH 2013 Annual Meeting. Abstract 2; 2. Facon T et al. *Lancet*. 2007;370:1209-1218; 3. Hulin C et al. *J Clin Oncol*. 2009;27:3664-3670.

FIRST Trial: Efficacy Analysis of Len/Dex vs MPT in SCT-Ineligible Patients With MM



Relapsed Multiple Myeloma

ASPIRE Study Design

Randomization

N=792

Stratification:

- **β_2-microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

28-day cycles

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

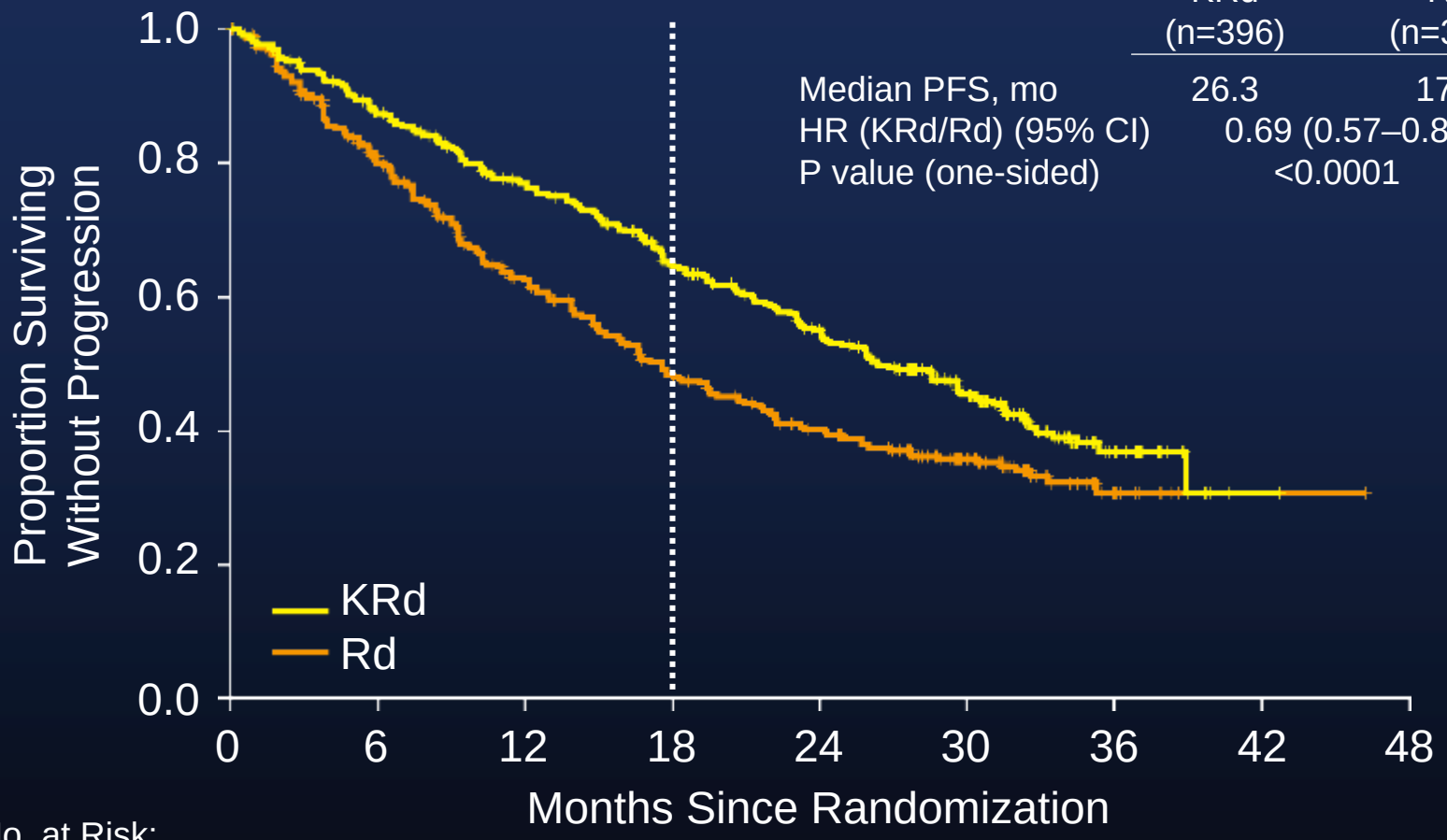
Rd

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. *N Engl J Med*. 2014 Dec 6. [Epub ahead of print],

Primary Endpoint: Progression-Free Survival
ITT Population (N=792)

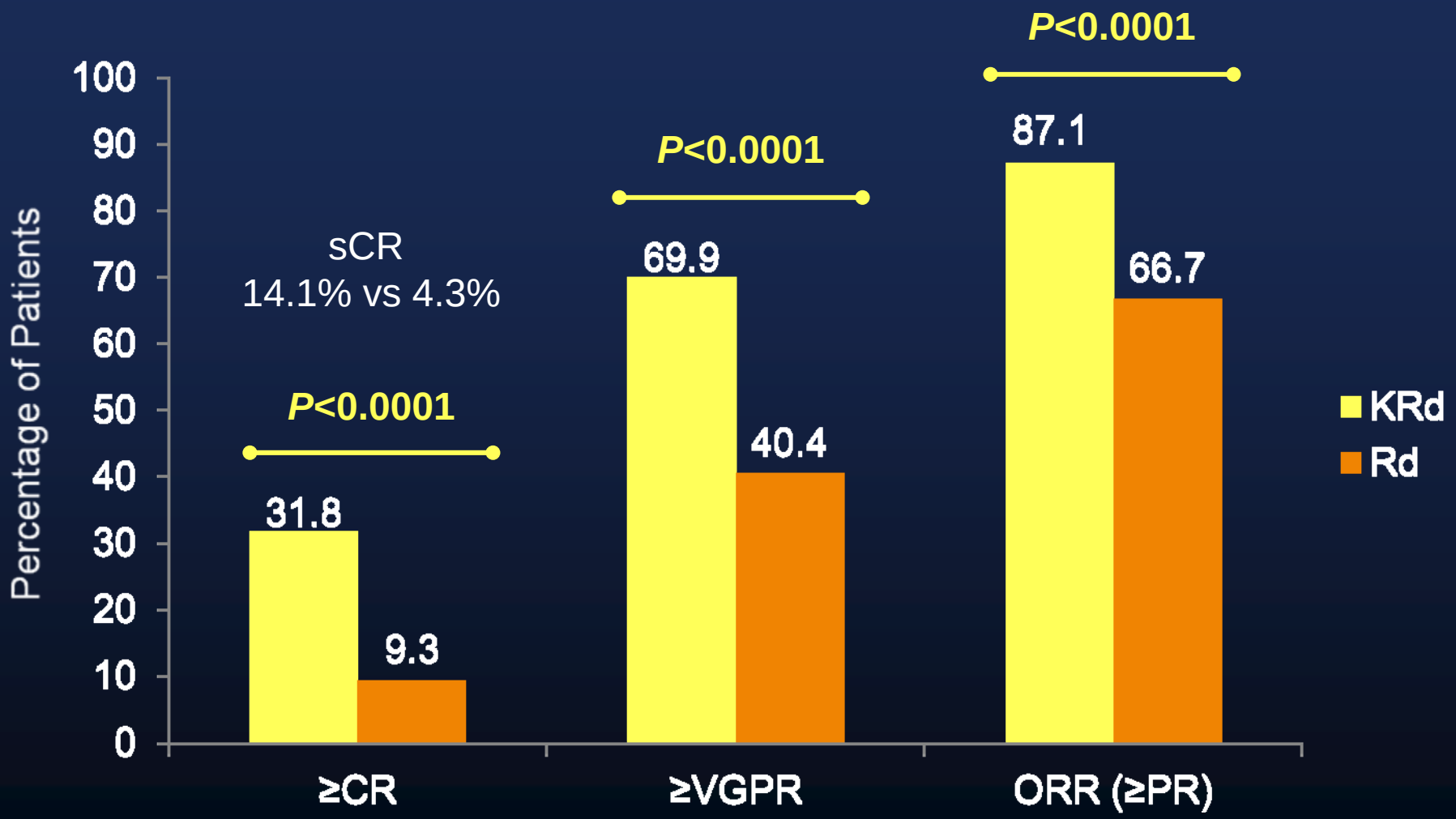


No. at Risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. *N Engl J Med*. 2014 Dec 6. [Epub ahead of print],

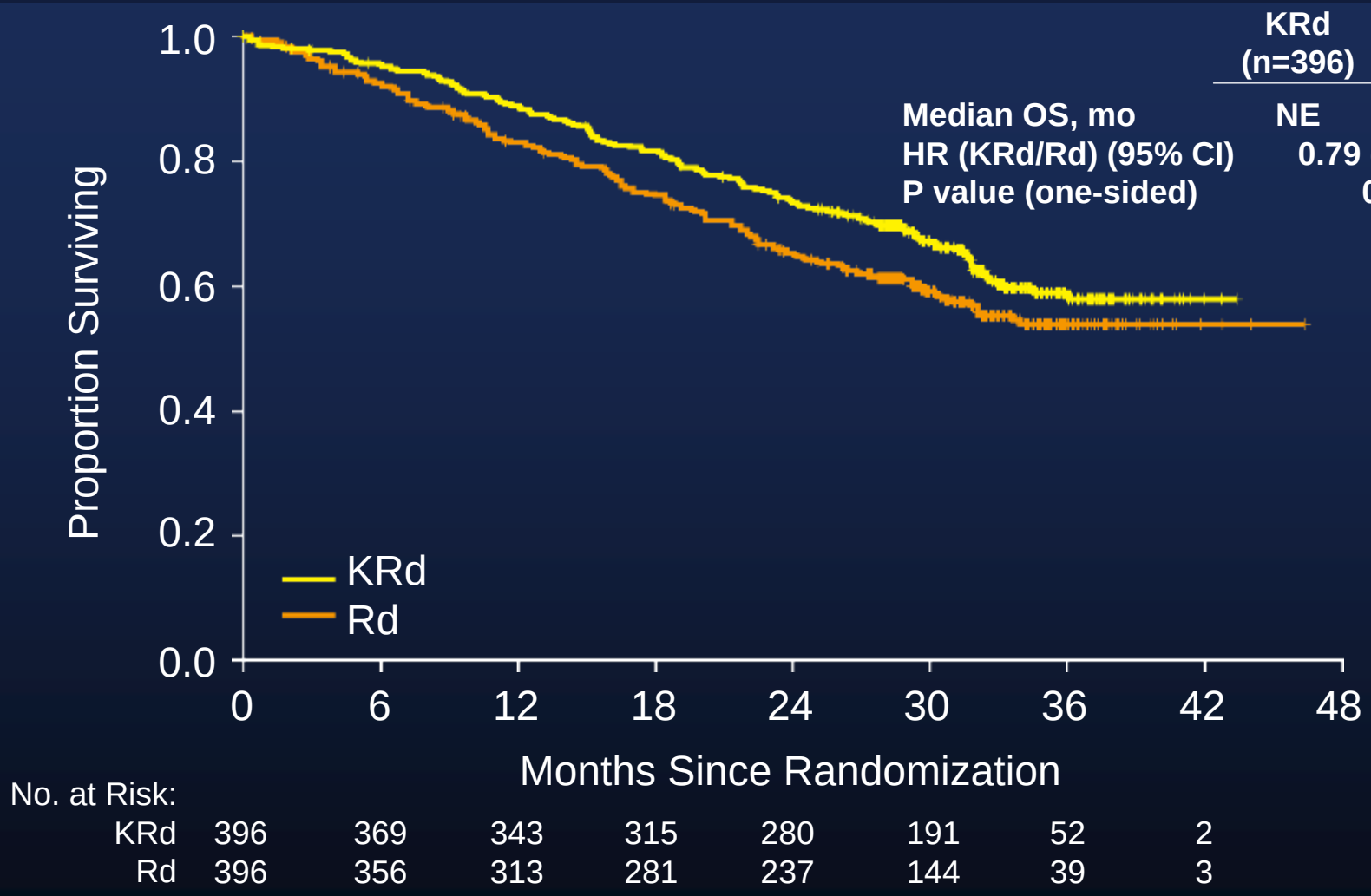
Secondary Endpoints: Response



- **Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group**

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. *N Engl J Med*. 2014 Dec 6. [Epub ahead of print],

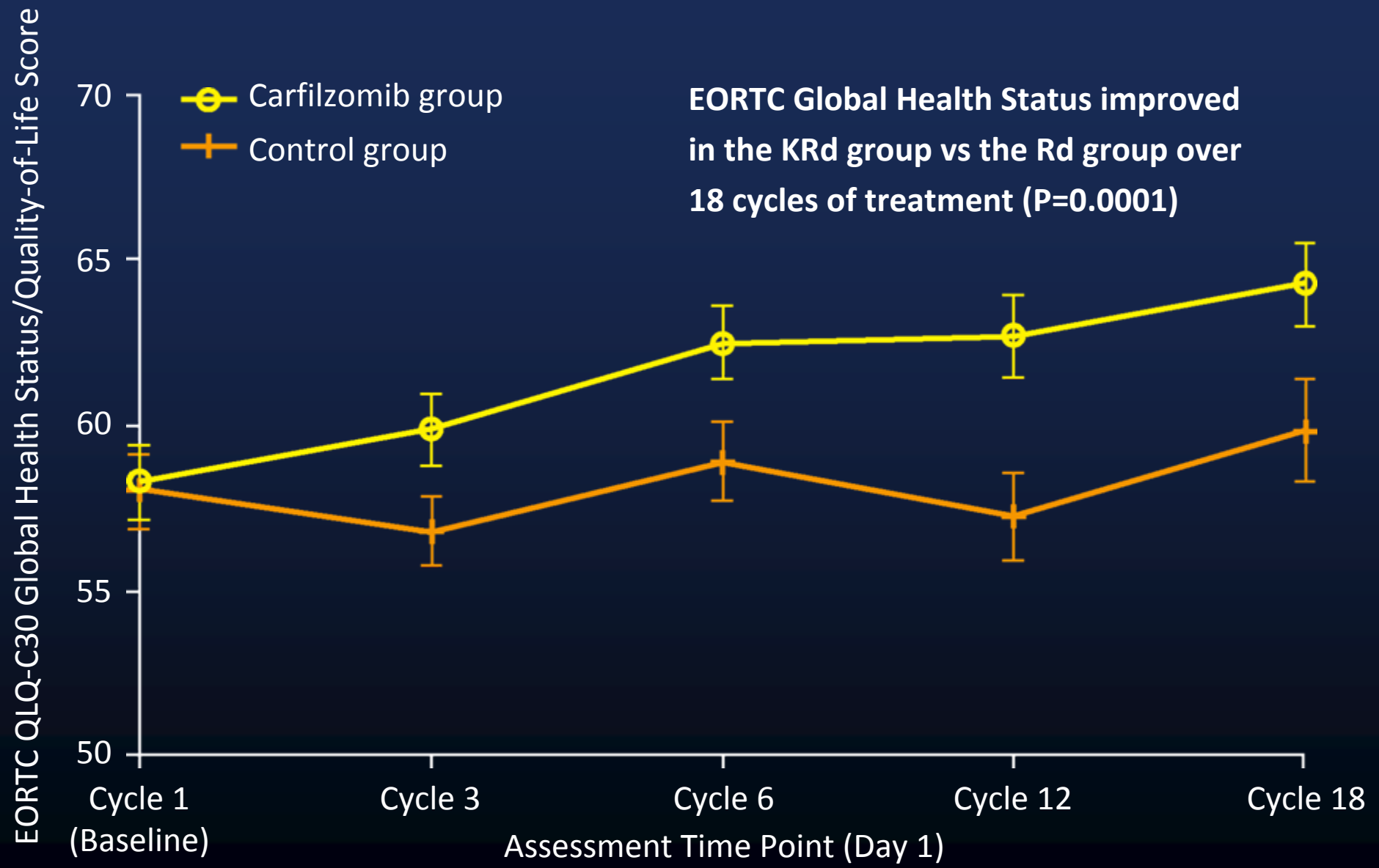
Secondary Endpoints: Interim Overall Survival Analysis
Median Follow-Up 32 Months



- **Median OS was not reached; results did not cross the prespecified stopping boundary (*P*=0.005) at the interim analysis**

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. *N Engl J Med*. 2014 Dec 6. [Epub ahead of print],

Health-Related Quality-of-Life

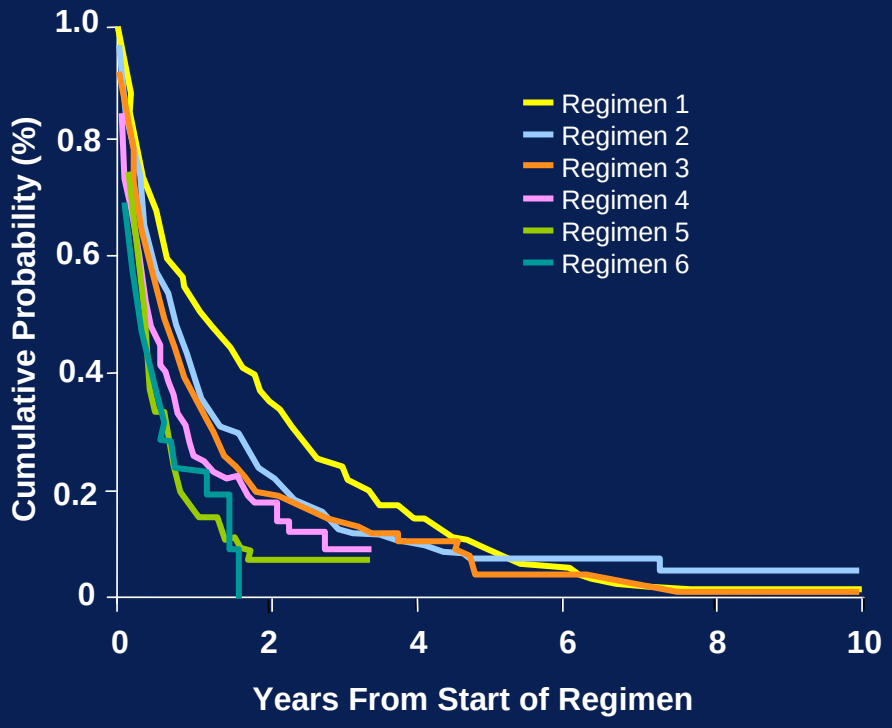


Stewart AK, Rajkumar SV, Dimopoulos MA, et al. *N Engl J Med*. 2014 Dec 6. [Epub ahead of print],

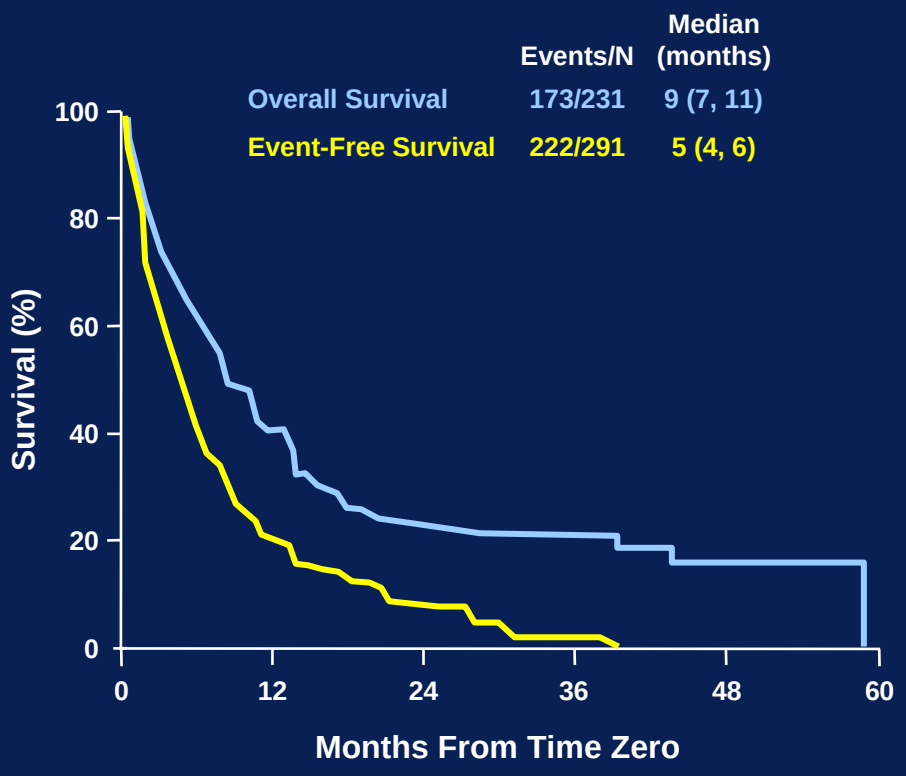
Relapsed/Refractory Myeloma

Once Treatment Fails, Trouble Begins

Overall Survival From Start of Therapy by Regimen Number

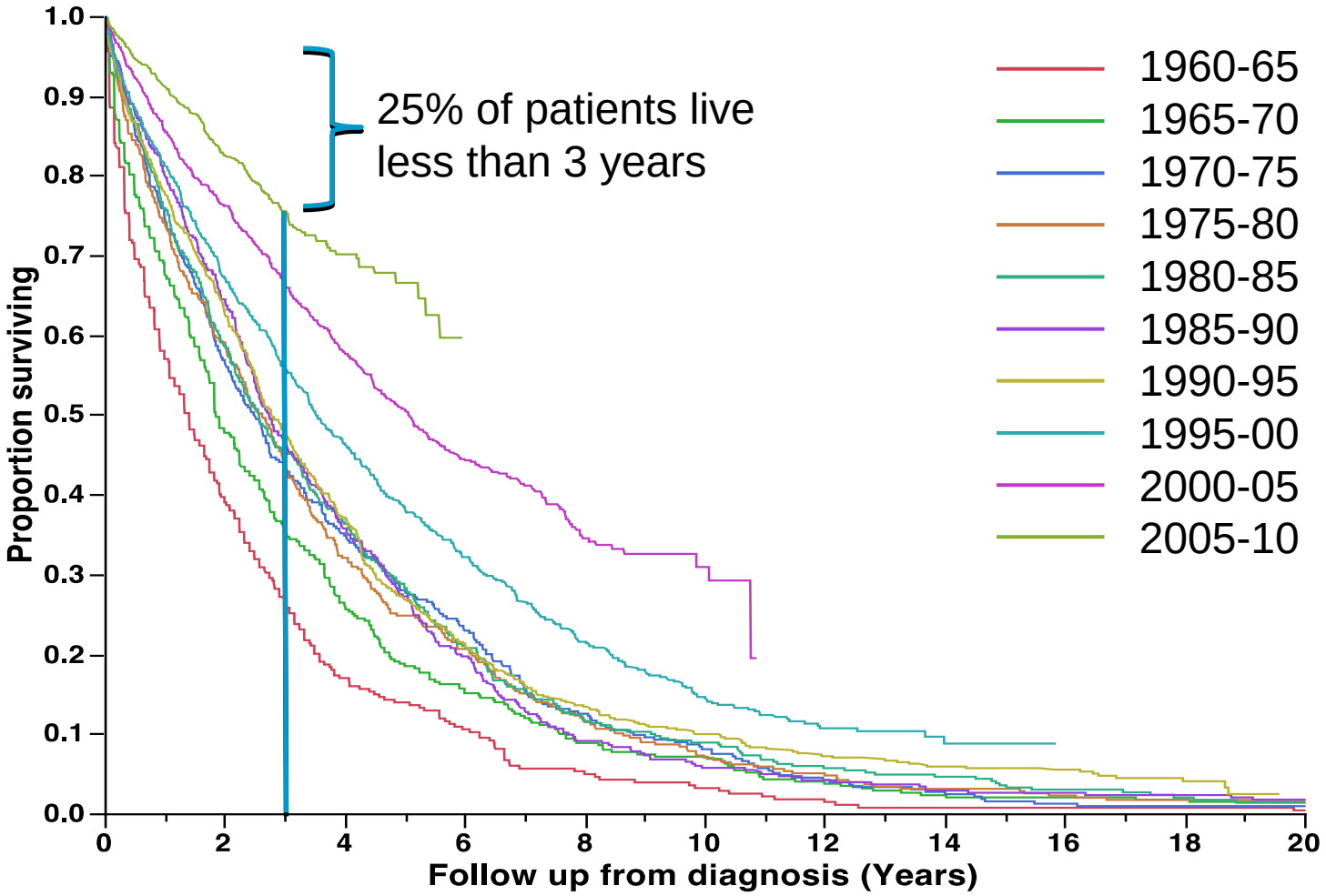


Survival With Bz/Len Refractory Disease



Kumar SK. *Mayo Clin Proc.* 2004;79:867-874.

Improving Survival in MM



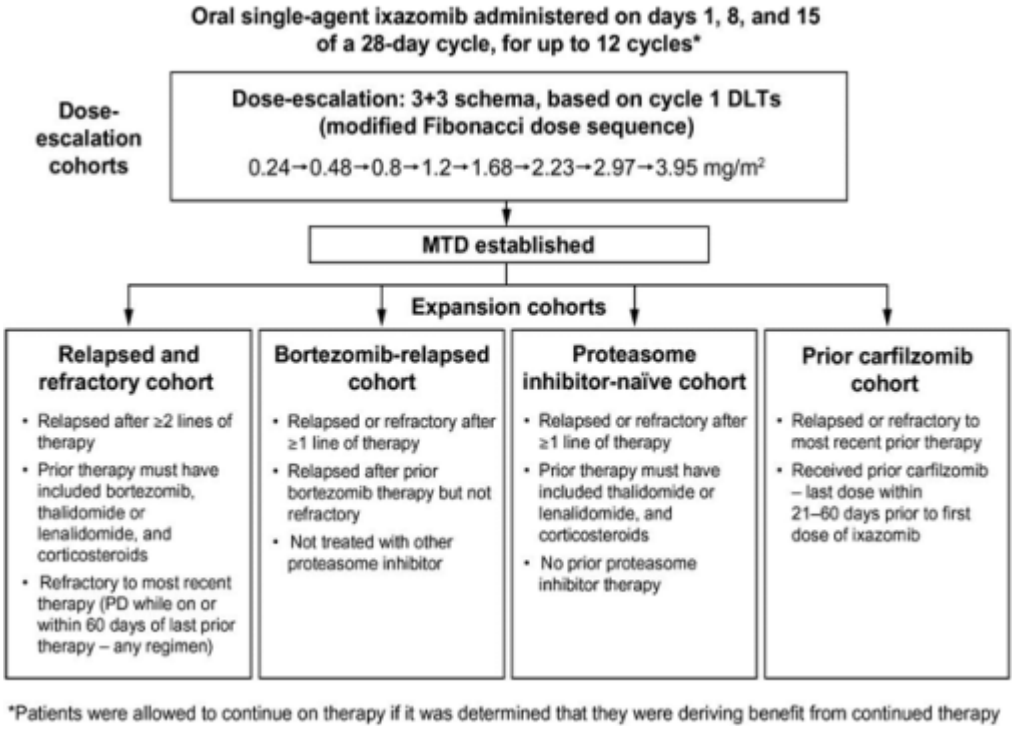
MAYO CLINIC

Ixazomib (MLN9708)

- Ixazomib (MLN9708) is an investigational oral, reversible, and specific 20S proteasome inhibitor
  - The first oral proteasome inhibitor in clinical development
  - Physiochemical properties distinct from bortezomib
  - Activity in preclinical models of MM

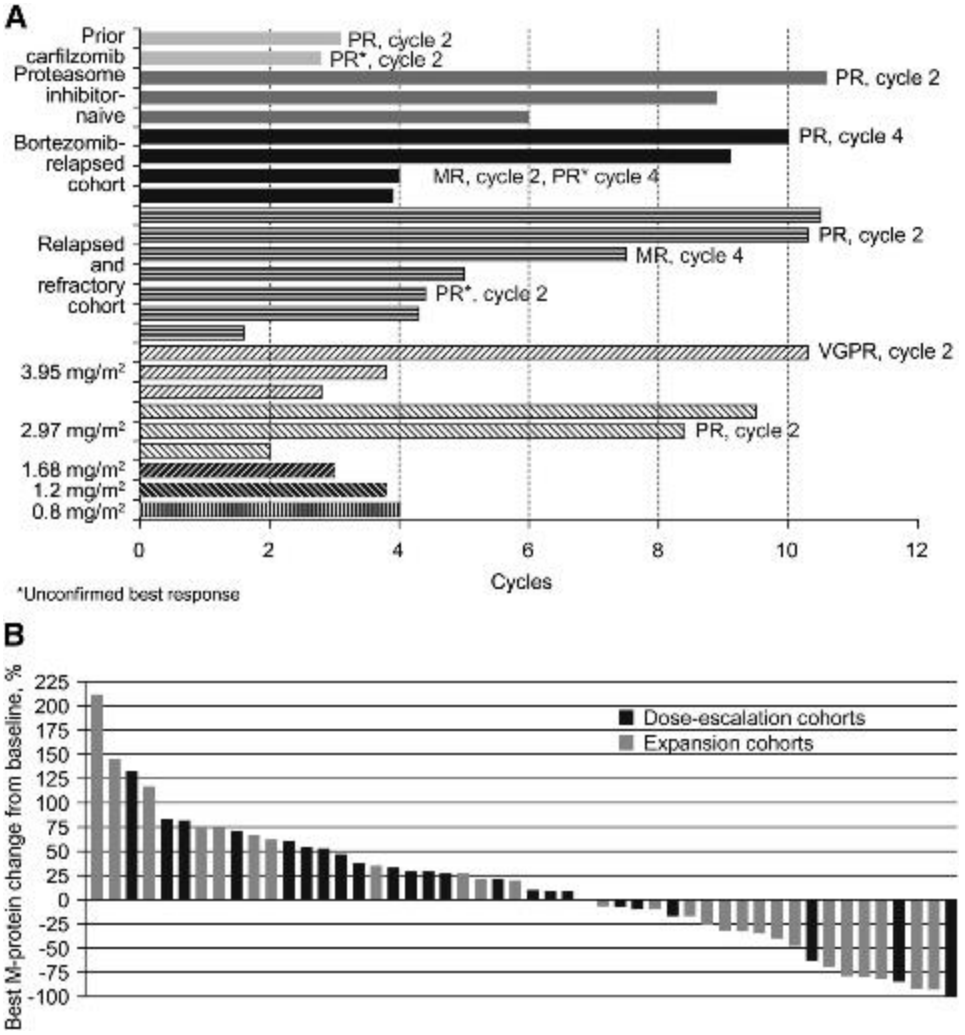
Oral Ixazomib – Phase 1 Weekly

- Oral weekly administration
- 60 patients with heavily pretreated disease
- DLTs due to nausea, vomiting, diarrhea, and rash
- AEs – thrombocytopenia, diarrhea, nausea, fatigue, vomiting
- Neuropathy 20% (but only 1 grade 3)
- 18% response rate (PR or better), 27% at MTD



Kumar SK, et al. *Blood*. 2014;124(7):1047-1055.

Ixazomib Treatment Duration and Response

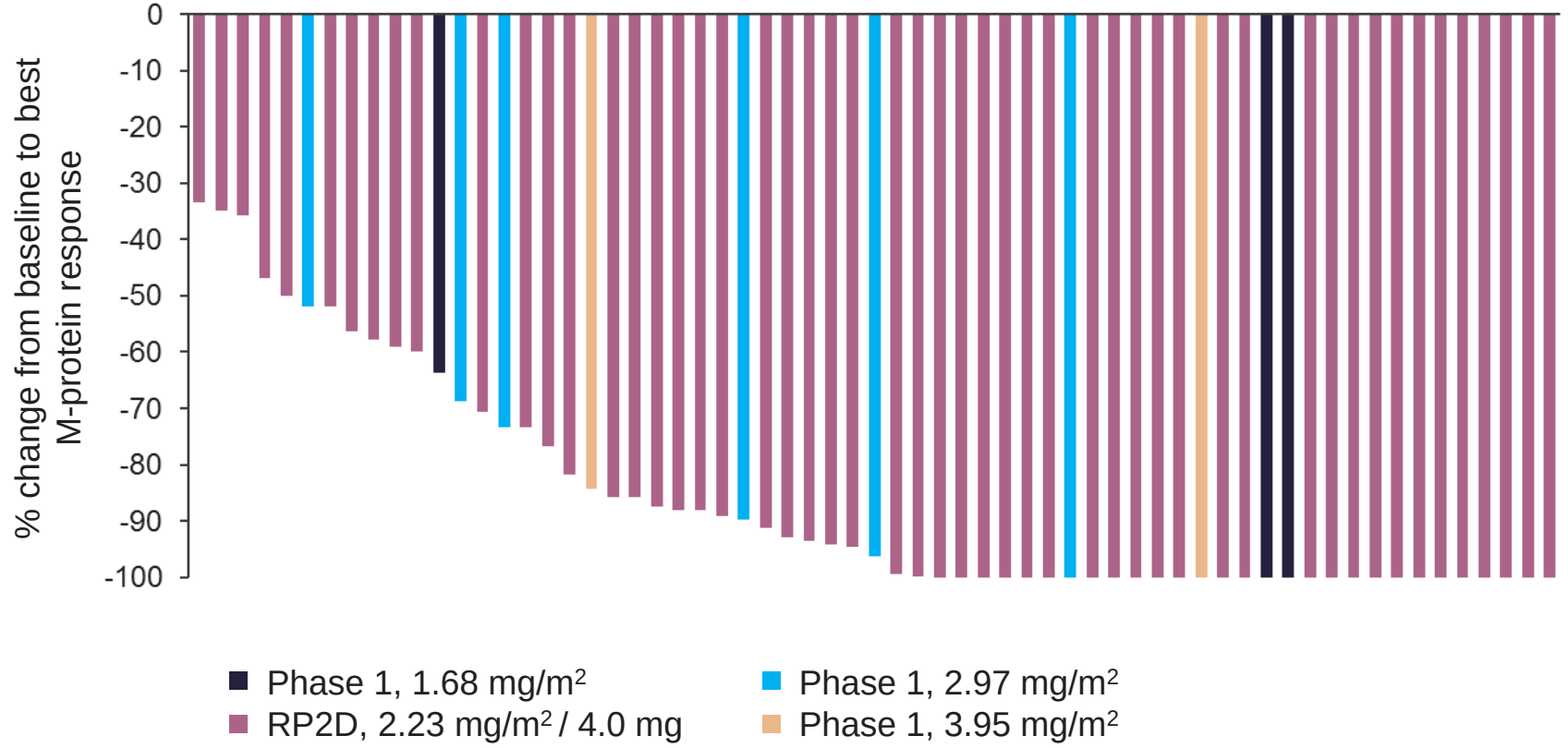


Kumar SK, et al. *Blood*. 2014;124:1047-1055.

Ixazomib Summary

- Well tolerated
- Single-agent activity in both weekly and twice weekly administration
- Less effective than bortezomib?
- Low neuropathy rate is encouraging
- Attractive oral regimen (esp in combination) – see next slide

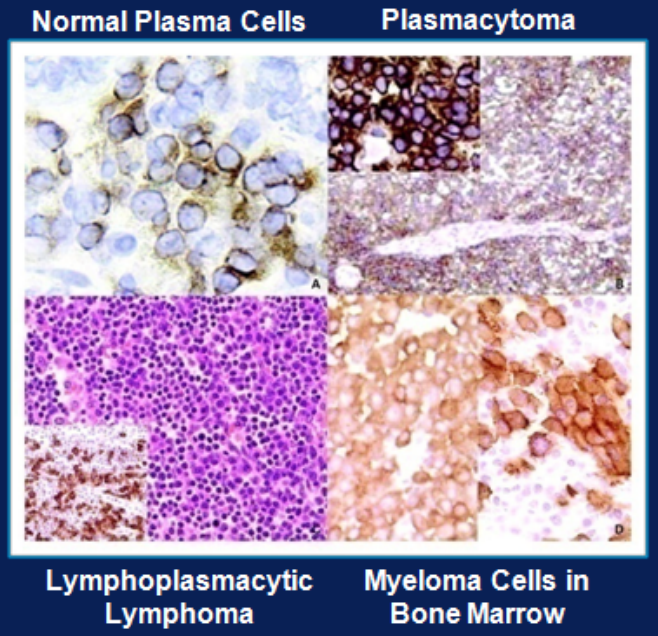
IRd (Ixazomib/Lenalidomide/Dex)- Best Percent Change in M-protein From Baseline in Response-Evaluable Patients



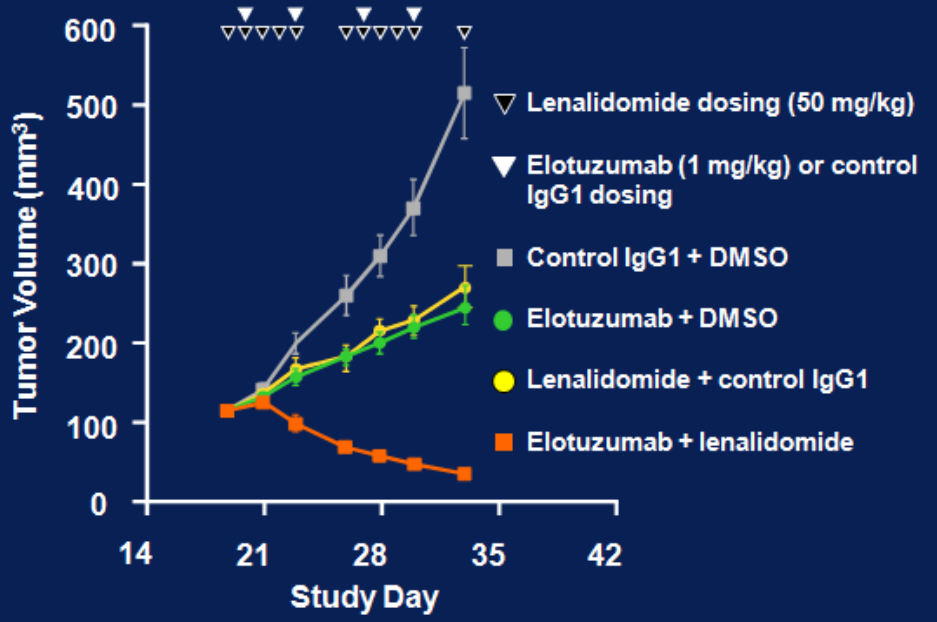
- 48% of patients achieved 100% reduction in M-protein
- Reductions were seen at multiple dose levels

Elotuzumab: Background

- Elotuzumab is a humanized IgG1 mAb-targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly expressed on >95% of MM cells[1-3]
  - Lower expression on NK cells
  - Little-to-no expression on normal tissues



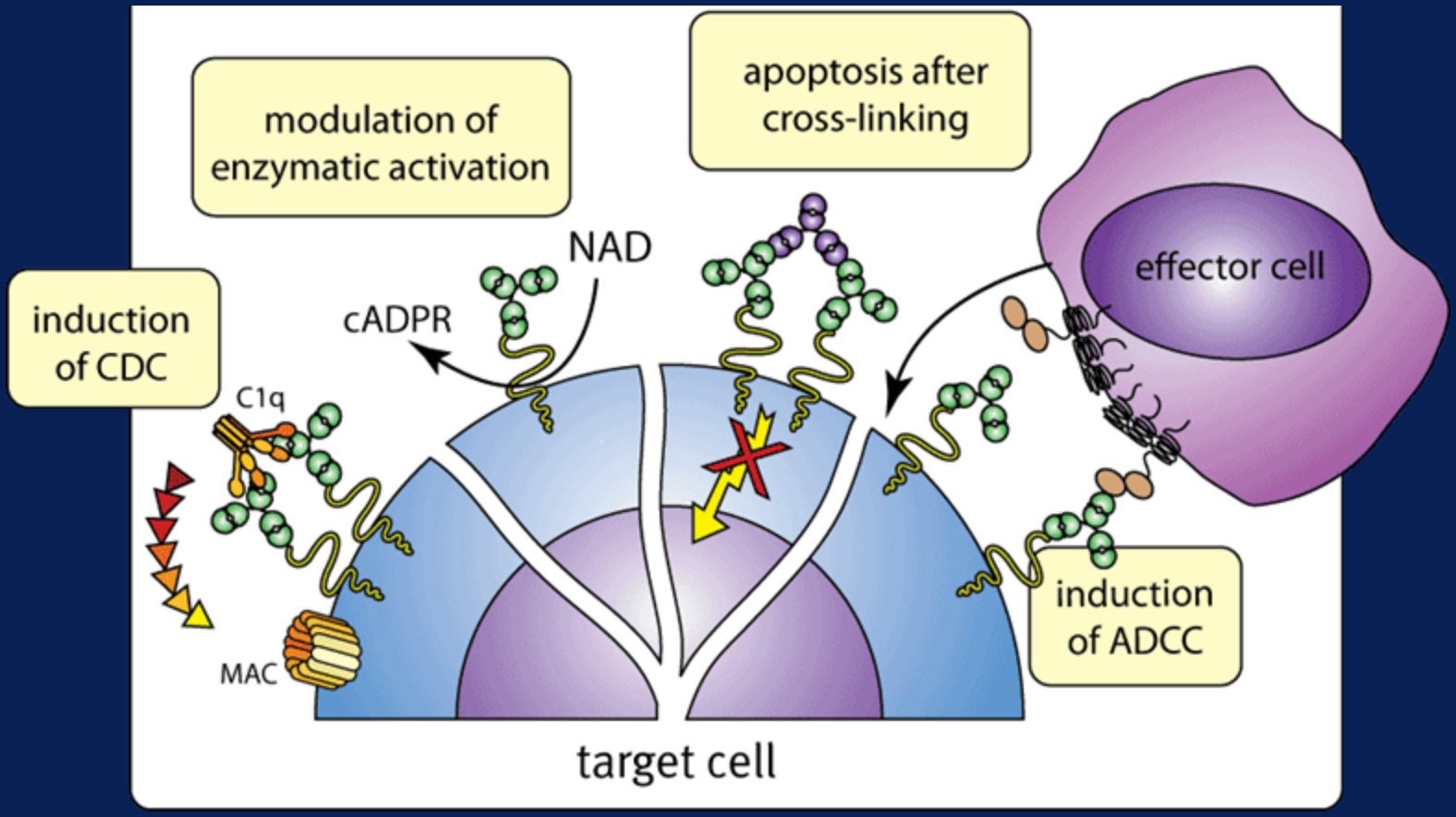
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells[1,2]
- In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone[4]



ADCC = antibody-dependent cellular cytotoxicity; DMSO = dimethyl sulfoxide; mAb = monoclonal antibody; MED = maximum efficacious dose; MoA = mechanism of action; NK = natural killer.

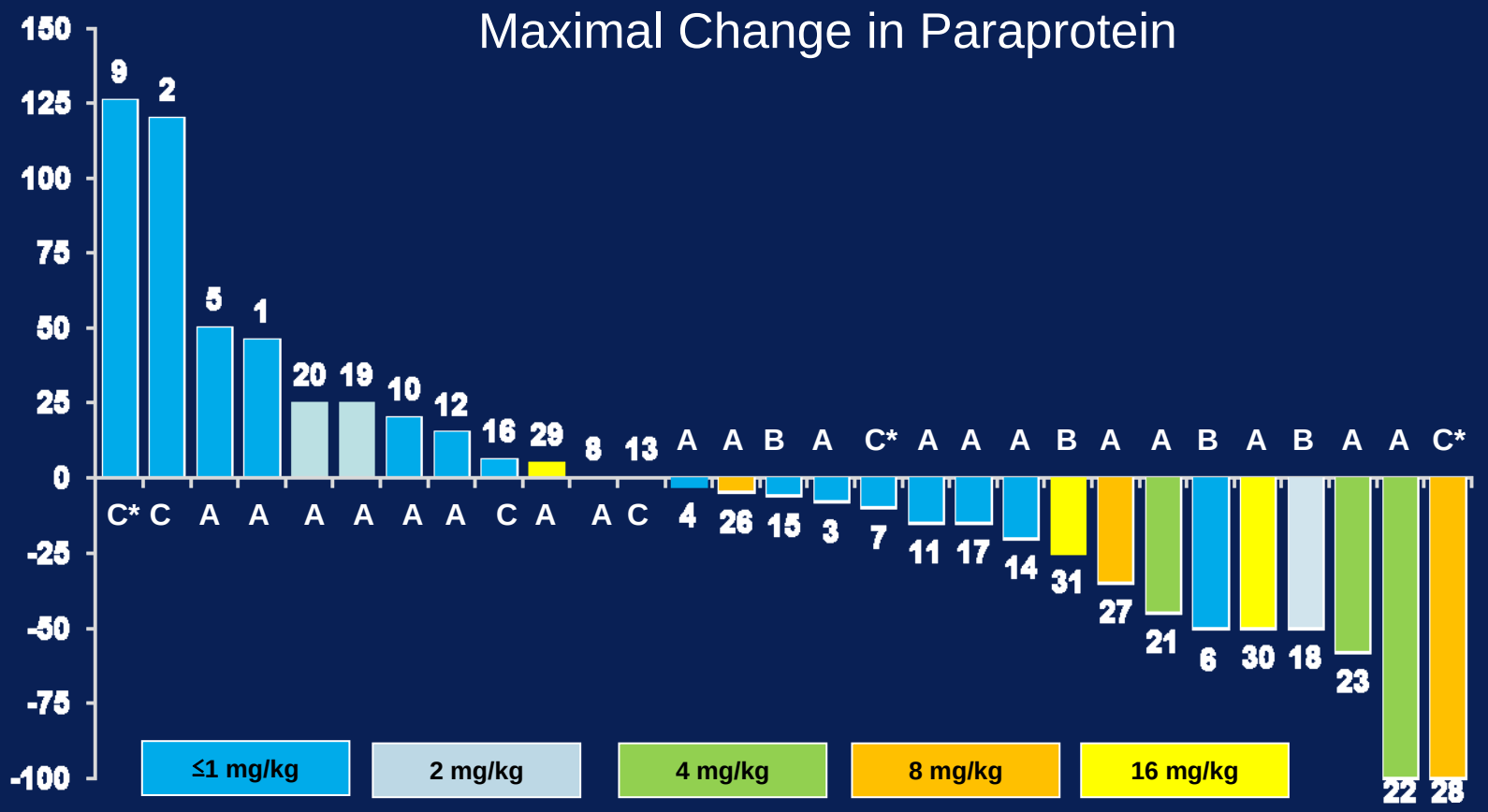
1. Hsi ED et al. *Clin Cancer Res*. 2008;14:2775-2784. Reproduced with permission from AACR. © 2008; 2. Tai YT et al. *Blood*. 2008;112:1329-1337; 3. Van Rhee F et al. *Mol Cancer Ther*. 2009;8:2616-2624; 4. Lonial S et al. ASH 2009 Annual Meeting. Abstract 432.

Daratumumab: A Human CD38 MAb With Broad-Spectrum Killing Activity



Plesner T. ASCO 2012 Annual Meeting. Abstract 8019.

Maximal Reduction of Serum M-Component (Part 1)



*Data at baseline below limits for measurable disease. Results are before database lock.
A = serum M-component; B = urine M-component; C = free light chains (FLC).
Plesner T. Annual Meeting. Abstract 8019.

CD38 Expressed in Hematological Malignancies

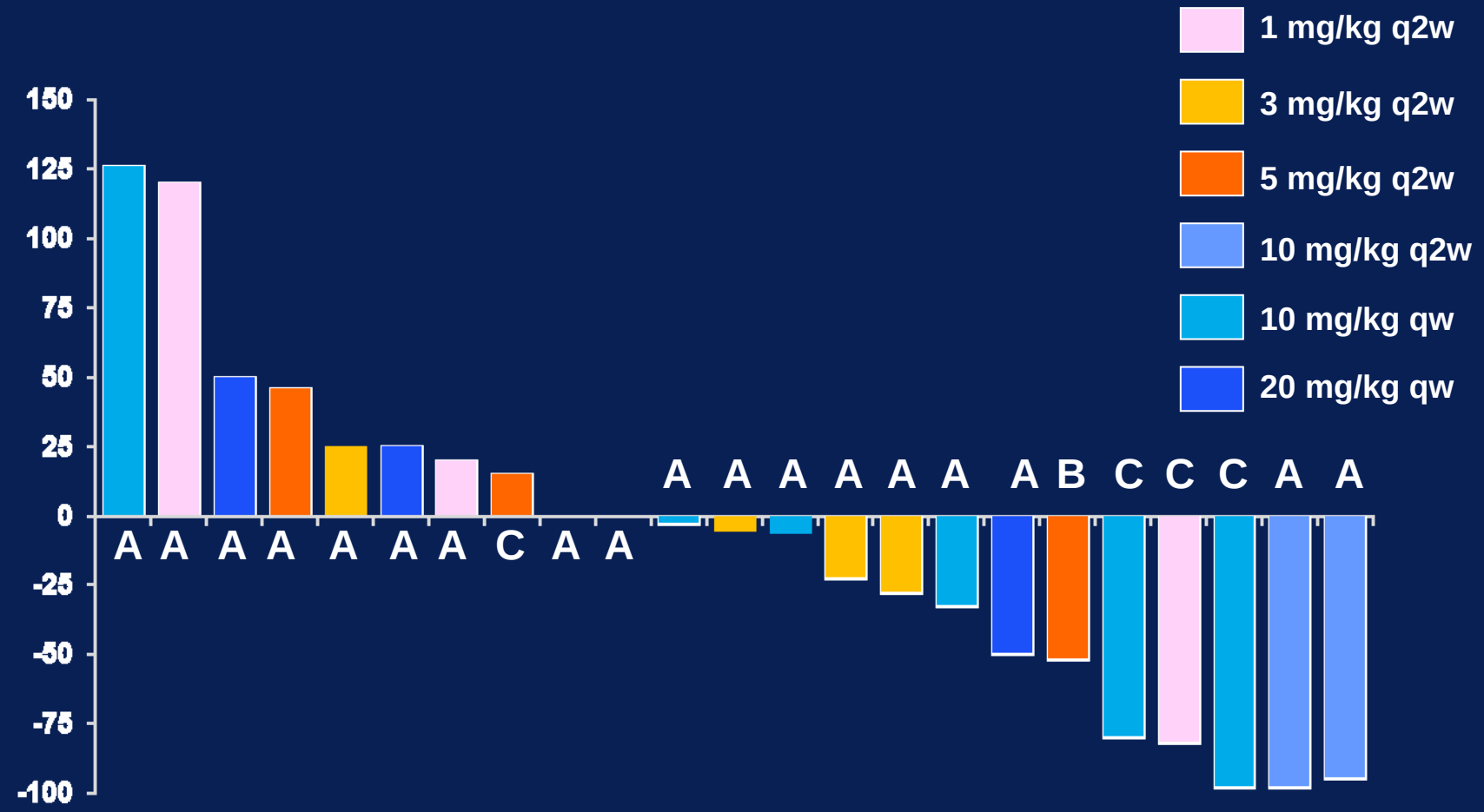
- Transmembrane glycoprotein and ectoenzyme
- High receptor density on MM cells

CD38 Expressed in Hematological Malignancies

Disease	CD38 + Expression (%)
Multiple myeloma	80-100[1]
Non-Hodgkin lymphoma	30-80[2,3]
Acute myeloid leukemia	58[4]
B chronic lymphocytic leukemia	20-25[5]

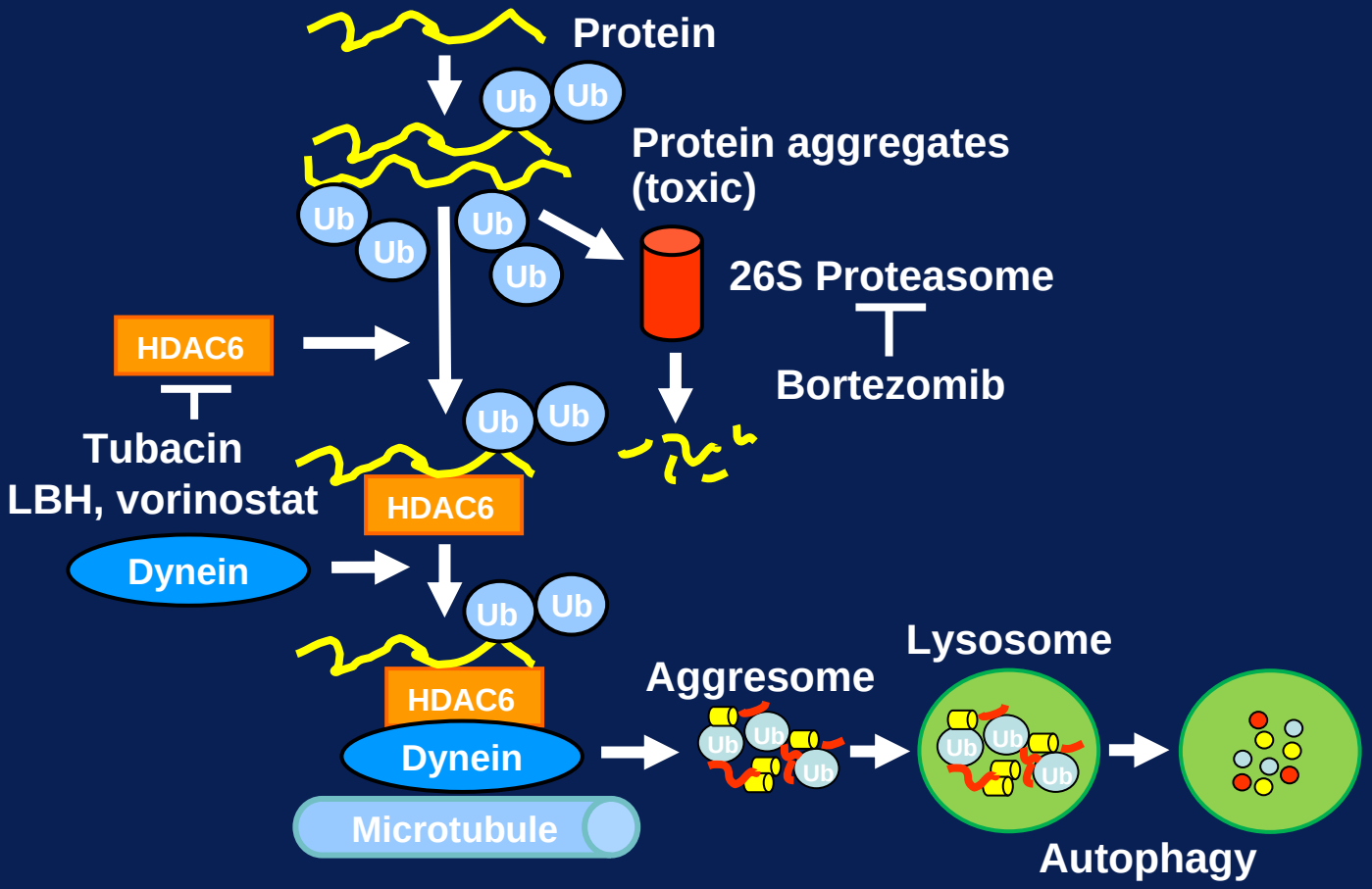
1. Lin P et al. *Am J Clin Pathol.* 2004;121:482-488; 2. Angelopoulou MK et al. *Eur J Haematol.* 2002;68:12-21; 3. Schwonzen M et al. *Br J Haematol.* 1993:83;232-239; 4. Keyhani A et al. *Leukemia Res.* 1999;24:153-159; 5. Domingo-Domenech E et al. *Haematologica*. 2002;87:1021-1027.

SAR650984: Maximal Change in Paraprotein Myeloma Patients Treated at Doses of 1 mg/kg or Higher Every 2 Weeks



A = serum M component; B = urine M component; C = free light chains (FLC).
One patient at 3 mg/kg and 20 mg/kg with 0% change; one patient at 20 mg/kg not-evaluable.
Martin TG III et al. ASH Annual Meeting. Abstract 284.

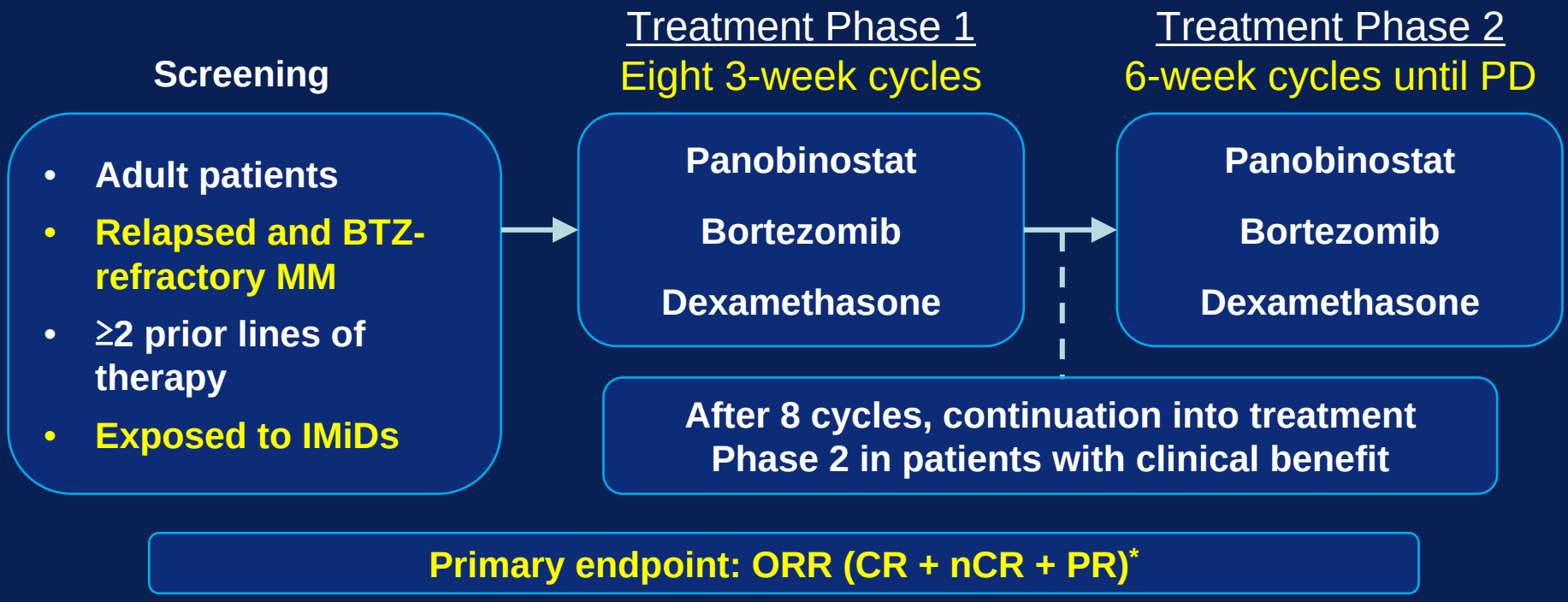
Blockade of Ubiquitinated Protein Catabolism



Tai YT et al. *Cancer Res*. 2005;65:5898-5906; Hideshima T et al. *Clin Cancer Res.* 2005;11:8530-8533. Reproduced with permission from AACR. © 2005; Catley L et al. *Blood*. 2006;108:3441-3449.

PANORAMA 2 Study Design: Phase 2, Simon 2-Stage Study in BTZ-Refractory MM

BTZ-refractory disease defined as relapse on or within 60 days of last BTZ-containing line of therapy[1]



*Response measured according to modified European Group for Blood and Marrow Transplantation 1998 criteria.

1. Anderson KC et al. *Leukemia*. 2008;22:231-239; Richardson PG et al. ASH 2011 Annual Meeting Abstract 814.

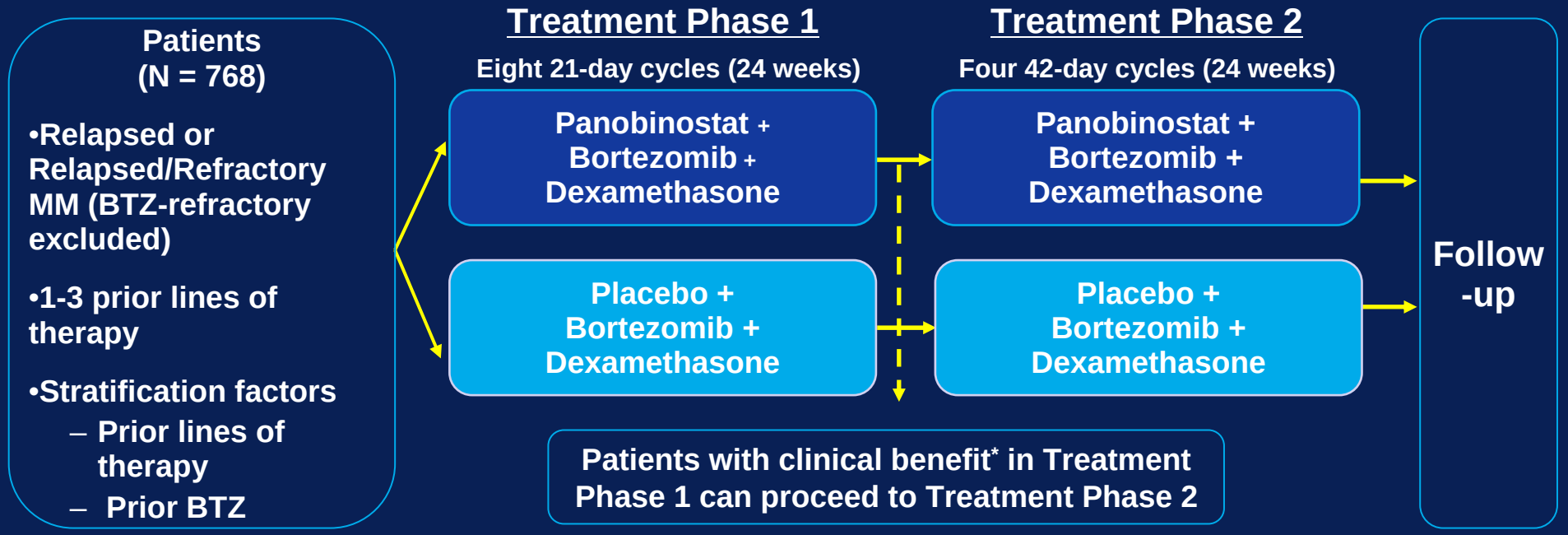
Preliminary Response Data: Activity in Patients With Bortezomib-Refractory MM

Best confirmed response (confirmed at 6 weeks)	N = 55
Overall response (CR + nCR + PR)	16 (29%)
Complete response	–
Near complete response	2 (4%)
Partial response	14 (25%)
Clinical benefit (CR + nCR + PR + MR)	27 (49%)
Minimal response	11 (20%)
VGPR	3 (6%)

- Responses were typically observed after 1 to 2 cycles
- Stable disease observed in 2 patients; progressive disease in 10 patients

Richardson PG et al. ASH 2011 Annual Meeting Abstract 814.

PANORAMA 1 Study Design: Randomized, Double-Blind, Phase 3 Study in Relapsed or RRMM



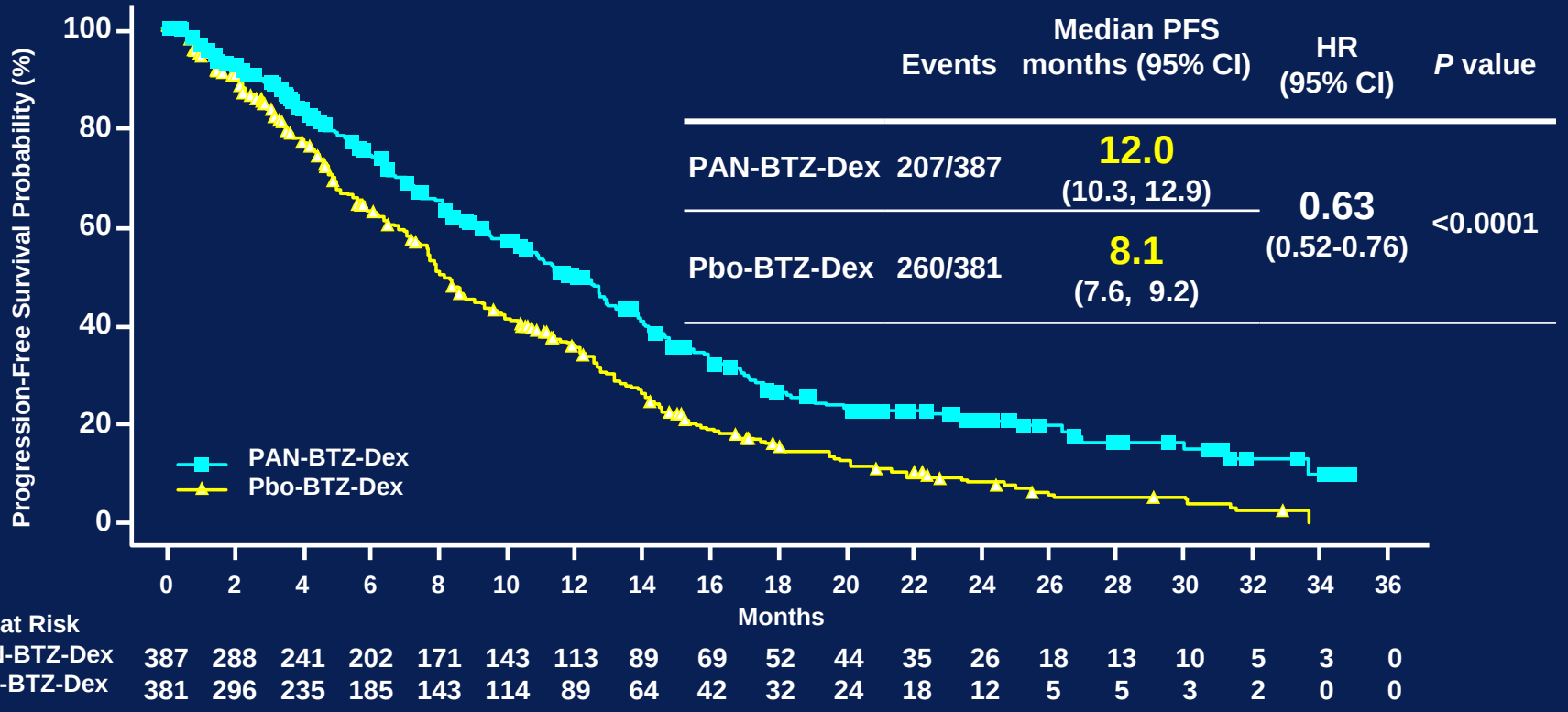
Study conducted at 215 centers across 34 countries

- **Primary endpoint: PFS (per modified EBMT criteria; confirmed by IRC)[1,2]**
- **Key secondary endpoint: OS**
- **Other secondary endpoints: ORR, nCR/CR rate, DoR, TTR, TTP, QoL, and safety**

*Achieving ≥no change according to modified EBMT criteria (SD or better).

1. Blade J et al. *Br J Haematol*. 1998;102:1115-1123.
2. Richardson PG et al. *N Engl J Med*. 2003;348:2609-2617.
Richardson PG et al. ASCO 2014 Annual Meeting. Abstract 8510.

PANORAMA 1: Primary Endpoint Met (PFS)



	Events	Median PFS months (95% CI)	HR (95% CI)	*P* value
PAN-BTZ-Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	<0.0001
Pbo-BTZ-Dex	260/381	8.1 (7.6, 9.2)		

- **Primary endpoint was met (*P*<0.0001), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm**

Richardson PG et al. ASCO 2014 Annual Meeting. Abstract 8510.

Conclusions

- Prolonged duration of therapy results in longer remission duration and potentially improved overall survival.
  - FIRST Trial
  - Maintenance therapy post transplant
- Combination therapy results in improved progression free survival and potentially overall survival.
  - ASPIRE Trial
  - Clonal Tides Theory
- Novel agents will help transform relapsed/refractory disease.
  - Oral proteasome inhibitors
  - Monoclonal antibodies