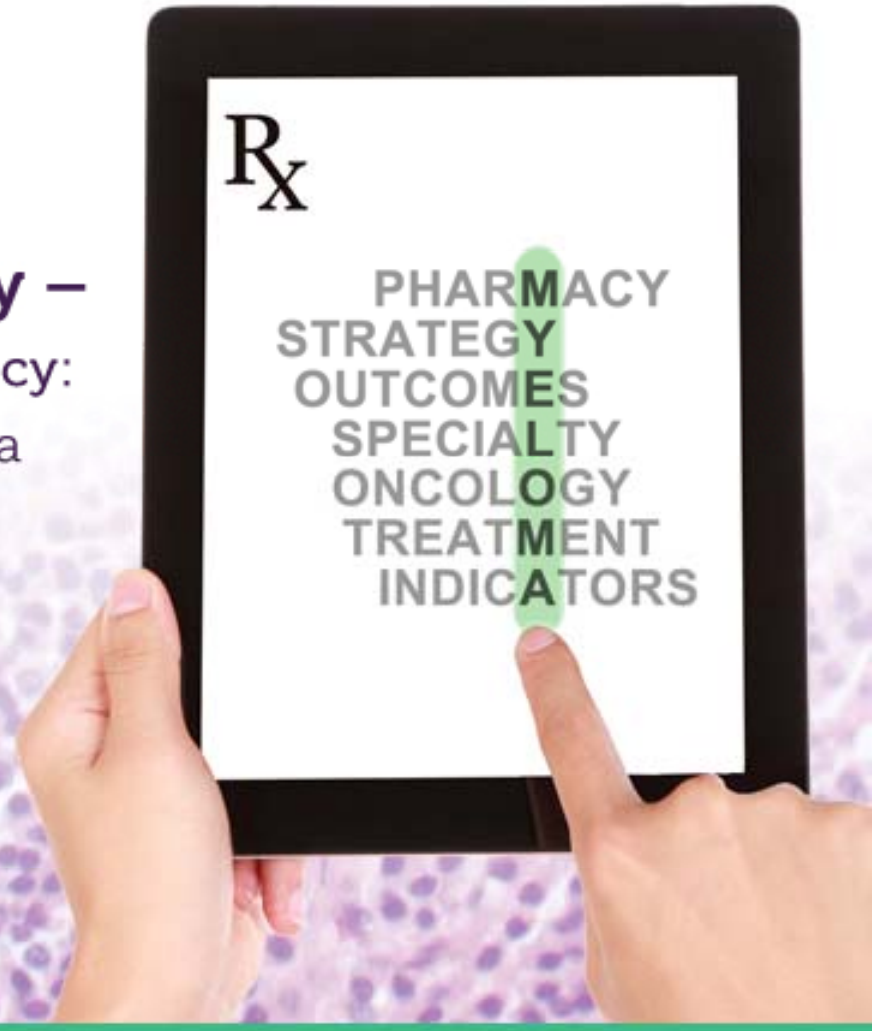
Applying a Congruent Oncology Pharmacy Strategy –

From Guidelines to Specialty Pharmacy:

Steps for Success with Multiple Myeloma



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ONYX Celgene Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

Educational Objectives

- Review current and emerging clinical data to optimize therapeutic decision-making based on indicators of efficacy outcomes for MM treatments
- Demonstrate the use of CER as a decision-support tool to appropriately invest resources and reduce treatment variability with MM therapies
- Recommend methods to improve MM patient outcomes with supportive care within a health plan setting
- Evaluate innovative oncology pharmacy benefit models and specialty management services
- Provide accurate and appropriate counsel as part of the managed care treatment team

Agenda

1:30 PM	**Introduction and Pre-Activity Assessment** *James Kenney, Jr., RPh, MBA*
1:35 PM	**Optimizing Therapeutic Decision-Making for Multiple Myeloma: Classifying Indicators of Outcomes** *Amrita Y. Krishnan, MD, FACP*
2:20 PM	**Decision-Support Tools to Reduce Treatment Variability and Optimize Costs** *James Kenney, Jr., RPh, MBA*
3:00 PM	**Collaborating to Improve Supportive Care Outcomes for Patients with Multiple Myeloma** *Sandra Kurtin, RN, MS, AOCN®, ANP-C*
3:40 PM	**Oncology Pharmacy Benefit Models and Specialty Management Services** *Atheer Kaddis, PharmD*
4:25 PM	**Question and Answer Session**
4:55 PM	**Closing Remarks** **Post-Activity Assessment and Evaluation**

Optimizing Therapeutic Decision-Making for Multiple Myeloma: Classifying Indicators of Outcomes

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Disclosures

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Amrita Y. Krishnan, MD, FACP

  – *Consulting Fees:* Onyx Pharmaceuticals, Celgene Corporation, and Sanofi-Aventis

  – *Fees for Non-CME/CE Services:* Onyx Pharmaceuticals, Celgene Corporation, and Millennium: The Takeda Oncology Company

  – *Ownership Interest:* Celgene Corporation

Outline

- Multiple Myeloma (MM): Definition and Description
- Principles of MM Management
  - NCCN guidelines
  - Indicators of Treatment Outcomes
  - Risk Stratification and Staging
- Treatment of MM
  - Initiating treatment
  - When to transplant
  - Post-transplant therapy
  - How to treat relapse
- Summary

Definition and Description

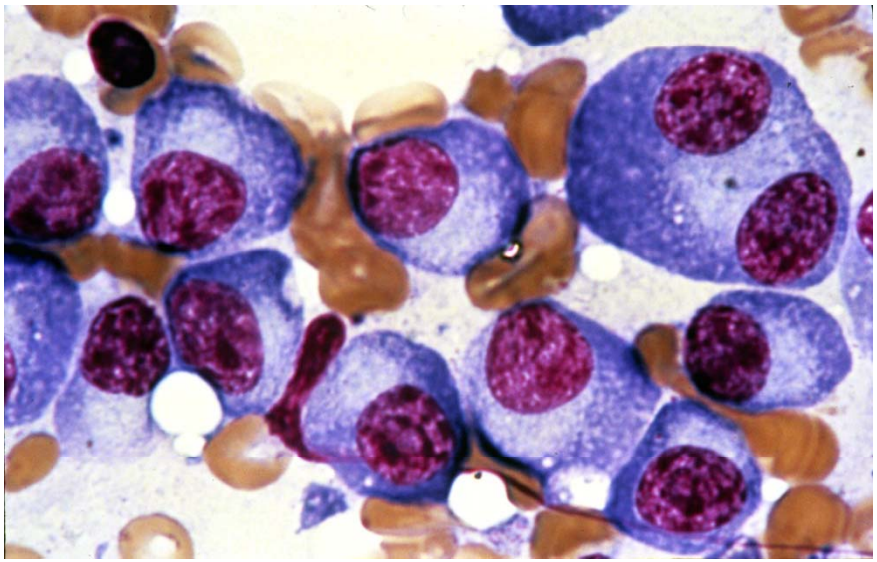
Prevalence and Burden of Multiple Myeloma

- 22,350 new cases and 10,710 deaths from MM are projected for the United States in 2013[1]
  - Accounts for 1% of all malignancies and about 10% of hematological cancers[2]
  - Accounts for 2% of deaths from all cancers and 20% of deaths from hematological cancers[2]
- **Slightly more common in men than women[3]**
- **Incidence in African Americans is about twice that of whites[3]**
- Median age at diagnosis is 69 years for men and 71 years for women[3]
  - Age <50 years: 10%
  - Age <40 years: 2%

1. American Cancer Society. http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics. Accessed February 15, 2013.
2. Siegel R, et al. *CA Cancer J Clin*. 2012;62:10–29.
3. American Cancer Society. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Accessed February 15, 2013.

Features of Multiple Myeloma

- B-cell malignancy derived from antibody-producing plasma cells in the bone marrow
- Proliferation of myeloma cells leads to
  - Excessive production of a monoclonal antibody (M-protein)
  - Adverse events on various organ systems

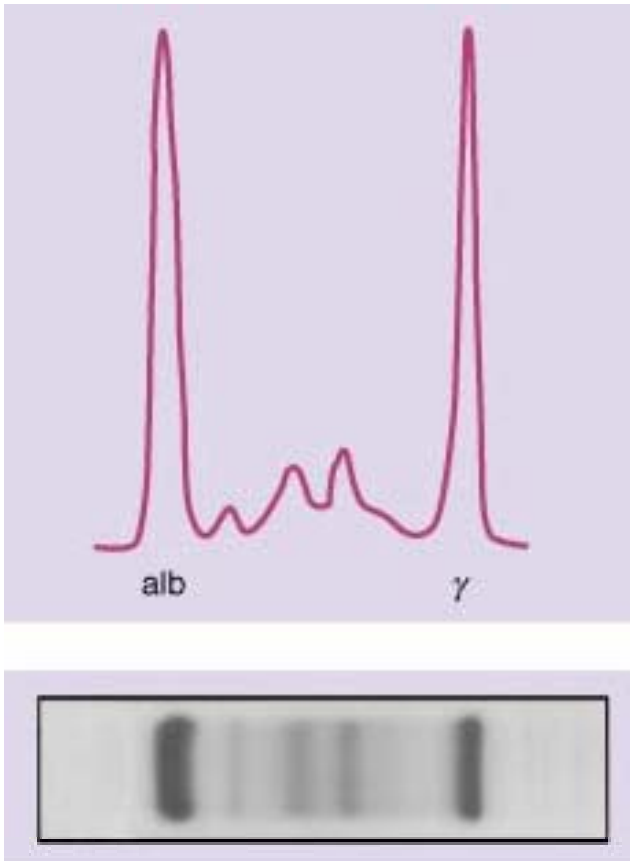


Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

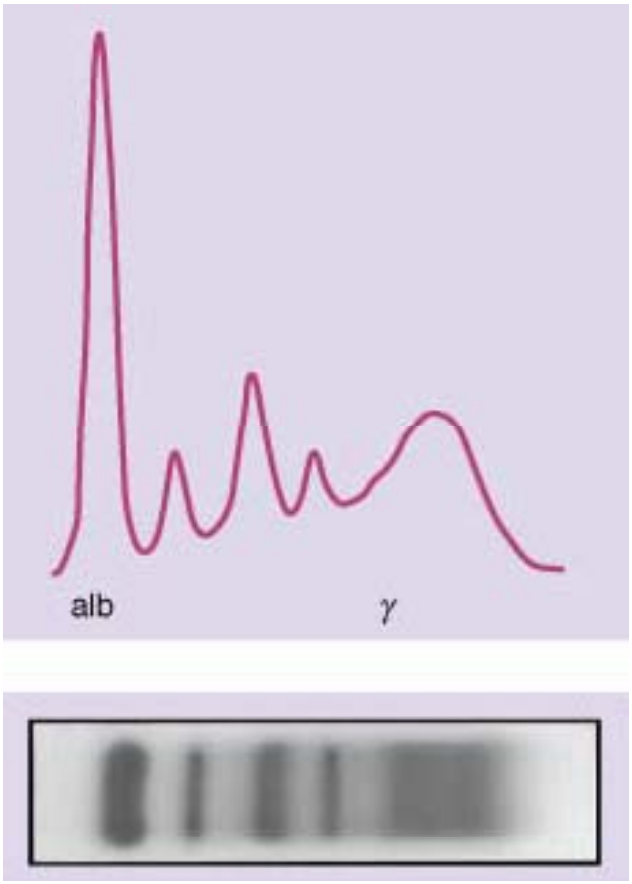
In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E III, eds. *Cancer Medicine, 6th Ed.*, *Vol. I*. Hamilton, Ontario: B.C. Decker. 2003;2219.
Durie BG. Concise review of the disease and treatment options: Multiple Myeloma. International Myeloma Foundation. 2011/2012. Available at: http://myeloma.org/pdfs/CR2011-Eng_b1.pdf. Accessed February 15, 2013.

Serum Protein Electrophoresis

Normal



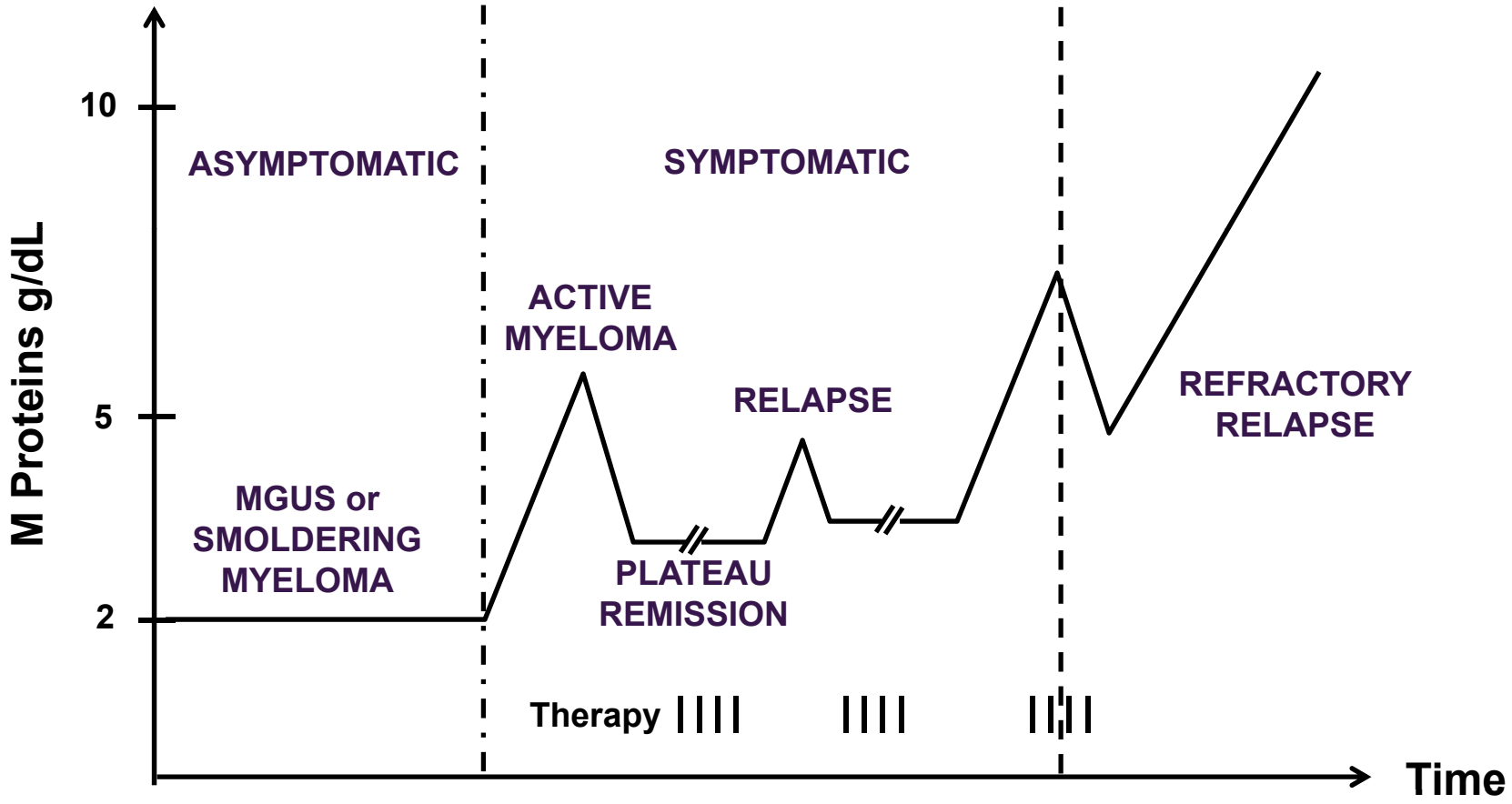
Monoclonal Protein in Myeloma



Kyle RA, Rajkumar SV. Plasma cell disorders. In: Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine, 22nd ed.* Philadelphia: WB Saunders; 2004:1184-1195.

Principles of Multiple Myeloma Management

MM Follows a Course of Response and Remission

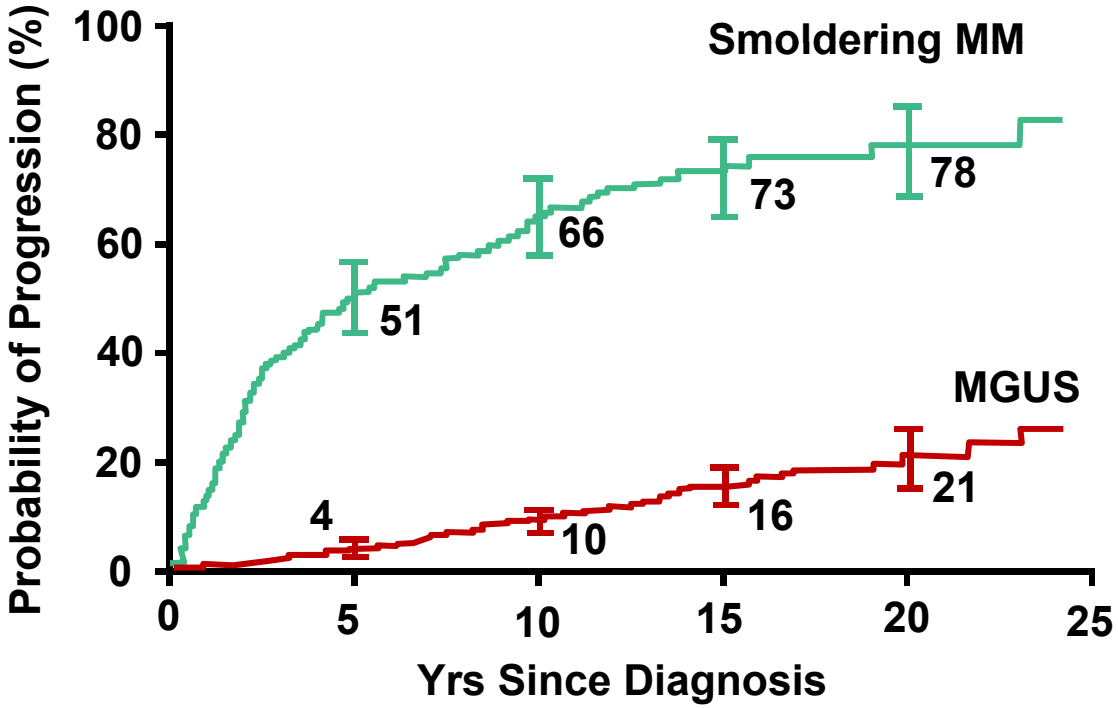


MGUS=monoclonal gammopathy of unknown significance.

Durie BG. Concise review of the disease and treatment options: Multiple Myeloma. International Myeloma Foundation. 2011/2012. Available at: http://myeloma.org/pdfs/CR2011-Eng_b1.pdf. Accessed February 15, 2013.

Progression to Symptomatic MM

- **MGUS: Up to 3% of persons 50 years of age or older and ~ 6% of those older than 70 years**
- **For asymptomatic myeloma, maximum risk in the first 5 years**

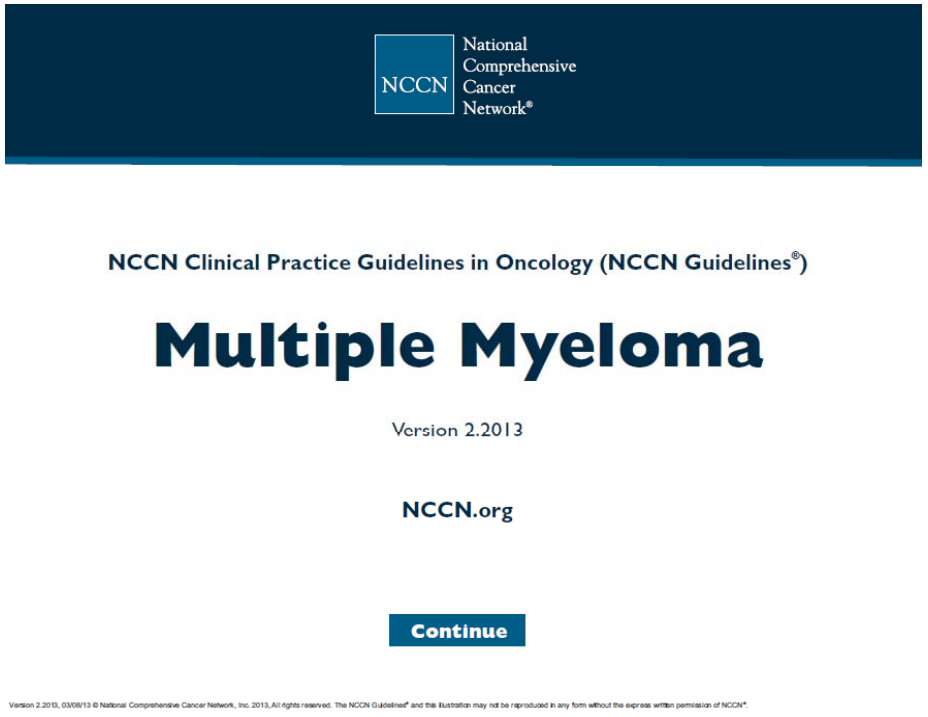


MGUS=monoclonal gammopathy of unknown significance.

Kyle RA, et al. *N Engl J Med*. 2007;356:2582-2590.
Greipp PR, et al. *J Clin Oncol*. 2005;23:3412-3420.

NCCN Clinical Practice Guidelines Provide Evidence-Based Direction to MM Care

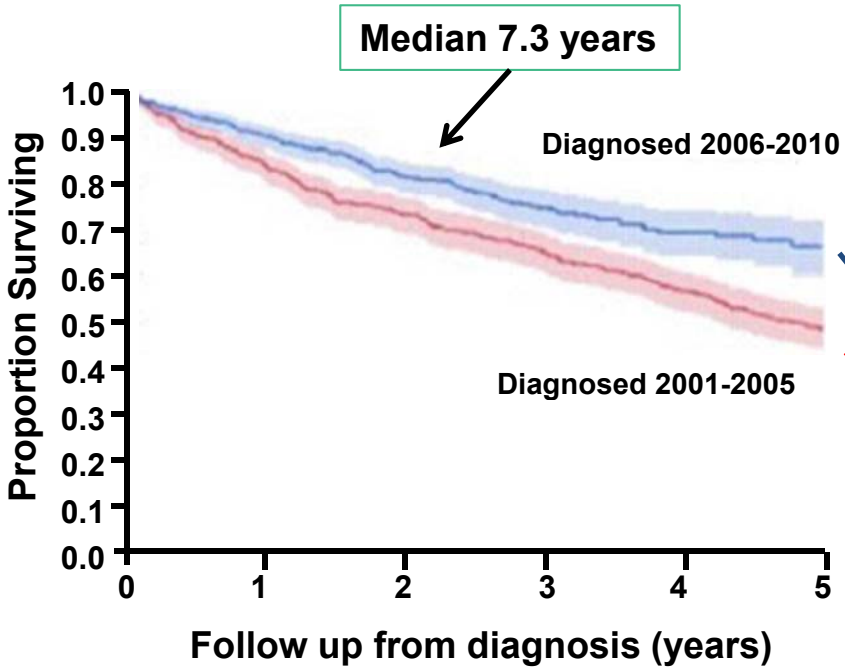
- Includes standards for diagnosis, prognosis, treatment, and follow-up
- Comprehensive guidance across the natural history of the disease
- Identifies primary treatment modalities
- Includes supporting references, background information, and discussion of ongoing controversies
- Integrates clinical data and expert judgment



NCCN=National Comprehensive Cancer Network.

National Comprehensive Cancer Network. Available at: NCCN.org.

MM Survival is Improving



5 Year Survival by Age

	≤ 65 years	> 65 years
2006-2010	73%	56%
2001-2005	63%	31%

Kumar SK, et al. Continued improvement in survival in multiple myeloma and the impact of novel agents. Presented at the American Society of Hematology Annual Meeting. Atlanta, GA. 2012. Abstract 3972.

Trial Endpoints Beginning to Influence MM Reimbursement Decisions

- Payers are increasingly insisting that agents and regimens demonstrate improvement in outcomes before their cost will be fully reimbursed
- Overall Survival (OS) has historically been the gold standard endpoint for a new oncology drug approval
- Recently, approval has been based on surrogate endpoints, including objective response rate (ORR), progression-free survival (PFS), disease-free survival (DFS), and time to progression (TTP)
  - However, surrogate endpoints do not always translate into a survival benefit as long-term data mature
- Use of different endpoints makes the practice of comparing therapies difficult

Kenney JT. *Value-based Healthcare Design*. 2011;2:54.

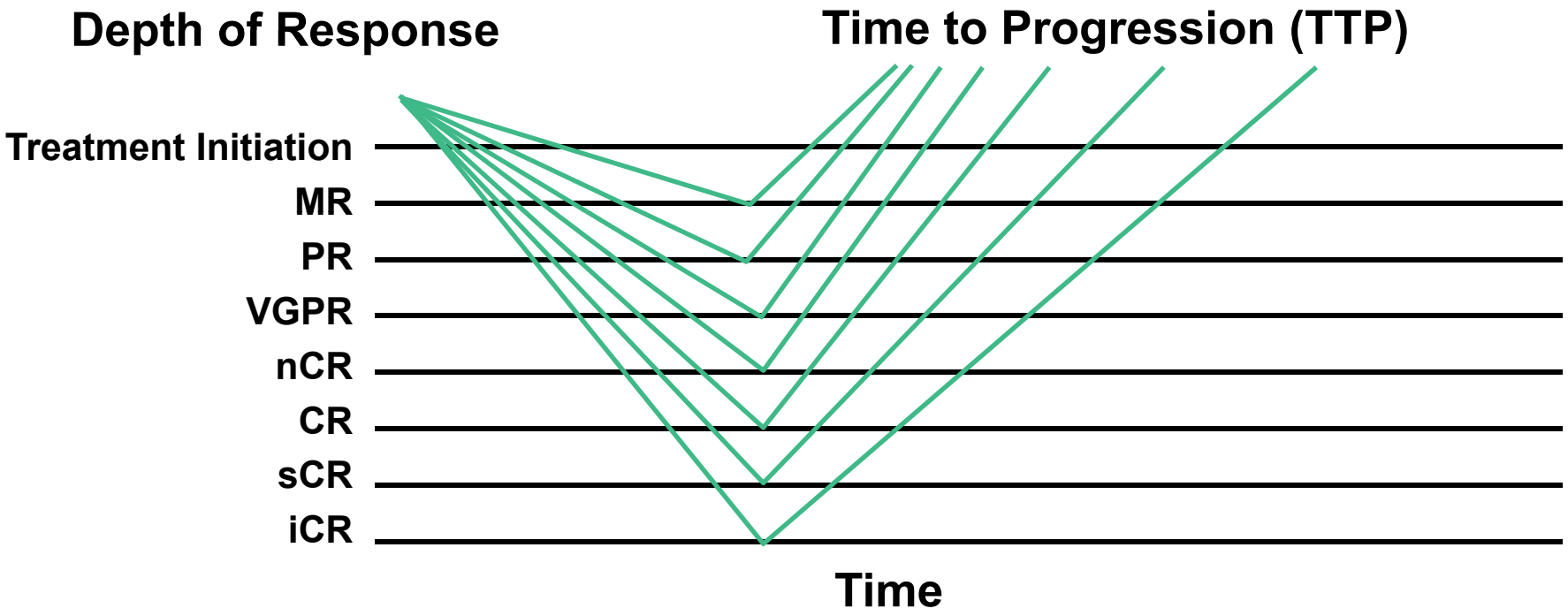
Multiple Myeloma Response Criteria

Overall response rate

Response category	Response criteria
Stringent complete response (sCR)	• CR as defined below plus: • Normal free light chain ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow
Very good partial response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hr
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24 hr urinary M-protein by ≥90% or to <200mg per 24 hr
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24 hr urine M-protein by 50%-89%

Durie BG, et al. *Leukemia*. 2006;20:1467-1473.
Rajkumar SV, et al. *Blood*. 2011;117:4691-4695.

Which Disease Response Criteria is Best?



Depth of response is related to TTP

TTP=time to progression; MR=minimal response; PR=partial response; VGPR=very good partial response; nCR=near complete response; CR=complete response; sCR=stringent complete response; iCR=initial complete response.

Adapted from: Niesvizky R, et al. *Br J Haematol*. 2008;143:46-53; Harousseau J-L, et al. *Blood*. 2009;114:3139-3146; Chanan-Khan AA, et al. *J Clin Oncol*. 2010;28: 2612-2624.

Staging of MM: Key Components

ISS Stage	Criteria	Median Overall Survival (mo)
I	Serum β2-microglobin <3.5 mg/dL AND Serum albumin ≥3.5 g/dL	62
II*	Neither Stage I nor Stage II	44
III	Serum β2-microglobin ≥5.5 mg/dL	29

*There are 2 categories for Stage II: serum b2-microglobin <3.5 mg/dL, but serum albumin <3.5 g/dL, or serum b2-microglobin <3.5 to <5.5 mg/dL, irrespective of the serum albumin level.

ISS=International Staging System.

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

Risk-Stratification Based on Tumor Biology

High Risk*	Intermediate Risk	Standard Risk
• 17p deletion • t(14;16) (C-MAF) • t(14;20) (MAF-B) • GEP	• **t(4;14)** (FGFR3/MMSET)	All others including: • Hyperdiploidy • t(11;14) (CCND1) • t(6;14) (CCND3)
Complete Response appears critical	Bortezomib critical	Excellent outcome

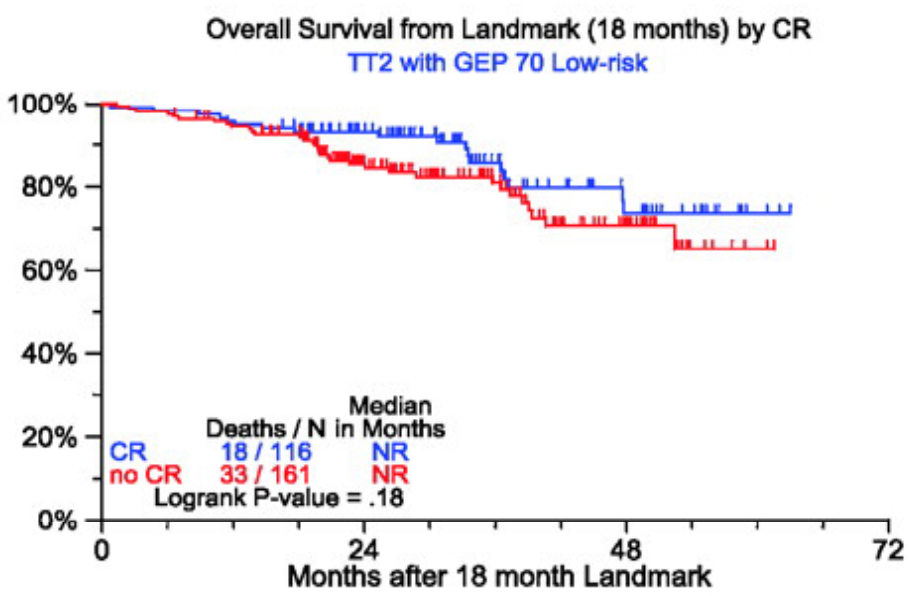
*Presence of trisomies ameliorates high risk.

C-MAF=cellular musculoaponeurotic fibrosarcoma oncogene homolog; MAF-B=musculoaponeurotic fibrosarcoma oncogene homolog B; GEP=gene expression programming; FGFR3=fibroblast growth factor receptor 3; MMSET=multiple myeloma set domain; CCND1= cyclin D1; CCND3= cyclin D3.

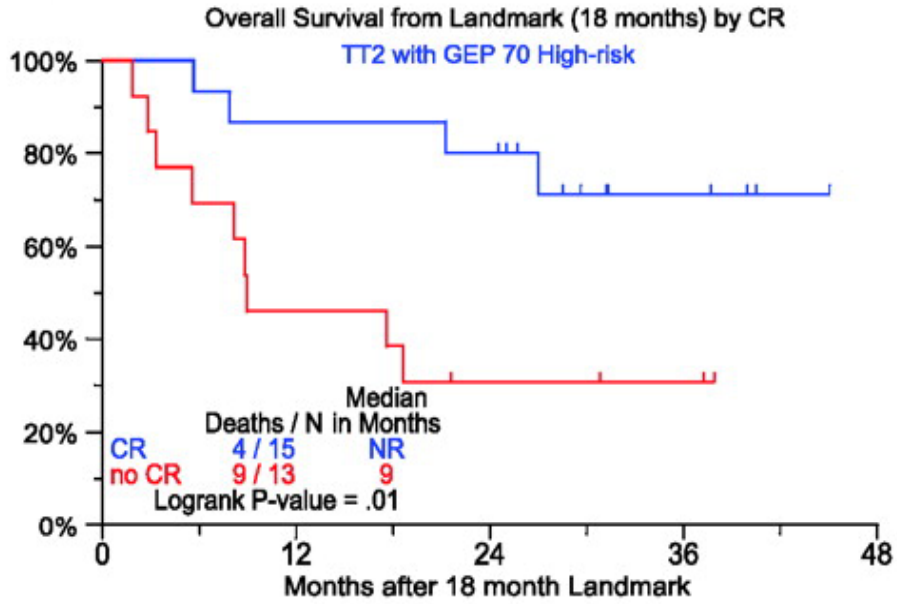
Rajkumar SV. *Am J Hematol.* 2012;87:78-88.

Complete Response (CR) is Critical in Patients With High-Risk Myeloma

Low-Risk MM (87%)



High-Risk MM (13%)

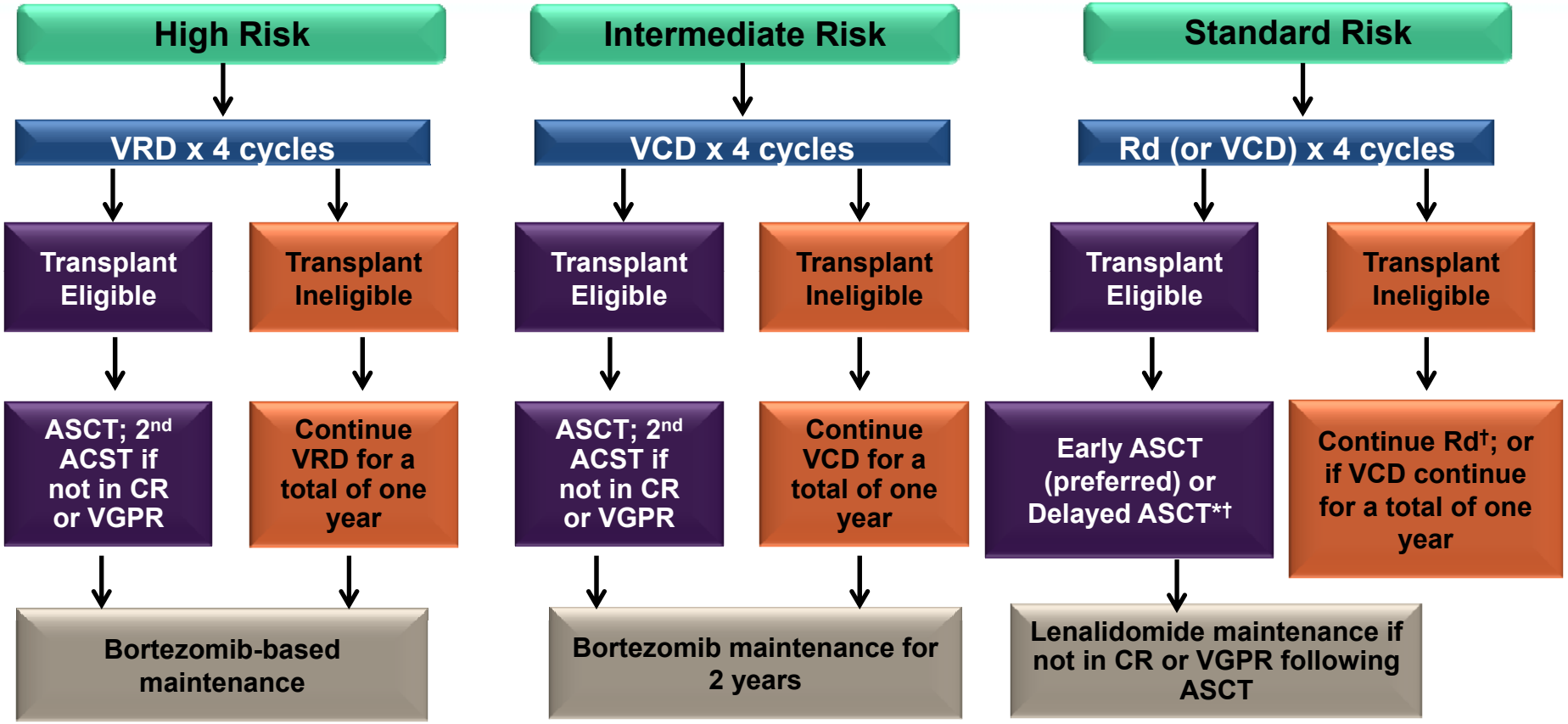


CR=complete response; NR=no response.

Haessler J, et al. *Clin Cancer Res*. 2007;13:7073-7079.

Multiple Myeloma Treatment Strategies

Approach to Newly Diagnosed MM

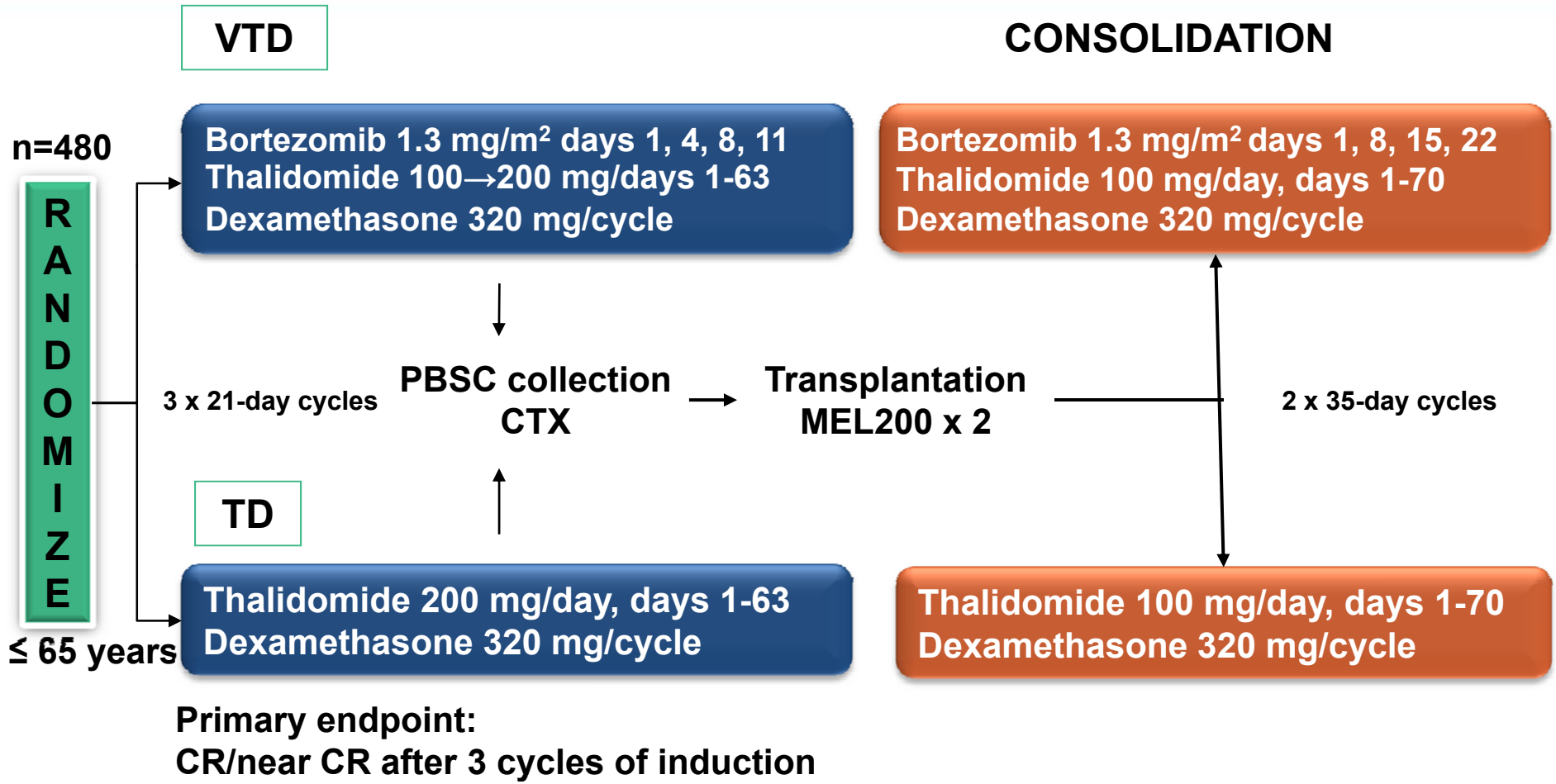


†Dexamethasone usually discontinued after 12 months; continued long-term lenalidomide is an option for patients who tolerate treatment well.

VRD=bortezomib + lenalidomide + dexamethasone; VCD=bortezomib + carfilzomib + dexamethasone; Rd=lenalidomide + low dose dexamethasone; ASCT=autologous stem cell transplant; CR=complete response; VGPR=very good progressive response.

Rajkumar SV. *Am J Hematol*. 2012;87:79–88.

VTD vs TD After Double ASCT in Newly Diagnosed MM

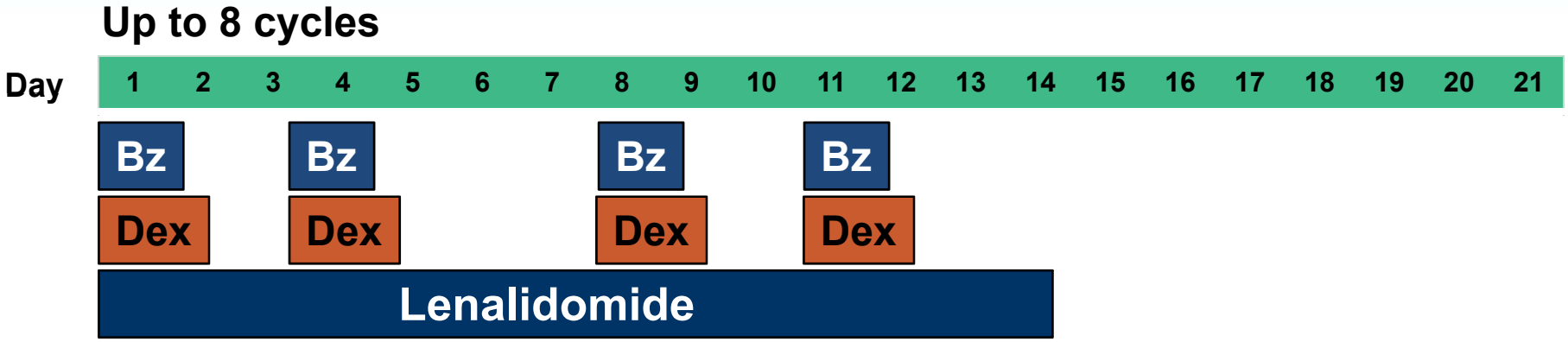


Primary endpoint:
CR/near CR after 3 cycles of induction

VTD=bortezomib + thalidomide + dexamethasone; TD=thalidomide + dexamethasone;
PBSC=peripheral blood stem cell; CTX=cyclophosphamida; MEL200=melphalan 200 Mg/m2; CR=complete response.

Cavo M, et al. *Lancet*. 2010; 376: 2075–2085.

VRD Phase Combination Therapy in Newly Diagnosed MM: Phase I/II Trial



- MTD based on phase I: lenalidomide 25 mg/day; bortezomib 1.3 mg/m2; dexamethasone 20 mg/day, cycles 1–4, 10 mg/day, cycles 5–8
- Antithrombotic therapy: Aspirin 81–325 mg daily; Acyclovir or equivalent for HZV prophylaxis
- With a median follow up of 27.3 months TTP, PFS, and OS have not been reached
  - 18-month PFS: 75%
  - 24-month OS: 97%

VRD=bortezomib (Bz) + lenalidomide + dexamethasone (Dex); MTD=maximum tolerable dose; HZV=herpes zoster virus; TTP=time to progression; PFS=progression-free survival; OS=overall survival.

Richardson PG, et al. *Blood*. 2010;5:679-696.

Best Response to VRD

Response	All Patients (n=66)	Phase II (n=35)
	n (%)	n (%)
CR	19 (29)	13 (37)
nCR	7 (11)	7 (20)
VGPR	18 (27)	6 (17)
PR	22 (33)	9 (26)
CR + nCR	26 (39)	20 (57)
(90% CI)	(29, 50)	(42, 71)
CR + nCR + VGPR	44 (67)	26 (74)
(90% CI)	(56, 76)	(59, 86)
At least PR	66 (100)	35 (100)
(90% CI)	(96, 100)	(92, 100)

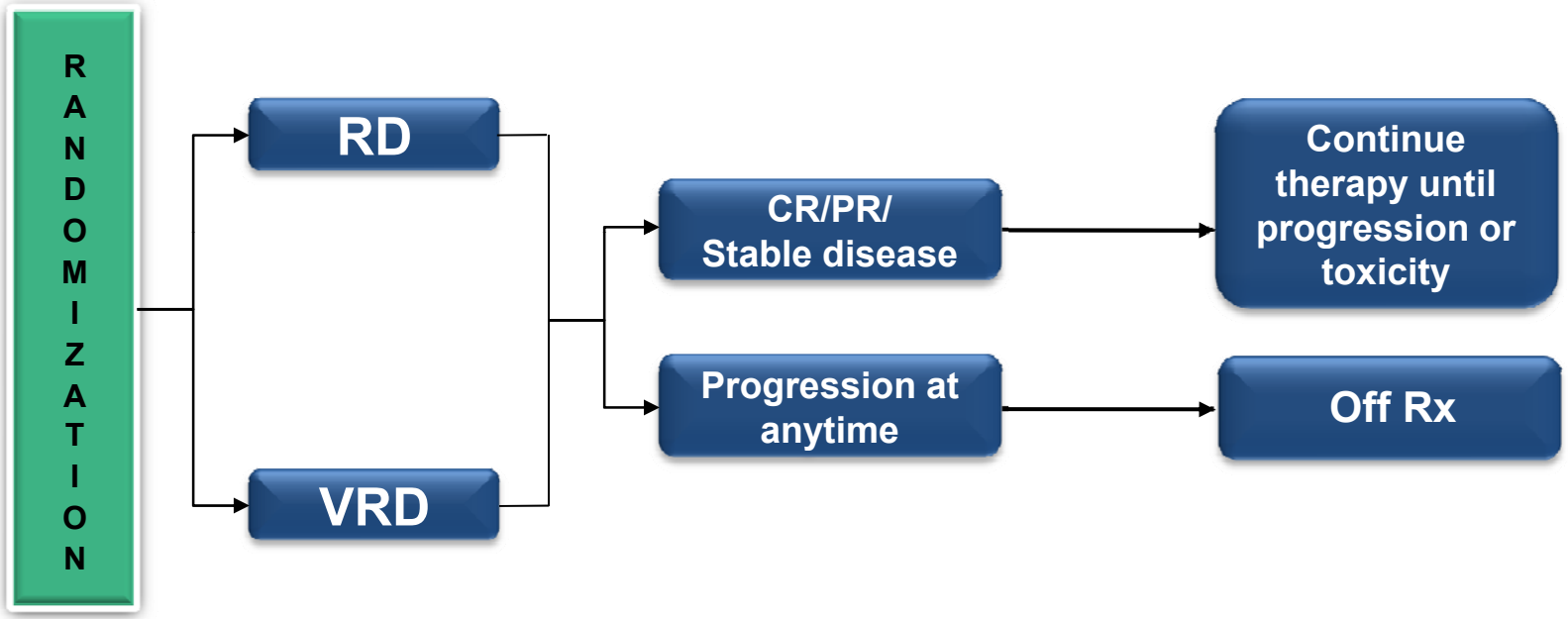
- Response improvement seen in 42/56 patients (75%) from Cycle 4–8 and 20/38 patients (53%) beyond Cycle 8
- Median (range time) to best overall response was 2.1 (0.6, 20) months

VRD=bortezomib + lenalidomide + dexamethasone; CR=complete response; nCR=near complete response; VGPR=very good partial response; PR=partial response; CI=confidence interval.

Richardson PG, et al. *Blood*. 2010;5:679-696.

Evaluation of the 3 Drug Combination VRD in Newly Diagnosed MM

SWOG/ECOG S0777: Phase III Newly Diagnosed MM



- **Primary Objective: Compare progression-free survival of patients with newly diagnosed MM treated with lenalidomide and low-dose dexamethasone with or without bortezomib.**
- **n=440**

VRD=bortezomib + lenalidomide + dexamethasone; SWOG=Southwest Oncology Group; ECOG=Eastern Cooperative Oncology Group; RD= lenalidomide + dexamethasone; CR=complete response; PR=partial response.

Clinical Trials.gov. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00644228?term=swog+AND+s0777&rank=1.

Bortezomib Induction with CyBorD in Newly Diagnosed MM

	CyBorD	Modified CyBorD
Response ITT	**n=33**	**n=30**
ORR (≥ PR)	**88%**	**93%**
≥ VGPR	**61%**	**60%**
CR/nCR	**39%**	**40%**
Toxicity		
Grade 3 AE	**48%**	**37%**
Grade 4 AE	**12%**	**3%**
PN Grades 1/2	**58%**	**57%**
PN Grade 3	**6%**	**0%**

- CyBorD: cyclophosphamide 300mg/m2 orally on days 1, 8, 15 and 22, bortezomib 1.3mg/m2 IV on days 1, 4, 8 and 11, and dexamethasone 40 mg orally on days 1–4, 9–12 and 17–20 on a 28-day cycle for 4 cycles
- Modified CyBorD: cyclophosphamide, weekly bortezomib, and reduced-dose dexamethasone

ITT=intention to treat; ORR=objective response rate; PR=partial response; VGPR=very good partial response; CR=complete response; nCR=near complete response.

Reeder CB, et al. *Leukemia.* 2009;23:1337-1341.

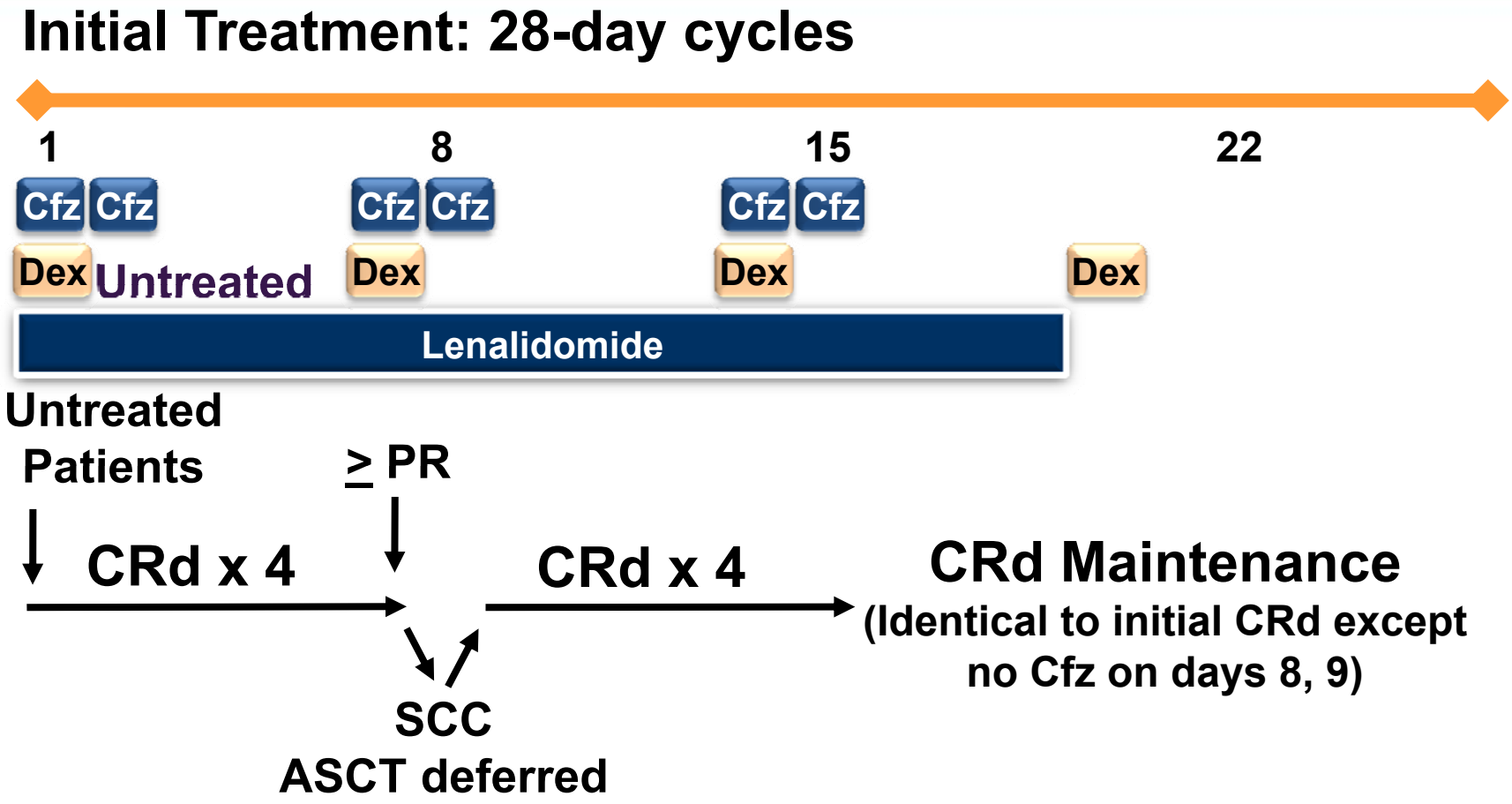
EVOLUTION Trial: VRD vs VCD vs VDCR in Previously Untreated MM

	Response (%)		
	VDCR (n=48)	VRD (n=42)	VCD (n=50)
CR	25%	24%	30%
≥ VGPR	58%	51%	44%
ORR (≥ PR)	88%	85%	82%

VRD=bortezomib + lenalidomide + dexamethasone; VCD=bortezomib + carfilzomib + dexamethasone; VDCR=bortezomib + dexamethasome + carfilzomib + lenalidomide; CR=complete response; VGPR=very good partial response; ORR=objective response rate; PR=partial response.

Kumar S, et al. *Blood*. 2012;119:4375-4382.

CRd in Newly Diagnosed MM



Dex, 40 mg/day days 1, 8, 15, and 22; 20 mg, cycles 5–8, and maintenance

CRd=carfilzomib (Cfz) + lenalidmide (Len) + dexamethasone (dex); PR=partial response; ASCT=autologous stem cell transplant; SCC=stem cell collection.

Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809.

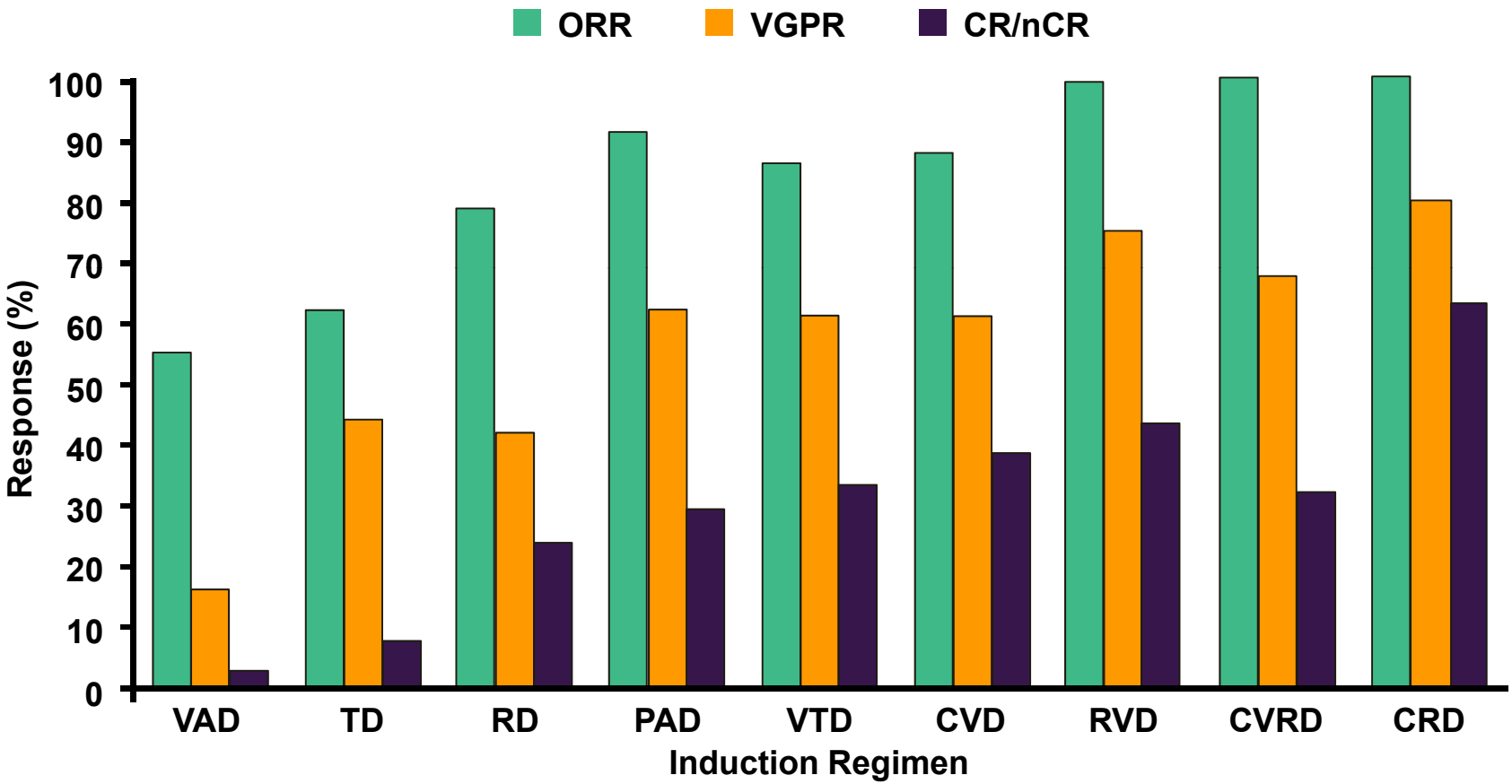
Response to CRd by Cycle

Response, %	2 cycles (n=25)	4 cycles (n=22)	8 cycles (n=12)
sCR/CR/nCR	24	36	67
≥ VGPR	40	59	83
≥ PR	96	100	100

CRd=carfilzomib (Cfz) + lenalidmide (Len) + dexamethasone (dex); sCR=stringent complete response; CR=complete response; nCR=near complete response; PR=partial response; VGPR=very good partial response.

Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809.

Combinations of Newer Agents in the Upfront Treatment of MM Results in Near 100% ORR



ORR=objective response rate; VGPR=very good partial response; CR=complete response; nCR=near complete response; VAD=vincristine + adriamycin + dexamethasone; TD=thalidomide + dexamethasone; RD= lenalidomide + dexamethasone; PAD=bortezomib + adriamycin + dexamethasone; VTD=bortezomib + thalidomide + dexamethasone; CVD=carfilzomib + bortezomib + dexamethasone; RVD=lenalidomide + bortezomib + dexamethasone; CRD= carfilzomib + lenalidomide + dexamethasone.

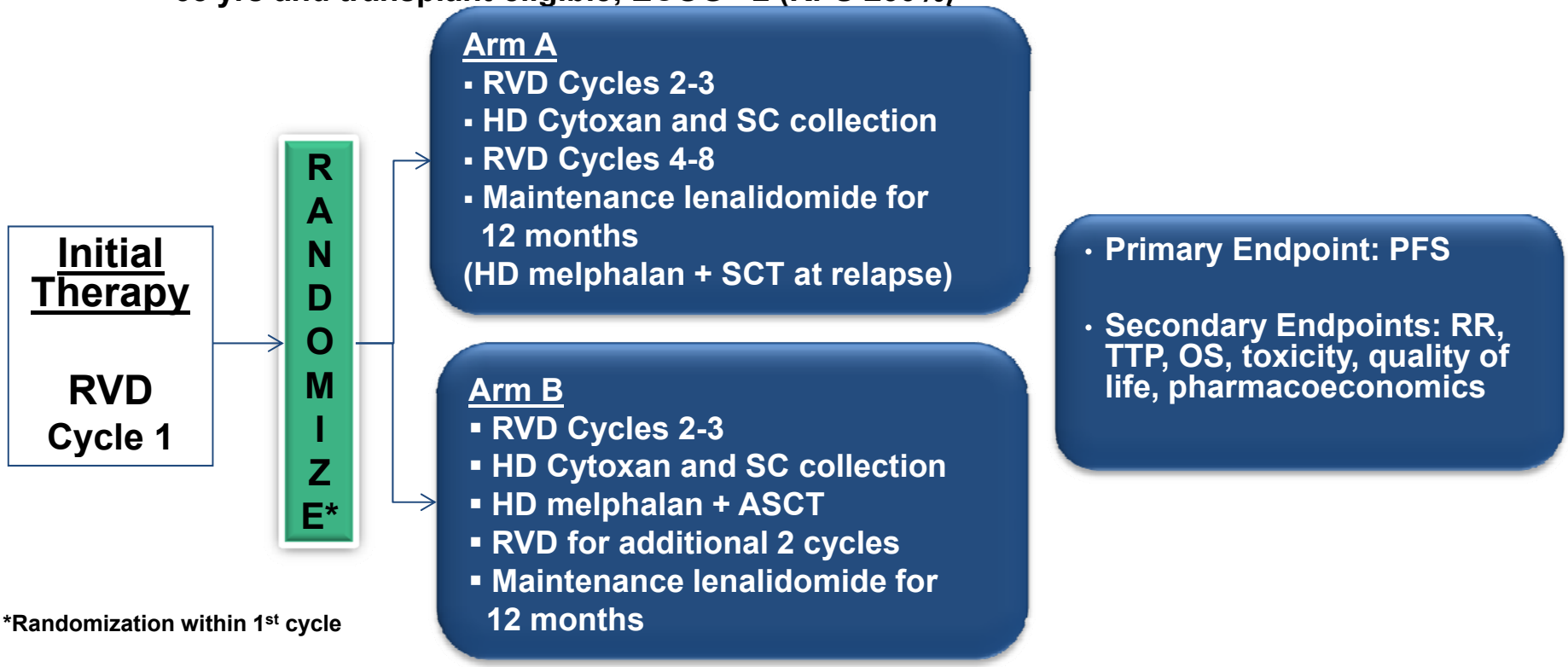
Stewart AK, et al. *Blood.* 2009;24:5436-5444.
Jakubowiak AJ, et al. *Blood*. 2012;120:1801-1809.

Transplant

- When do I take patients to transplant?
- How do I manage poor risk cytogenetics?
- What about maintenance therapy?

IFM DFCI 2009: Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT

- **Randomized, international, phase III trial in previously untreated MM patients who are candidates for HDT-ASCT**
- **Patients: Symptomatic MM with measurable disease**
  - **<65 yrs and transplant-eligible; ECOG <2 (KPS ≥60%)**



*Randomization within 1st cycle

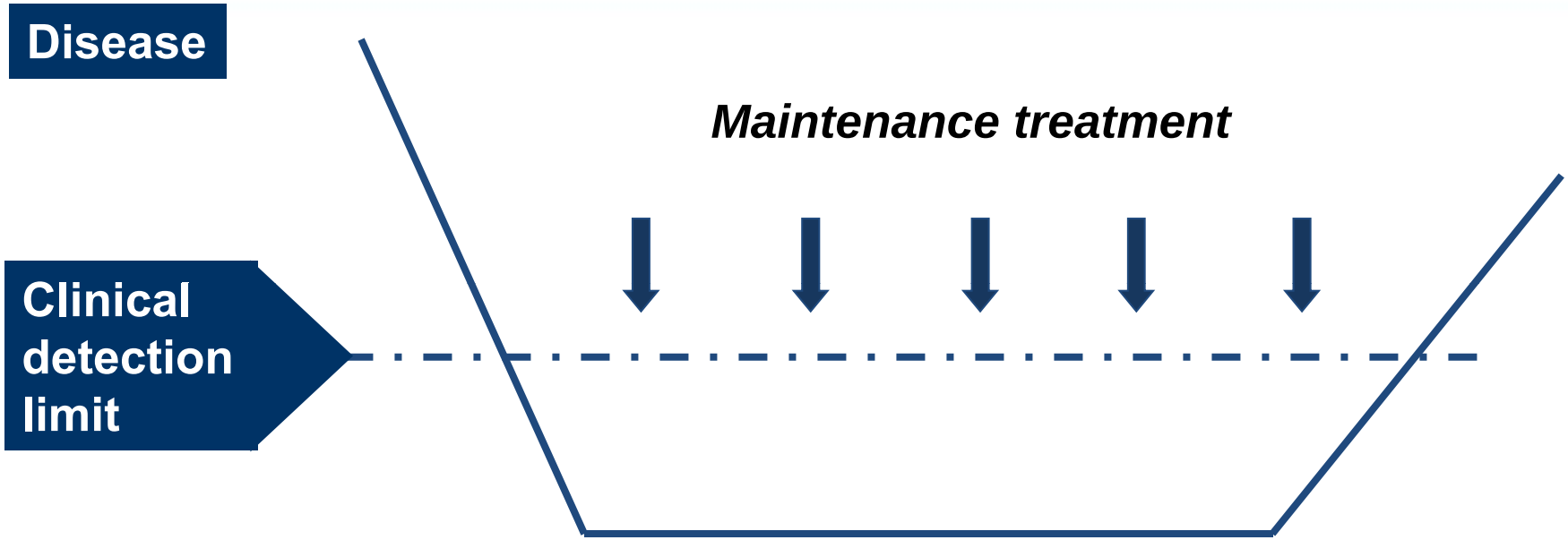
SCT=stem cell transplant; HDT=high-dose therapy; ASCT=autologous stem cell transplantation; ECOG=Eastern Cooperative Oncology Group; RVD=lenalidomide + bortezomib + dexamethasone; HD=high-dose; PFS=progression-free survival; RR=; TTP=time to progression; OS=overall survival.

Clinical Trials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01208662?term=IFM%2Fdfci+2009&rank=1.

Maintenance

- Which patient receives maintenance therapy?
- Which drug should be used?
- How long should maintenance be continued?

Usual Maintenance Scenario

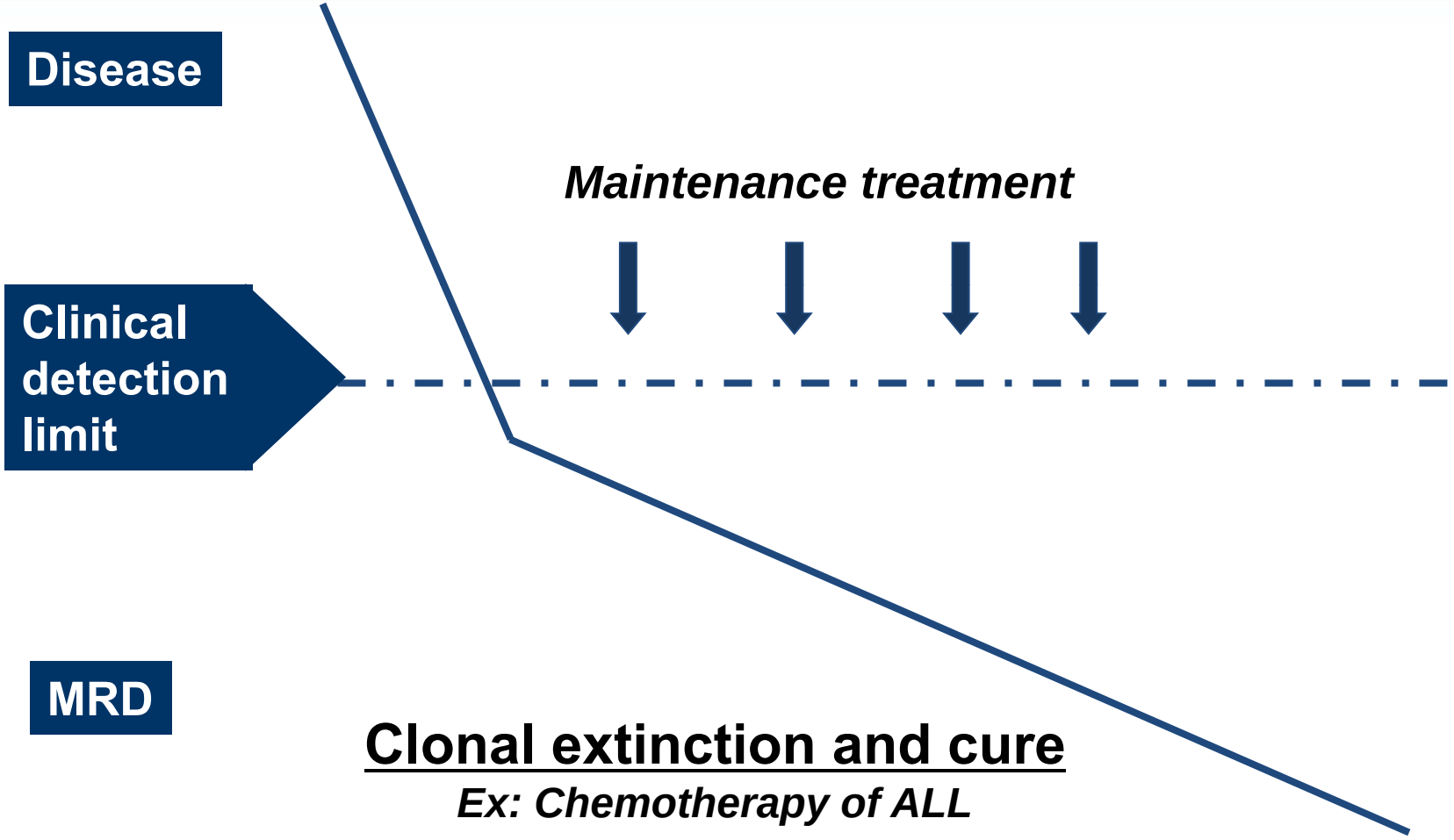


Clonal selection or secondary resistance and relapse
(ex: Imatimib and CML)

MRD=minimal residual disease; CML=chronic myelogenous leukemia.

Adapted from Gareth Morgan.

Ideal Maintenance Treatment



MRD=minimal residual disease; ALL=acute lymphoblastic leukemia.

Adapted from Gareth Morgan.

Overview: Thalidomide Maintenance Studies

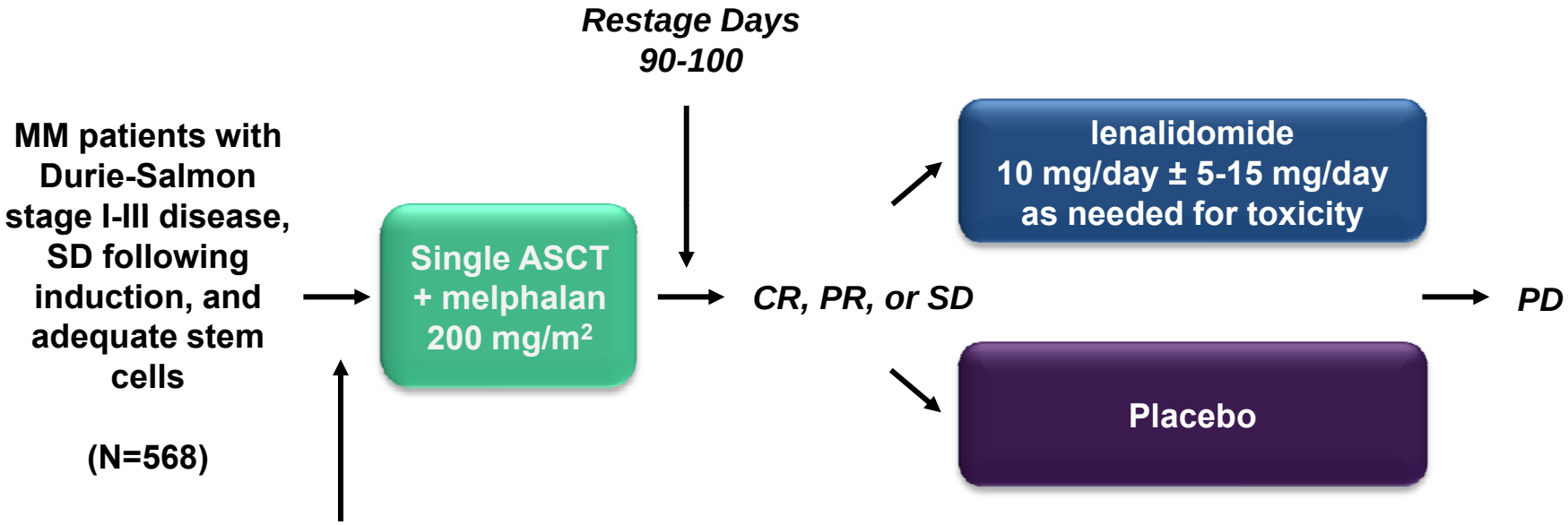
Trial	N	Maintenance	EFS or PFS	OS
IFM 99-02[1]	597	Thal + pamidronate vs no maintenance	3-yr EFS: 52% vs 37%; *P*<.009	4-yr OS: 87% vs 74%; *P*<.04
Spencer, 2009[2]	243	Thal (12 mos) + prednisone vs prednisone	3-yr PFS: 42% vs 23%; *P*<.001	3-yr OS: 86% vs 75%; *P*=.004
Total Therapy 2[3]	668	Thal vs no maintenance, until progression	5-yr EFS: 56% vs 45%; *P*=.0005	5-yr OS: 67% vs 65%, 8-yr OS: 57% vs 44%; *P*=.09
Lokhorst, 2010[4]	556	Thal vs IFN, until progression	Median PFS: 34 vs 25 mos; *P*<.001	Median: 73 vs 60 mos; *P*=NS
Ludwig, 2010[5]	289	Thal + IFN vs IFN, until progression	Median PFS: 27.7 vs 13.2 mos; *P*<.0068	Median: 52.6 vs 51.4 mos; *P*=NS
MRC Myeloma IX[6]	820	Thal vs no maintenance, until progression	Median PFS: 23 vs 15 mos; *P*<.0003	Median: 60 vs 58 mos; *P*=NS

EFS=event-free survival; PFS=progression-free survival; OS=overall survival; Thal=thalidomide; IFM=Intergroupe Francophone du Myélome; IFN=interferon; NS=not significant; MRC=Medical Research Council.

1. Attal M, et al. Blood. 2006;108:3289-3294. 2. Spencer A, et al. *J Clin Oncol*. 2009;27:1788-1793.
3. Barlogie B, et al. *Blood*. 2008;112:3115-3121. 4. Lokhorst HM, et al. *Blood*. 2010;115:1113-1120.
5. Ludwig H, et al. *Haematologica*. 2010;95:1548-1554. 6. Morgan GJ, et al. *Blood*. 2012;119:7-15.

CALGB 100104: Lenalidomide Maintenance vs Placebo

- Randomized, double-blind, placebo-controlled phase III trial

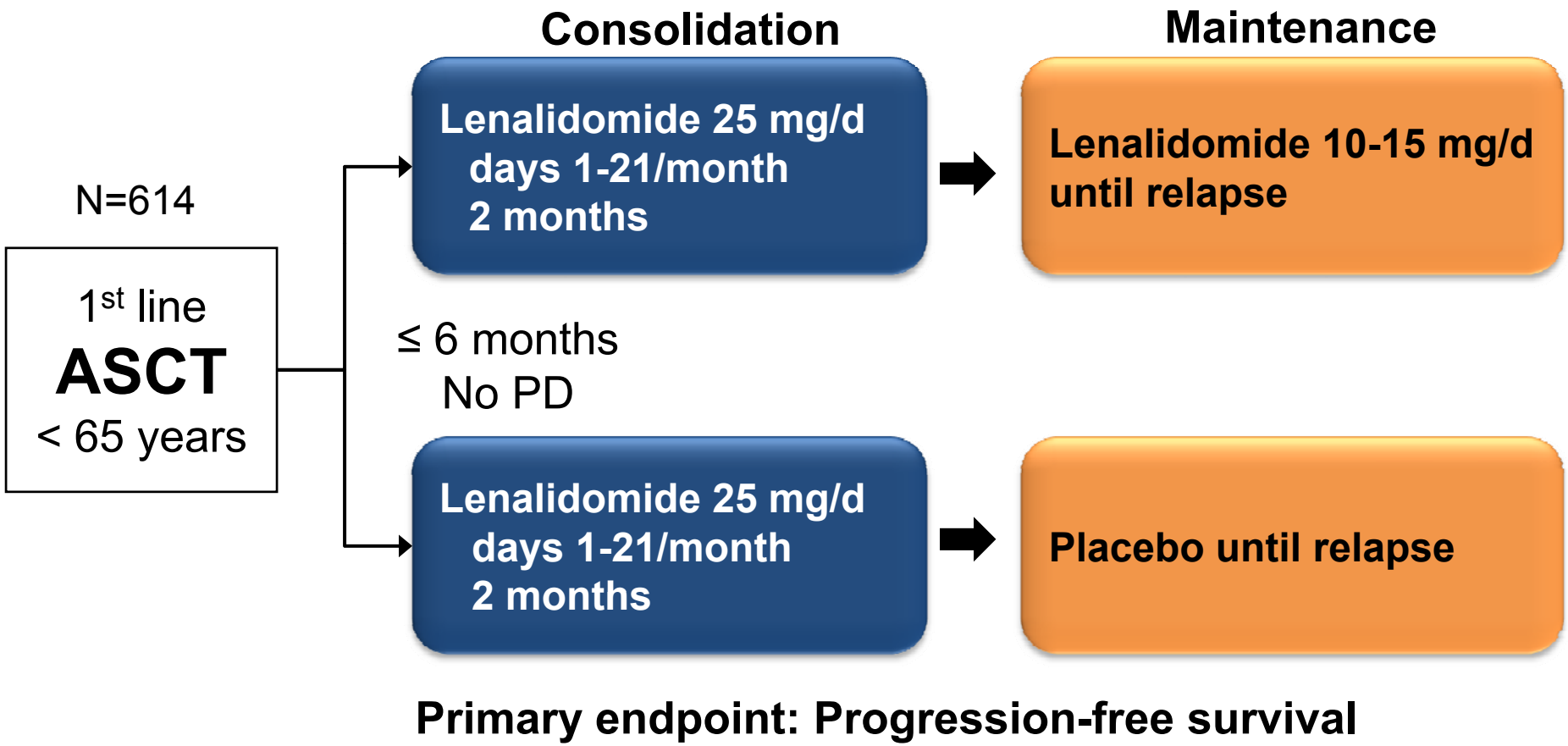


Primary endpoint: TTP following ASCT
Secondary endpoints: CR after ASCT, PFS, OS, feasibility of long-term lenalidomide

SD=stable disease; ASCT=autologous stem cell transplantation; CR=complete response; PR=partial response; PD=progressive disease; TTP=time to progression; PFS=progression-free survival; OS=overall survival.

McCarthy PL, et al. Presented at the American Society of Hematology Annual Meeting. Orlando, FL. 2010. Abstract 37.
McCarthy PL, et al. *N Engl J Med*. 2012;366:1770-1781.

Phase III IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT



ASCT=autologous stem cell transplantation; PD=progressive disease.

Attal M, et al. Presented at the American Society of Hematology Annual Meeting. 2009; abstract 529.

Maintenance with Lenalidomide

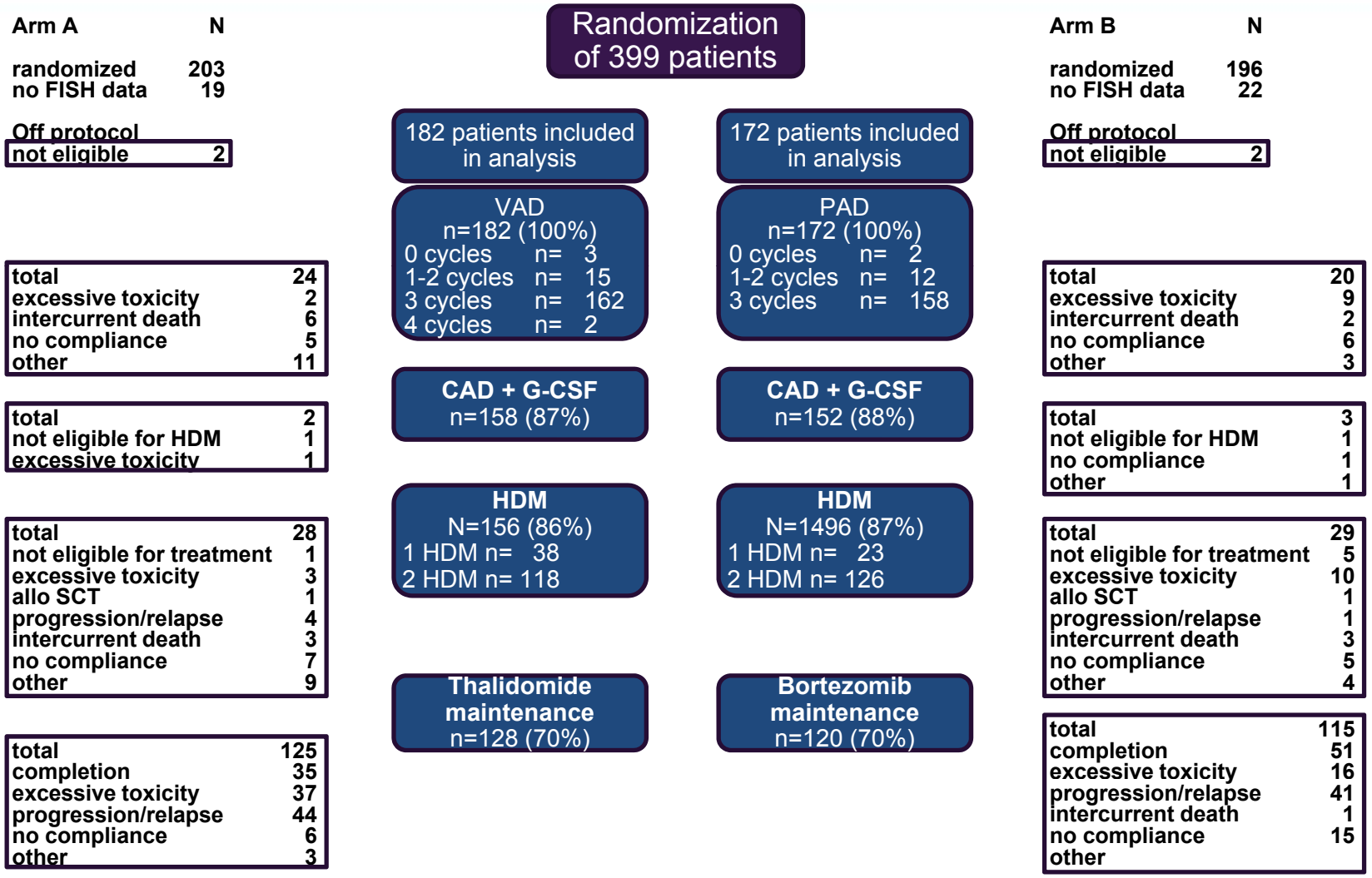
	Initial Therapy	n	At Randomization	Lenalidomide vs Placebo	
				Median PFS after Randomization	OS after Randomization
Attal et al[1]	**SCT**	**614**	**3 m post SCT**	**41 m vs 23 m***	**4-year OS 73% vs 75%**
McCarthy et al[2]	**SCT**	**460**	**SCT**	**39 m vs 21 m***	**3-year OS 88% vs 80%†**
Palumbo et al[3]	**MPR**	**305**	**Diagnosis**	**31 m vs 14 m***	**3-year OS 70% vs 62%**

*P<0.001; †P=0.03.

PFS=progression-free survival; OS=overall survival; SCT=stem cell transplantation; MPR=melphalan + prednisone + lenalidomide.

1. Attal M, et al. *N Engl J Med*. 2012;366:1782-1791.
2. McCarthy PL, et al. *N Engl J Med*. 2012;366:1770-1781.
3. Palumbo A, et al. *N Engl J Med*. 2012;366:1759-1769.

Bortezomib Before and After ASCT Improves Outcomes in MM Patients with Deletion 17p



Neben K, et al. *Blood*. 2012;119:940-948.

Bortezomib Induction and Maintenance in Patients with Newly Diagnosed MM

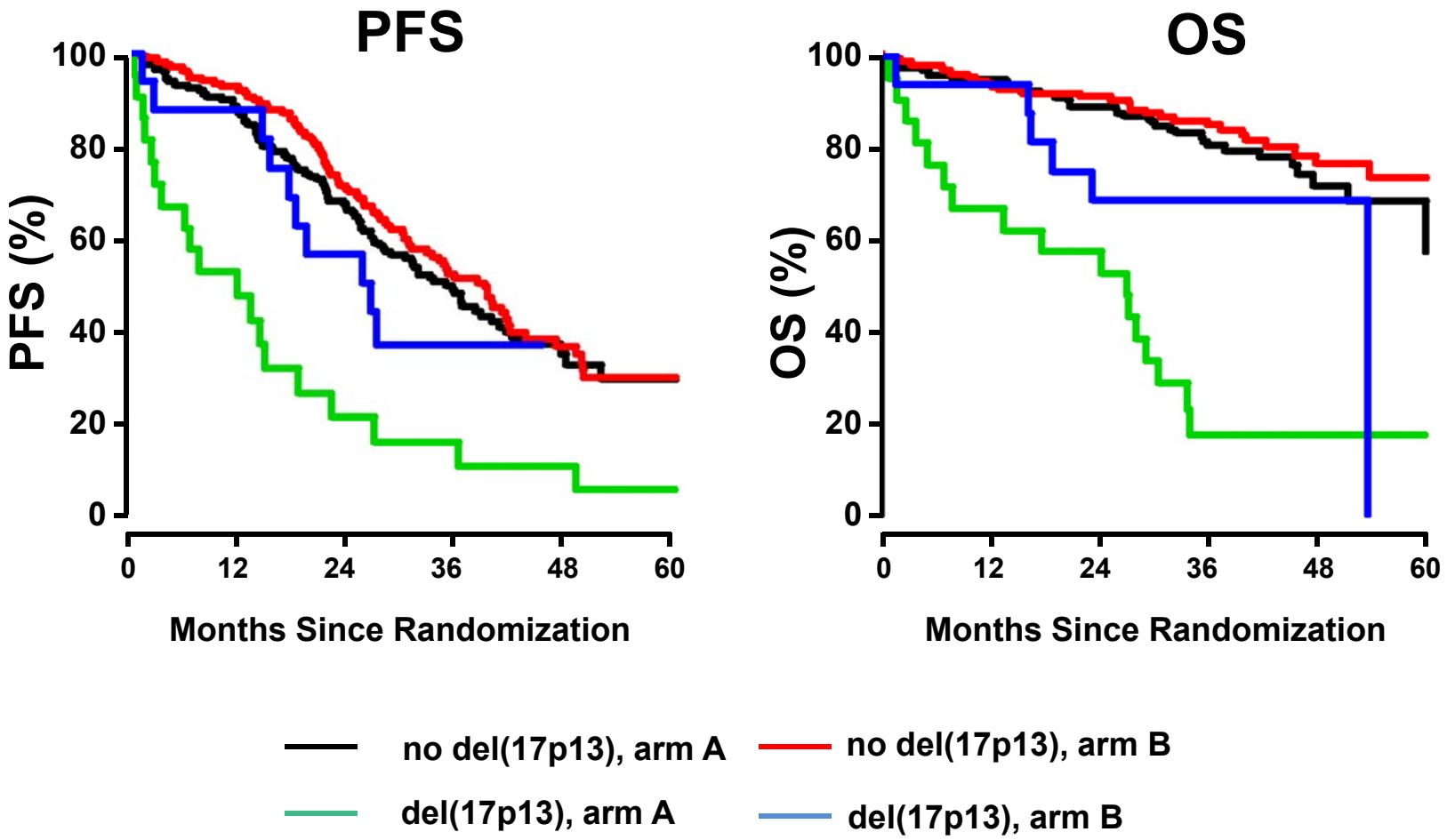
Adverse Events in the HOVON-65/GMMG-HD4 Trial

	VAD arm thalidomide		PAD arm bortezomib	
WHO CTC grade	**1-2**	**3-4**	**1-2**	**3-4**
DVT %	1	8	1	9
PNP %	54	12	50	26
HZV %	1	4	2	7

VAD=vincristine + adriamycin + dexamethasone; PAD=bortezomib + adriamycin + dexamethasone; WHO=World Health Organization; CTC=common toxicity criteria; DVT=deep vein thrombosis; PNP=peripheral neuropathy; HZV=herpes zoster virus.

Sonneveld P, et al. *J Clin Oncol*. 2012;30:2946-2955.

Bortezomib Improved Median PFS and 3-year OS Rates in MM Patients with Deletion 17p



PFS=progression-free survival; OS=overall survival; del=deletion.

Neben K, et al. *Blood*. 2012;119:940-948.

How I Treat Relapse

Treatment Approaches to Relapse

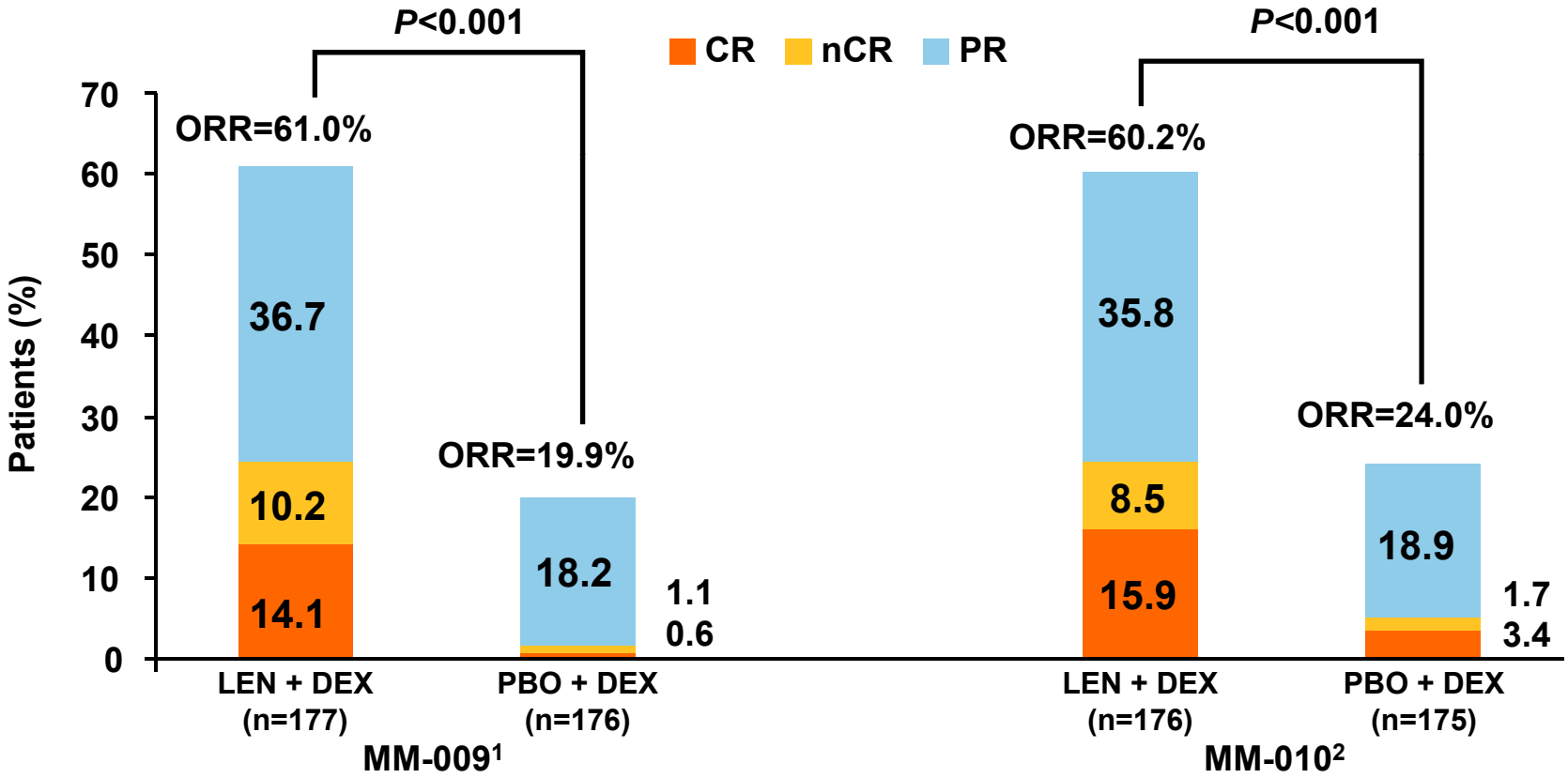
Salvage Therapy	Factors to Consider
Early relapse	
Lenalidomide-based	• Prior treatment with bortezomib • Long duration of response (>1 year) with initial lenalidomide therapy, eg, maintenance intensification) • Pre-existing neuropathy • Patient wants an oral regimen
Bortezimib-based	• Prior treatment with lenalidomide or thalidomide • Long duration of response (>1 year) with bortezomib therapy • Existing renal insufficiency • Prior thrombosis
Autologous Stem Cell Transplant	• No previous autologous stem cell transplant • Long remission post-ASCT (>2 year)
Aggressive Relapse	
	• Chemotherapy plus novel agents • DT PACE; EDAP • Salvage transplant; second autologous or allo-stem cell transplant

DTPACE= dexamethasone + thalidomide + cisplatin +doxorubicin +cyclophosphamide +etoposide;
EDAP=etoposide + dexamethasone + cytarabine + cisplatin

Kumar A, et al. *Acta Haematol*. 2011;125;8-22.

Lenalidomide + Dexamethasone for Relapsed MM: MM-009/010 Trial Response Rates

- **Overall and CR rates were significantly higher in the LEN + DEX arm of each trial compared with placebo + DEX (*P*<0.001)**

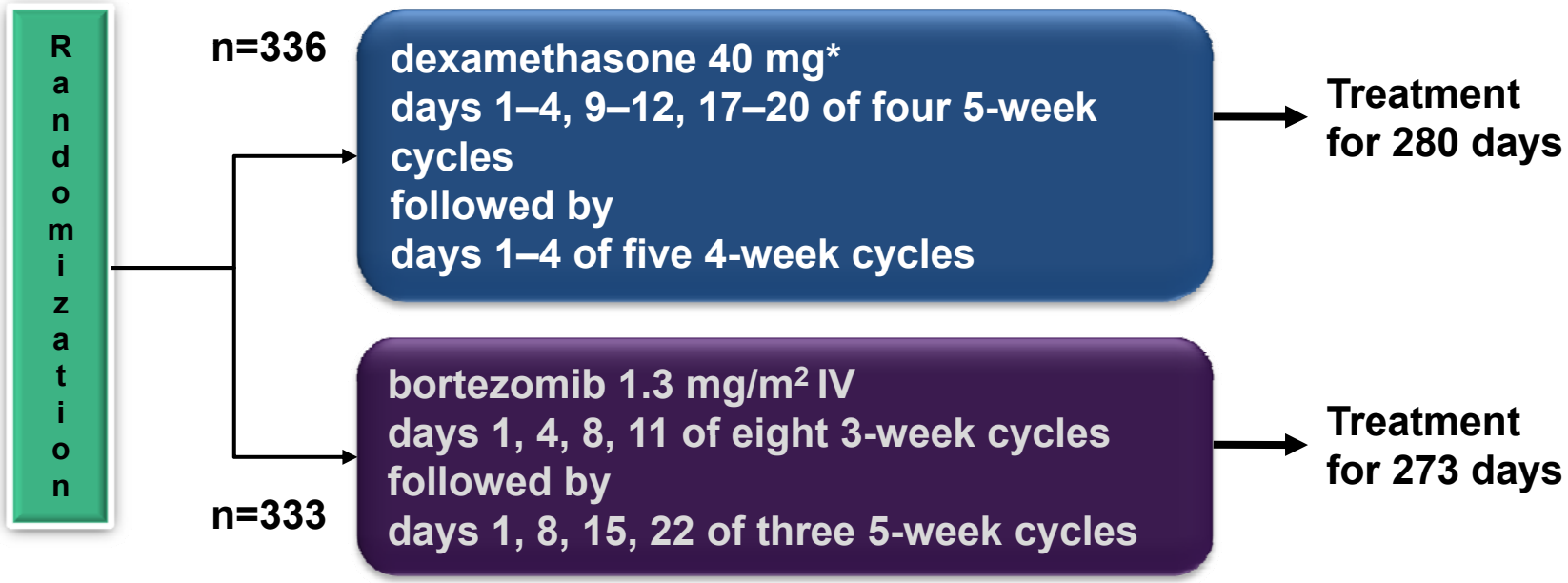


CR=complete response; LEN=lenalidomide; DEX=dexamethasone; nCR=near complete response; PR=partial response; ORR=overall response rate; PBO=placebo.

1. Weber DM, et al. *N Engl J Med*. 2007;357:2133-2142. 2. Dimopoulos M, et al. *N Engl J Med*. 2007;357:2123-2132.

APEX Trial: Bortezomib in Relapsed MM

- **N=669 pts with 1-3 prior therapies (not DEX refractory)**
- **Primary endpoint: time to progression**
- **Secondary endpoints: OS, 1-yr OS, ORR, DOR**



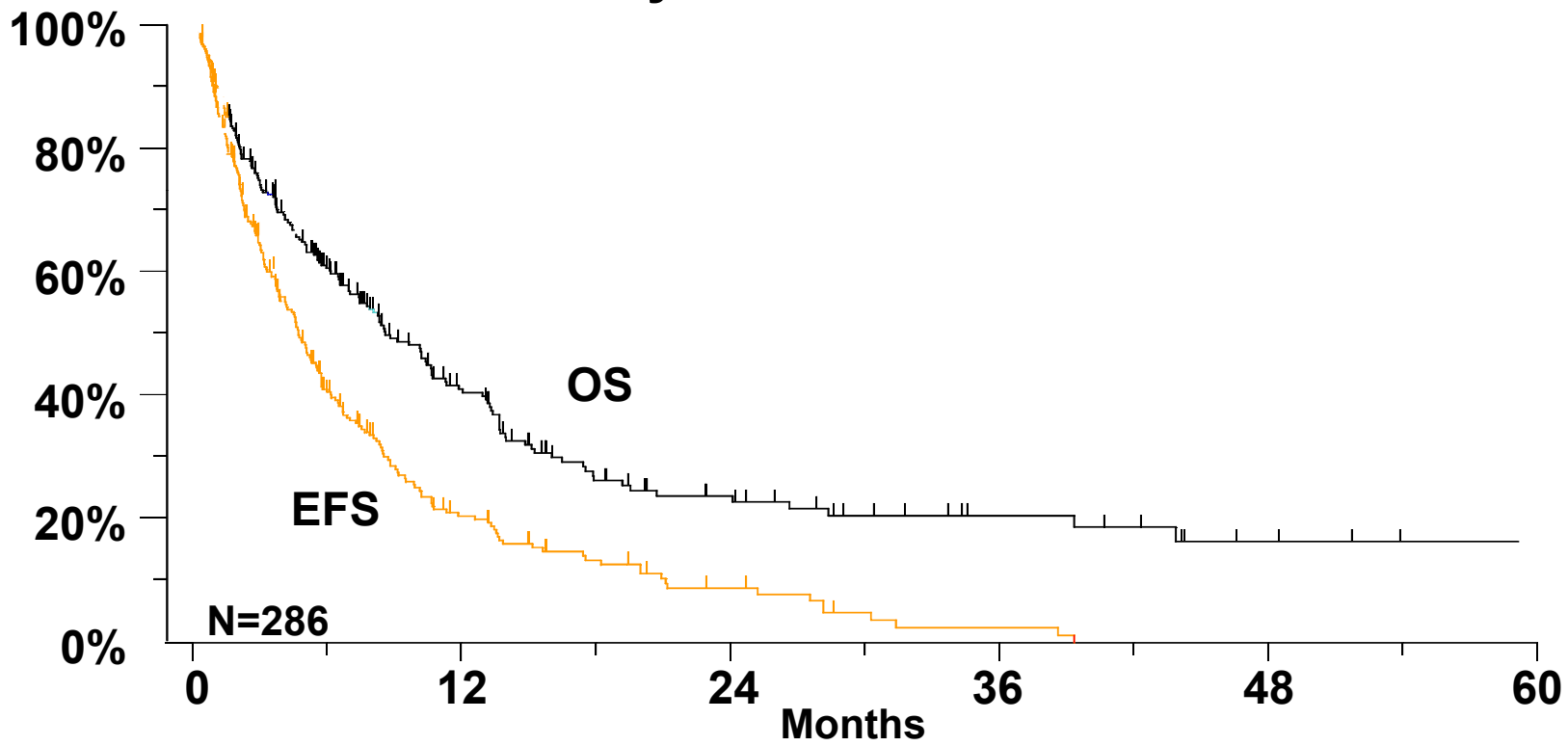
***Patients on DEX who had disease progression were eligible to cross over to BORT in a companion study.**

APEX=Assessment of Proteasome Inhibition for Extending Remissions; DEX=dexamethasone; OS=overall survival; ORR=overall response rate; DOR=duration of response; IV=intravenous; BORT=bortezomib.

Richardson PG. *N Engl J Med*. 2005;352:2487-2498.

Survival for Dual Refractory Disease

Median EFS of 5 months and Median OS of 9 Months for Patients Refractory to Both BTZ* and THAL/LEN**



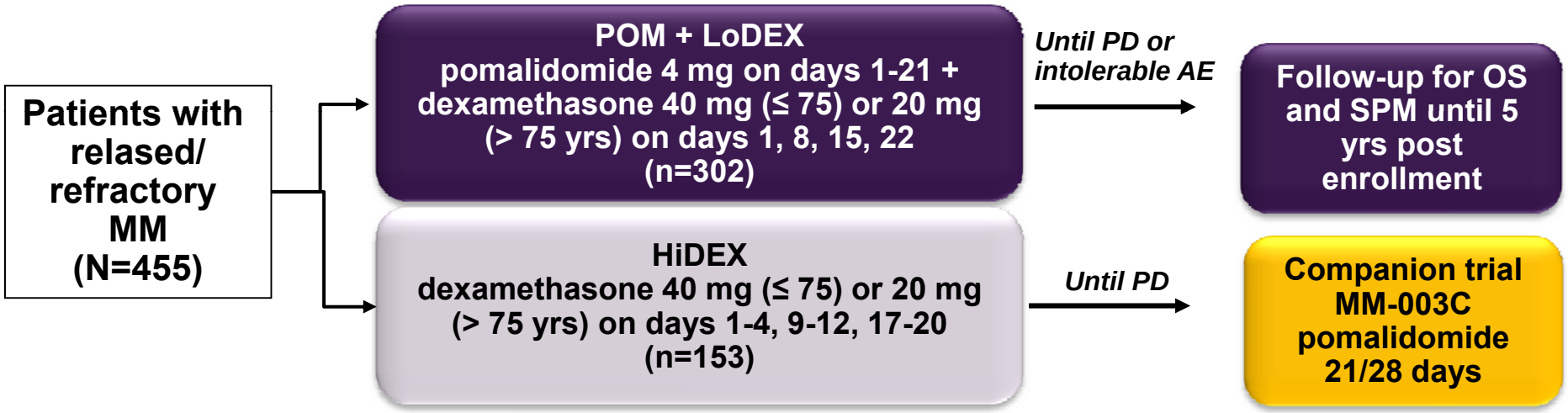
*BTZ refractory defined as no response, progression on therapy, or progression within 60 days of stopping therapy.
**Pts were relapsed and/or refractory, intolerant, or ineligible to receive therapy with LEN or THAL.

EFS=event-free survival; OS=overall survival; BTZ=bortezomib; THAL=thalidomide; LEN=lenalidomide.

Kumar S, et al. *Leukemia*. 2012;26:149-157.

MM-003 Trial: Pomalidomide + LoDEX vs Single-Agent HiDEX in Relapsed/Refractory MM

- **Patients with relapsed/refractory myeloma have few therapeutic options, except high-dose dexamethasone as a salvage therapy**



- **Patients stratified by number of previous therapies, refractory and relapsed/refractory disease**
  - **Refractory to both lenalidomide and bortezomib: 73% in POM + LoDEX and 71% in HiDEX arms**

DEX=dexamethasone; POM=pomalidomide; PD=progressive disease; AE=adverse event; OS=overall survival; SPM=secondary primary malignancy.

Dimopoulos MA, et al. ASH 2012. Abstract LBA-6.

MM-003: PFS and OS in Relapsed/Refractory MM

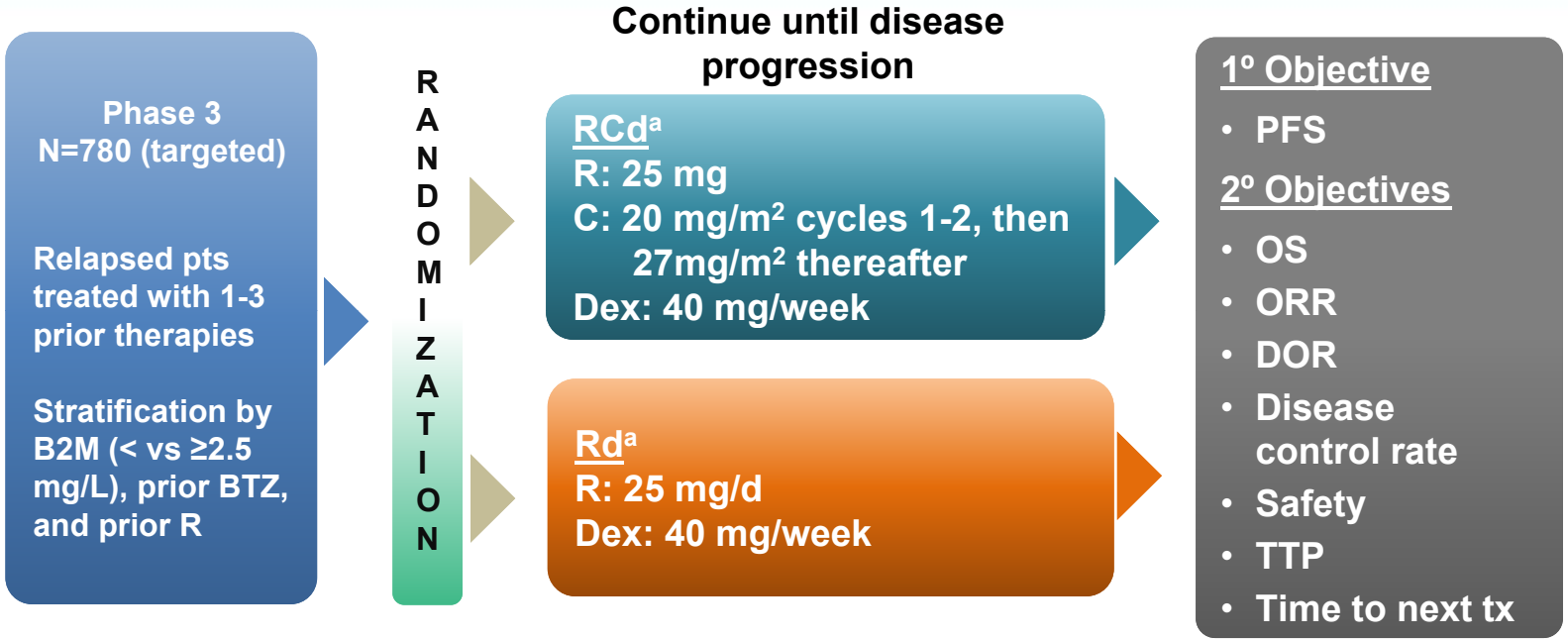
Survival Outcomes by Patient Group, Months	POM + LoDEX (n=302)	HiDEX (n=153)	Hazard Ratio	*P* Value
Median PFS				
▪ Intent to treat population	3.6	1.8	0.45	<.001
▪ Refractory to bortezomib	3.6	1.8	0.47	<.001
▪ Refractory to lenalidomide	3.7	1.8	0.38	<.001
▪ Refractory to bortezomib and lenalidomide	3.2	1.7	0.48	<.001
Median OS				
▪ ITT population	NR	7.8	0.53	<.001
▪ Refractory to bortezomib	NR	8.1	0.56	.037
▪ Refractory to lenalidomide	NR	8.6	0.39	.003
▪ Refractory to bortezomib and lenalidomide	NR	7.4	0.56	.003

- In patients with poor renal function, POM + LoDEX provided longer PFS and OS as compared with HiDEX

OS=overall survival; POM=pomalidomide; DEX=dexamethasone; PFS=progression-free survival; NR=no response.

Dimopoulos MA, et al. ASH 2012. Abstract LBA-6.

Phase 3 ASPIRE Trial: Carfilzomib + Lenalidomide + Dexamethasone in Relapsed MM

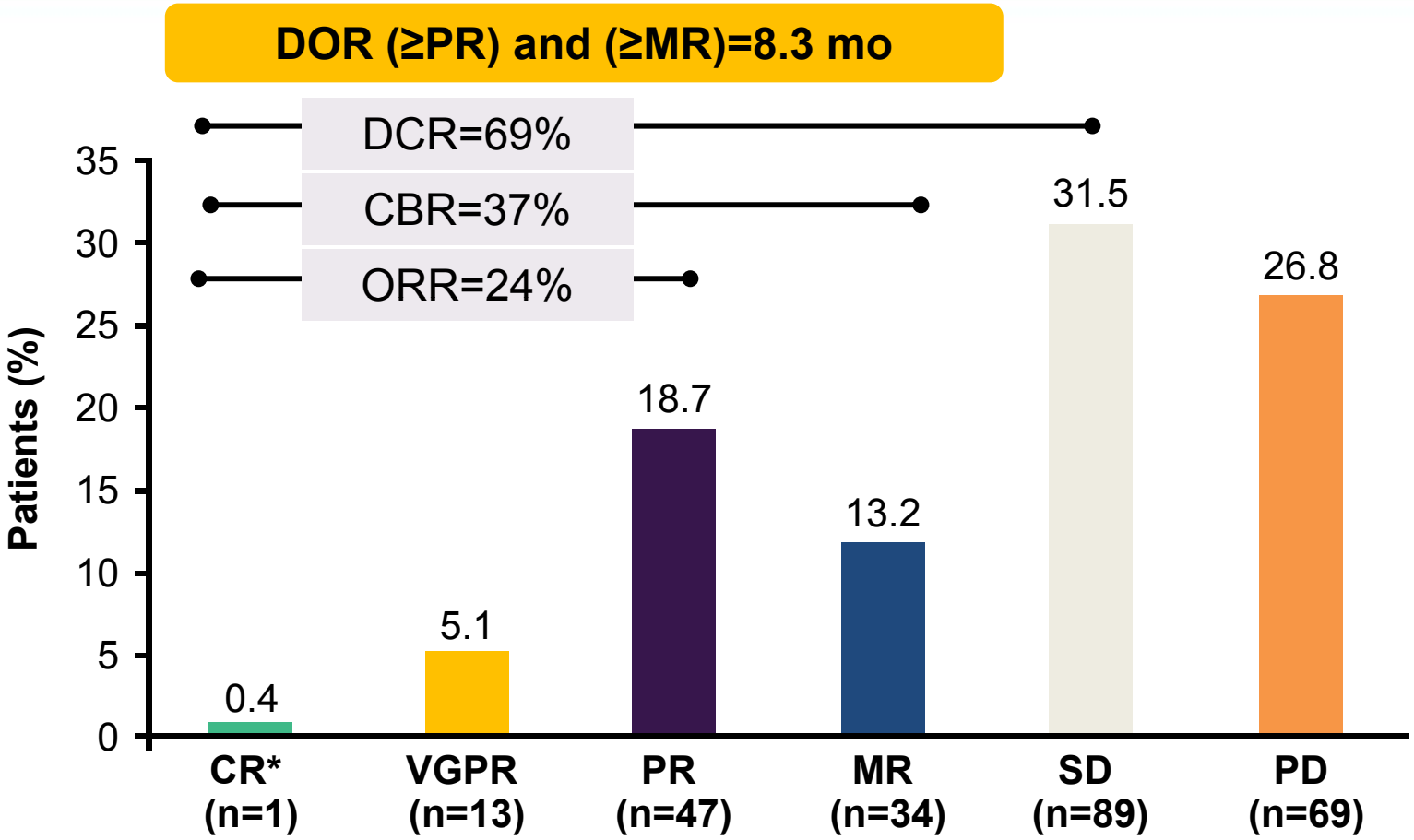


[a]R: days 1-21 of each 28-day cycle.
C: days 1, 2, 8, 9, 15, 16 (cycles 1-12); days 1, 8, 15 (cycles 13-18); cycles 19+ no CFZ will be given.
Dex: weekly

ASPIRE= c**A**rfilzomib, lenalidomide, and dexametha**S**one versus lenalidomide and dexamethasone for the treatment of **P**at**I**ents with **R**elapsed multiple my**E**loma; RRMM=relapsed/refractory multiple myeloma; B2M= β2 microglobulin levels; BTZ=bortezomib; RCd=lenalidomide + carfilzomib+low dose dexamethasone; R=lenalidomide; C=carfilzomib; R=lenalidomide; Dex=dexamethasone; PFS=progression-free survival; OS=overall survival; ORR=overall response rate; DOR=duration of response; TTP=time to progression.

1. Clinical trials.gov. http://www.clinicaltrials.gov/ct2/show/NCT01080391?term=NCT01080391&rank=1. Accessed February 15, 2013.
2. ASPIRE press release. Feb 22, 2012. http://www.prnewswire.com/news-releases/onyx-pharmaceuticals-completes-enrollment-in-aspire-phase-3-carfilzomib-combination-trial-for-the-potential-treatment-of-relapsed-multiple-myeloma-140047353.html. Accessed February 15, 2013.

Carfilzomib in Relapsed/Refractory MM: Results in Response-Evaluable Patients (n=257)



*response-evaluable population
DOR=duration of response; MR=minimal response; DCR=disease control rate; CBR=clinical benefit rate; ORR=overall response rate; CR=complete response; VGPR=very good partial response; PR=partial response; SD=stable disease; PD=progressive disease.

Siegel DS, et al. *Blood*. 2012;120:2817-2825.

Elotuzumab: An Anti-CS1 Monoclonal Antibody for the Treatment of MM

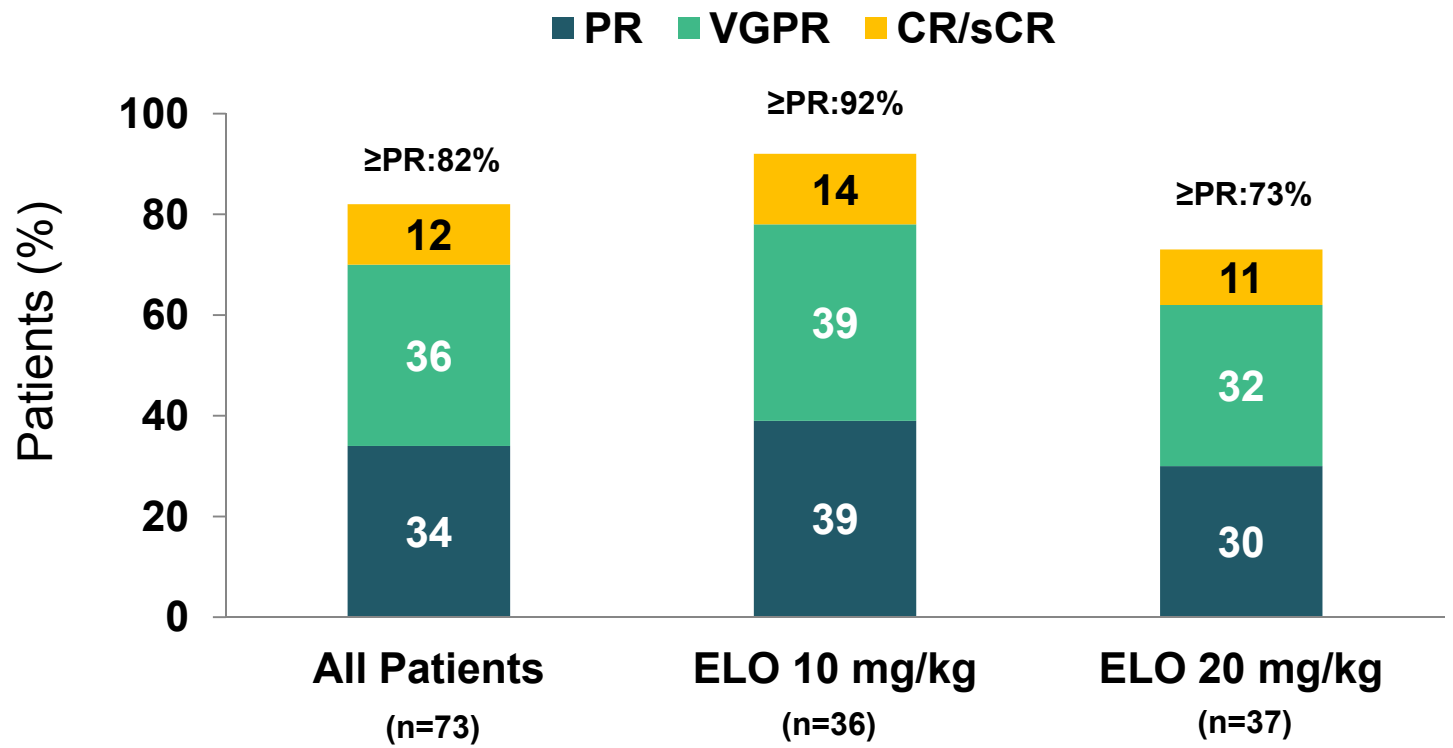
- CS1 is highly and uniformly expressed on MM cells
- Elotuzumab is a humanized monoclonal IgG1 antibody targeting CS1
- Clinical trial of elotuzumab in MM achieved SD
- Anti-MM activity of elotuzumab enhanced by lenalidomide in preclinical models
- Phase I/II trials: 80% to 90% response to lenalidomide/DEX/elotuzumab in relapsed MM
- Phase III trial of lenalidomide/DEX/elotuzumab vs lenalidomide/DEX in relapsed MM for new drug approval

CS1=cell surface gylycoprotein; IgG1=immunoglobulin G; SD=stable disease; DEX=dexamethasone.

Hsi ED, et al. *Clin Cancer Res*. 2008;14:2775-2784. Tai YT, et al. *Blood*. 2008;112:1329-1337. Van Rhee F, et al. *Mol Cancer Ther*. 2009;8:2616-2624. Lonial S, et al. *Blood*. 2009;114:432. Richardson PG, et al. *Blood*. 2010;115:864.

Elotuzumab (+ LEN + DEX): Efficacy

- **Response rates were high with combination therapy**
- **Median PFS was not reached with a median follow-up of 14.1 months**



LEN=lenalidomide; DEX=dexamethasone; PFS=progression-free survival; PR=partial response; VGPR=very good partial response; CR=complete response; sCR=stringent complete response; ELO=elotuzumab.

Lonial S. *Blood.* 2011;118:141-142.

Oral Proteasome Inhibitor MLN9708 for Front Line MM Treatment: Preliminary Phase 2 Results

- Patients received 4.0 mg/kg MLN9708 on days 1, 8, and 15 (plus lenalidomide and dexamethasone on the same schedule)
- 53 patients received a median of 7 cycles of therapy (range, 1-19 cycles)
- At data cutoff, 52/53 patients were evaluable for response; 26 remained on therapy
- Efficacy
  - ORR: 90%
  - 58% of patients achieved ≥VGPR
  - 3patients completed 12 cycles; 2 achieved a CR; 1 achieved a VGPR
  - Minimal residual disease was assessed in 8 patients who had a complete response and found negative in 88%
  - At data cutoff, 50/52 responders remained in response, with responses durable for up to 13.2+ months
  - Median time to first response was 0.92 months (range 0.89–6.44)

ORR=overall response rate; VGPR=very good partial response; CR=complete response.

Kumar, SK, et al. Presented at the American Society of Hematology Annual Meeting. Atlanta, GA. 2012. Abstract 332.

Oral Proteasome Inhibitor MLN9708 for Front Line MM Treatment: Preliminary Phase 2 Results (cont'd)

- Safety
  - Treatment-emergent peripheral neuropathy reported in 21 patients (32%); 13 patients, grade 1; six patients, grade 2; and two patients, grade 3
  - There was one on-study death
  - Most common grade 3/4 adverse events: rash (18%); neutropenia (9%); vomiting (8%); back pain (7%); thrombocytopenia, anemia, fatigue, diarrhea, and hyponatremia (all 6%); and nausea, dehydration, hypokalemia, and hypophosphatemia (all 5%)

Kumar, SK, et al. Presented at the American Society of Hematology Annual Meeting. Atlanta, GA. 2012. Abstract 332.

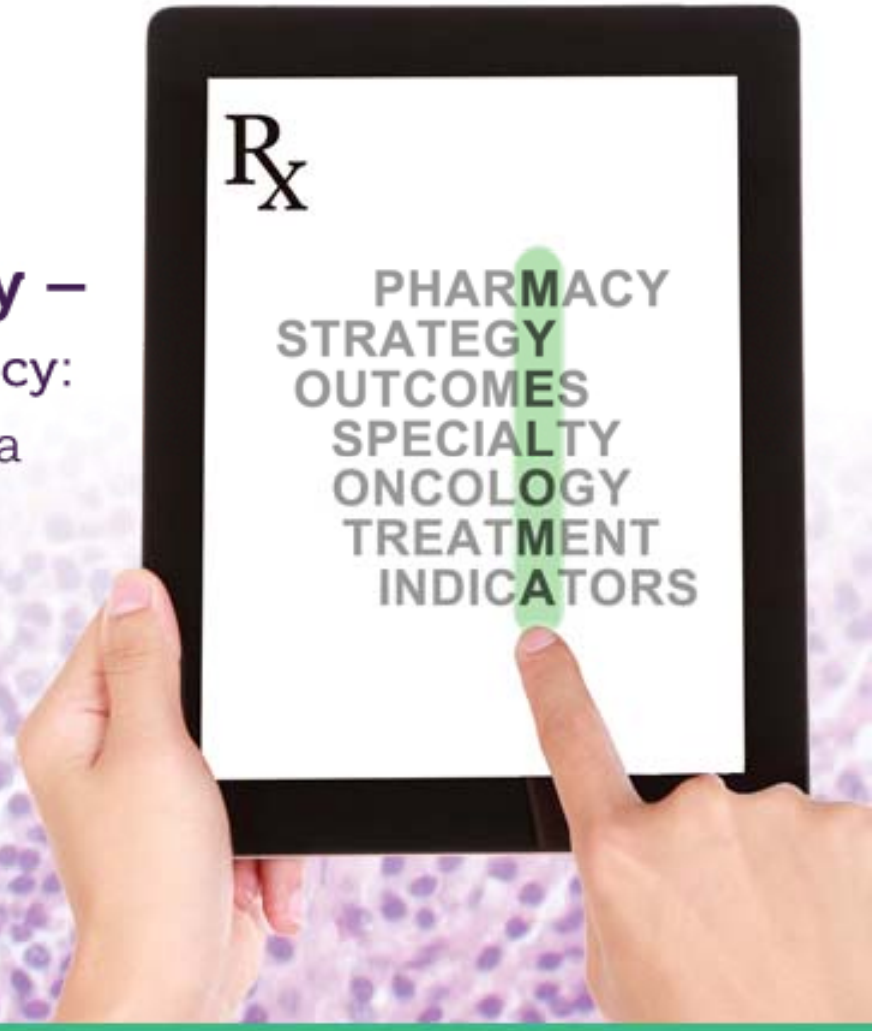
Summary

- Myeloma is not one size fits all disease
- Toxicity
- Efficacy
- Quality of life
- Survival

Applying a Congruent Oncology Pharmacy Strategy –

From Guidelines to Specialty Pharmacy:

Steps for Success with Multiple Myeloma



Jointly sponsored by: PIM Postgraduate Institute for Medicine; Impact Education, LLC

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ONYX Celgene Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

Decision Support Tools to Reduce Treatment Variability and Optimize Costs

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Disclosures

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  James Kenney, Jr., RPh, MBA

  – *No financial interest/relationships relating to the topic of this activity*

Outline

- Decision support tools to reduce treatment variability
- Integration of decision support tools to reduce treatment variability and enhance outcomes
- Data synthesis, evaluation, and application
- Summary

Decision Support Tools

Why the Need for Decision Support Tools?

"Virtually every patient experiences a gap between the best evidence and the care they receive."[1]

Crossing the Quality Chasm
—Institute of Medicine, 2001

"Quality, like life, is not a destination but a journey."[2]

Still Crossing The Quality Chasm—Or Suspended Over It?
– Susan Dentzner
Editor-in-Chief
Health Affairs, 2011

1. Institute of Medicine. Available at: http://www.nap.edu/html/quality_chasm/reportbrief.pdf. Accessed March 4, 2013.
2. Dentzer S. *Health Aff.* 2011;30(4):544-555. doi:10.1377/hlthaff.2011.0287. Accessed March 7, 2013.

Need for Oncology Decision Support Tools

- Payer reactions to the growing costs of oncology care, such as increasing patient cost-sharing or cutting physician reimbursements, are not sustainable solutions
- Status of oncology treatments has changed from a position where the price and value of therapies was rarely questioned
- Payers are actively applying payment reforms and quality measurement to cancer services
- There is a need for oncology decision support tools and resources that are:
  - Simple
  - Easily replicated
  - Measurable
  - Flexible enough to be customized on a local or regional scale

Soper AM, et al. *Am J Manag Care*. 2010;16:e94-e97.

Economic Impact of Multiple Myeloma

- Multiple myeloma (MM) accounts for only 1% of cancers[1]
- Despite relatively low incidence, economic impact is high[1]
  - Even though the incidence of lung cancer is 11 times greater than the incidence of MM, costs associated with MM are more than $100 million greater than the total costs for patients who have lung cancer with metastatic bone disease[2]
- These combined factors make MM a target for new management approaches to optimize care

1. Cook R. *J Manag Care Pharm*. 2008;14(suppl S):S18-S21.
2. Schulman KL, Kohles J. *Cancer*. 2007;109:2234-2243.

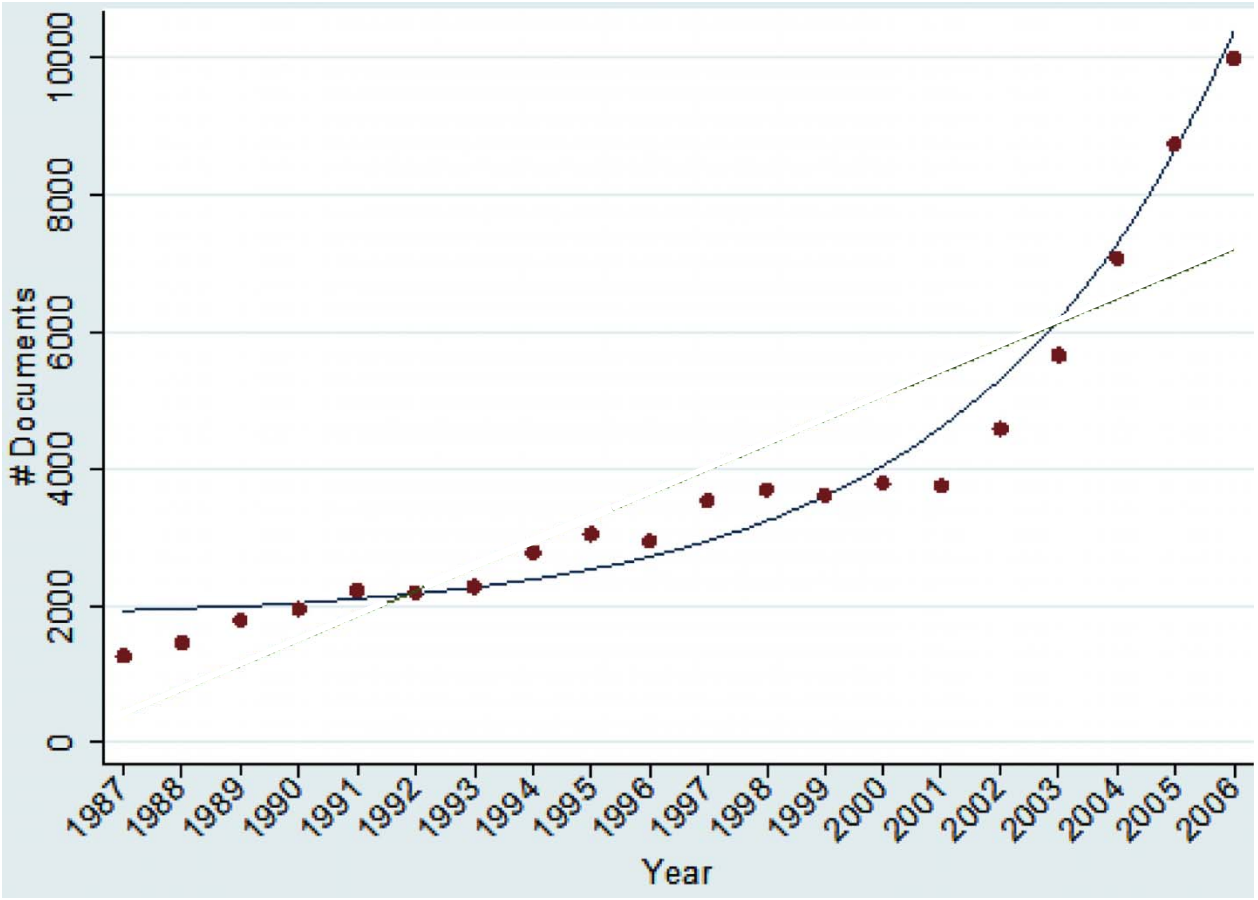
Lack of Access to Information Can Impede Delivery of High Quality Health Care

- Health plan providers cannot deliver high-quality medicine without constantly updating their knowledge and performance
- Experienced providers utilize 2 million discrete pieces of information to manage their patients
- Most information used when interacting with patients is obtained from memory
  - There is a risk that information recalled from memory may be incorrect, incomplete, or out-of-date

Gonzales-Gonzalez AI, et al. *Ann Fam Med*. 2007;5:345-352.

Exponential Growth in the Medical Literature Over the Past 20 Years

12% Annual Publication Growth Rate
1987 – 2007



DeShazo JP, et al. *BMC Medical Informatics and Decision Making* 2009, 9:7.

What is a Clinical Decision Support System?

- Definition
  - Information systems that provide clinicians with patient-specific assessments or recommendations to reduce errors and improve decision making[1]
- Components[1-3]
  - Diagnostic support
  - Clinical guideline alerts
  - Reminders for recommended care
  - Analysis of existing care
  - Formulary alerts and drug ordering support
  - Future patient care recommendations
  - Patient data reports and treatment summaries
  - Documentation templates

1. Shaffer VA, et al. *Med Decis Making*. 2013;33:108–118.
2. Teich JM, et al. *J Am Med Inform Assoc*. 2005;12:365–376;
3. Clinical Decision Support. HealthIT.gov. Available at: http://www.healthit.gov/policy-researchers-implementers/clinical-decision-support-cds. Accessed March 4, 2013.

Important Aspects of Decision Support Systems

Features[1-3]

- Available at the point of care
- Integrated into the EMR
- Retrieves/processes information quickly
- Aligned with accepted clinical treatment guidelines, quality indicators, formularies, and other benefit design features
- Accurate
- Easy to use

Benefits[1-3]

- Increased quality of care and enhanced health outcomes
- Avoidance of errors and adverse events
- Improved efficiency, cost-benefit, and provider and patient satisfaction

1. Shaffer VA, et al. *Med Decis Making*. 2013;33:108–118.
2. Teich JM, et al. *J Am Med Inform Assoc*. 2005;12:365–376;
3. Clinical Decision Support. HealthIT.gov. Available at: http://www.healthit.gov/policy-researchers-implementers/clinical-decision-support-cds. Accessed March 4, 2013.

Characterizing Clinical Decision Support Systems

- System function
  - Determining *what is true* about a patient (eg, correct diagnosis)
  - Determining *what to do* (eg, what test to order, to treat or not, what therapy plan, etc)
- Mode for giving advice
  - Passive role
    - System used when advice needed
  - Active role
    - System gives advice automatically under certain conditions

Integration of Decision Support Tools to Reduce Treatment Variability and Enhance Outcomes

Decision Support Tools: Examples

- Electronic medical records (EMR)
- E-prescribing
- Data synthesis, evaluation, and application for oncology care
  - Comparative effectiveness research (CER)
  - Treatment pathways

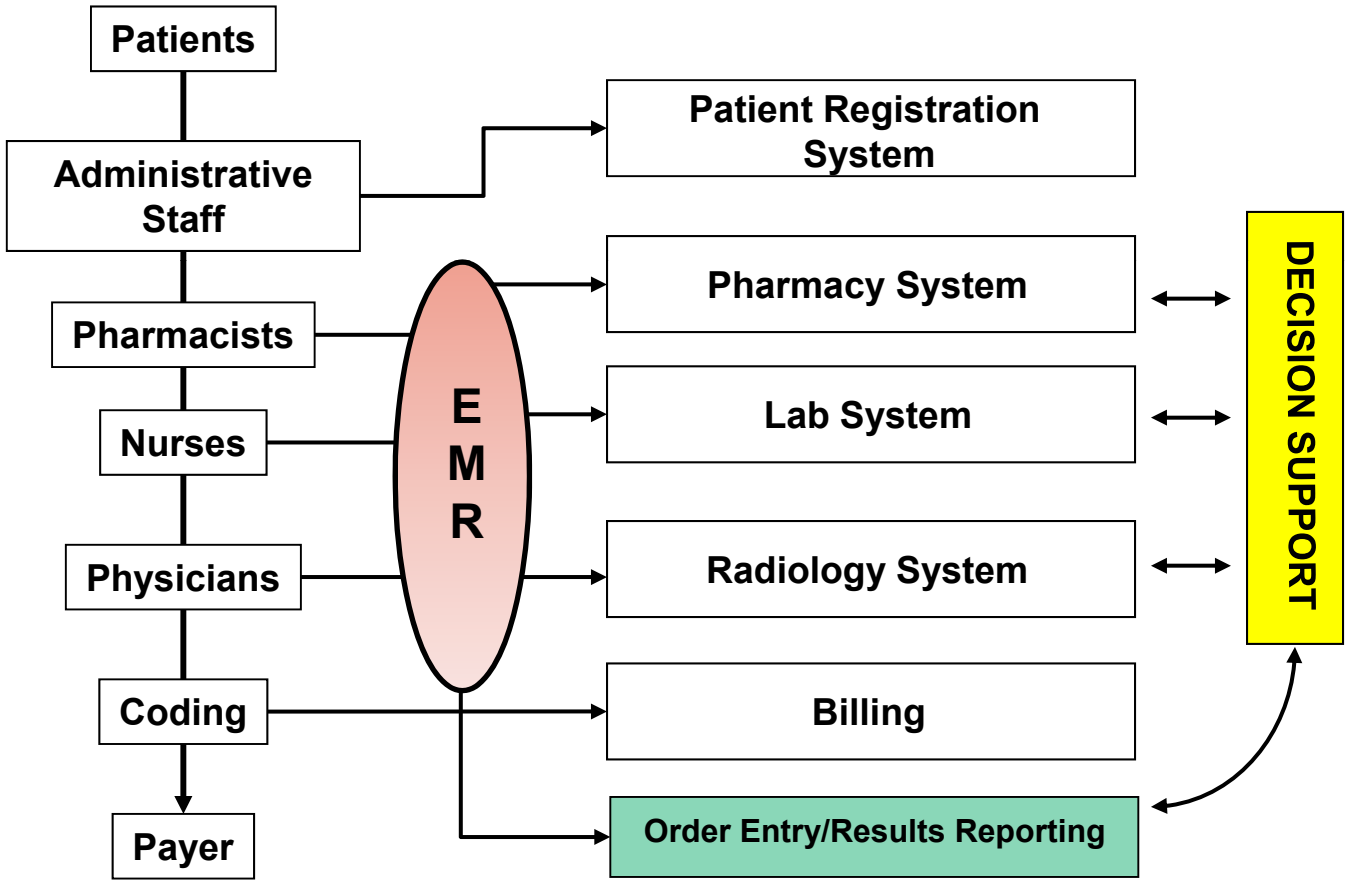
Electronic Medical Records

Features of the Electronic Medical Record

EMR Feature	Potential Benefit
Order entry	Bring needed data to attention at time of order; eliminate transcription error
Order sets/ quick orders	Pick lists influence ordering selection and standardize care processes
Order checks	Reduce errors, warn of possible adverse outcomes, document exceptions
Clinical Reminders	Increase patient-specific compliance with care guidelines, prompt for needed care
View alerts	Focus attention on abnormal results or documents requiring review, prompt for signature, etc
Electronic notes	Improve note availability and accessibility
Notes template	Guide appropriate documentation
Overall	Standardize care delivery processes, allow automated tracking of quality outcomes

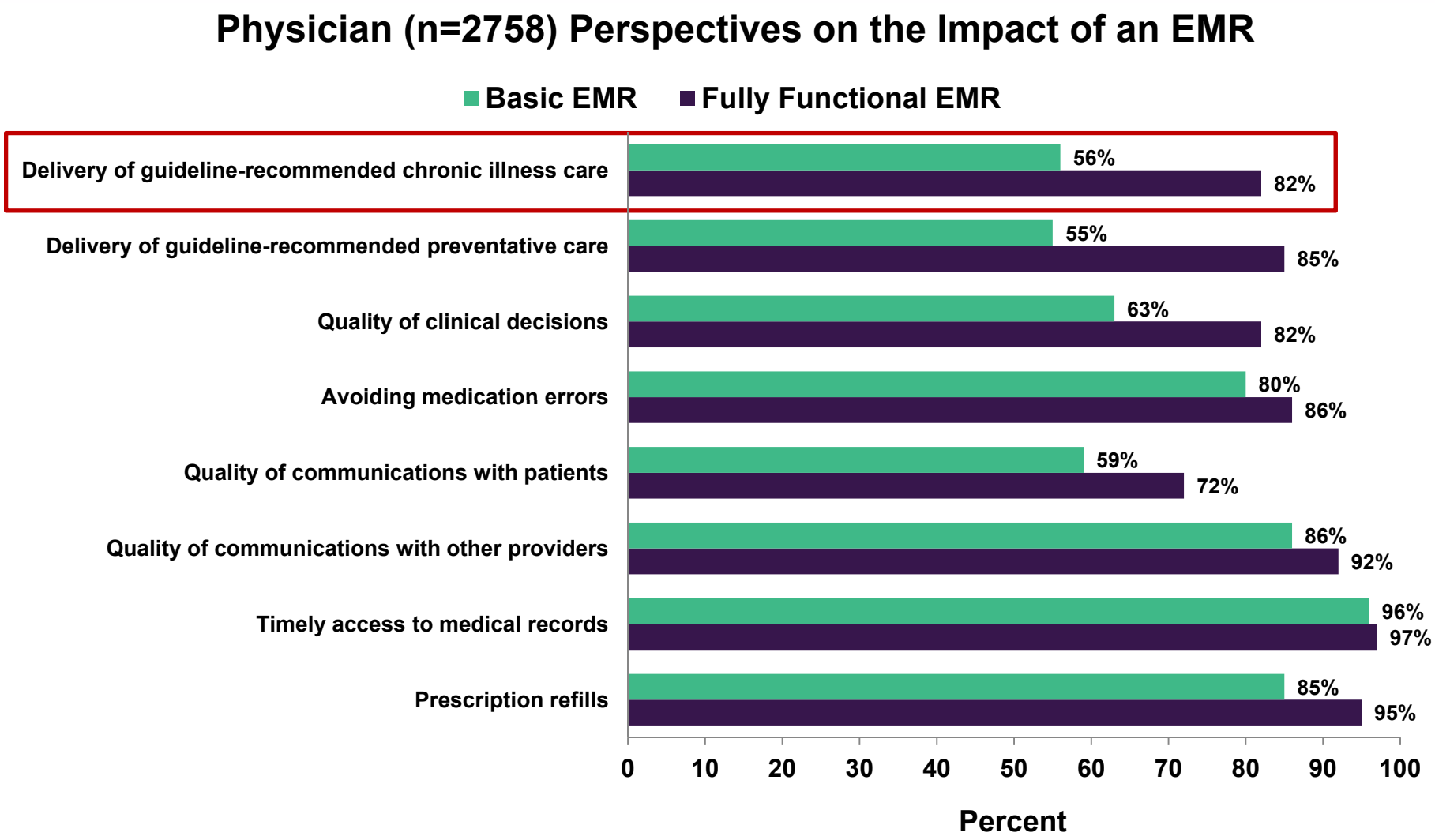
EMR=electronic medical record.

System Interactions with an EMR



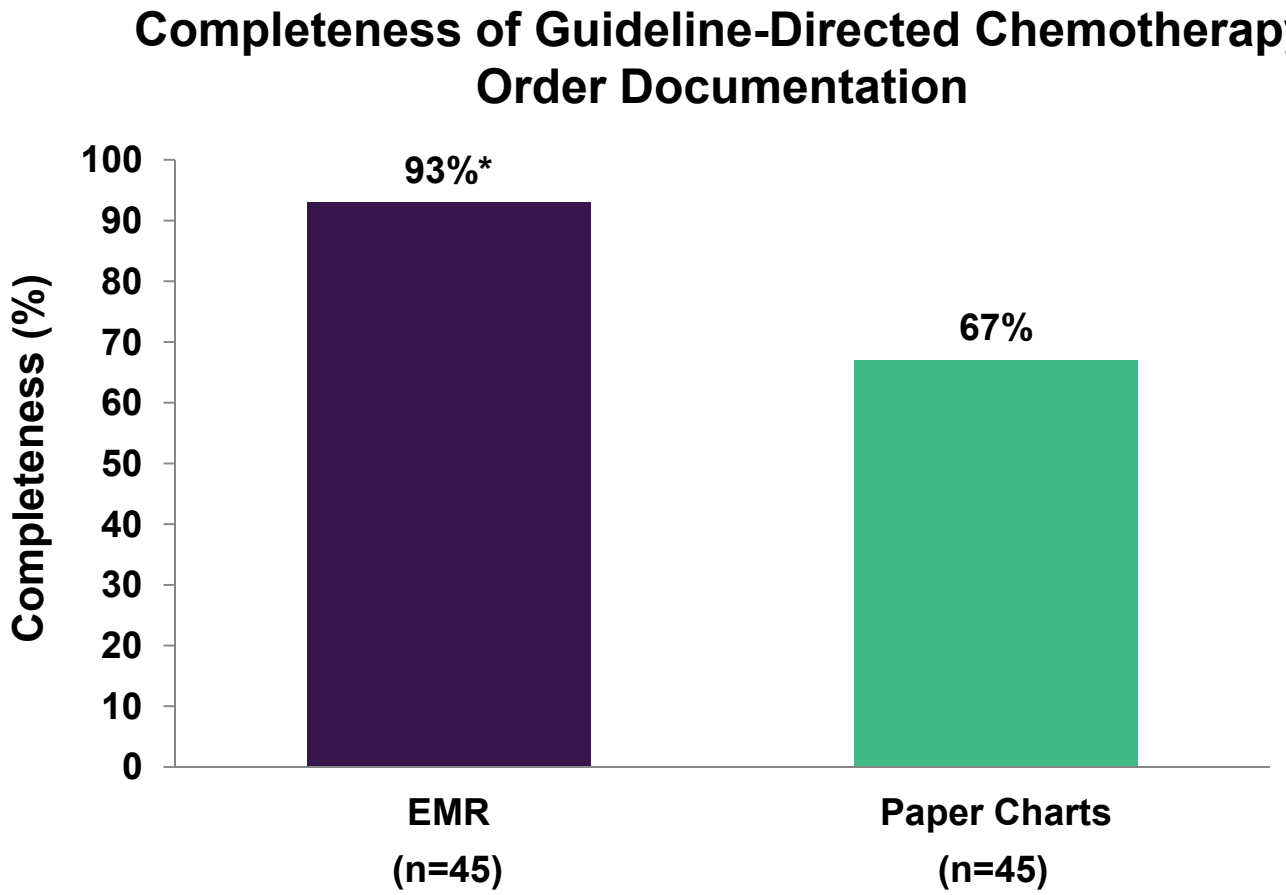
EMR=electronic medical record.

Adoption of EMR Systems Have a Positive Effect on Care and Treatment Variability



DesRoches CM, et al. *N Engl J Med*. 2008;359:50-60.

EMR Implementation Can Improve Documentation and Delivery of Guideline-Directed Oncology Care



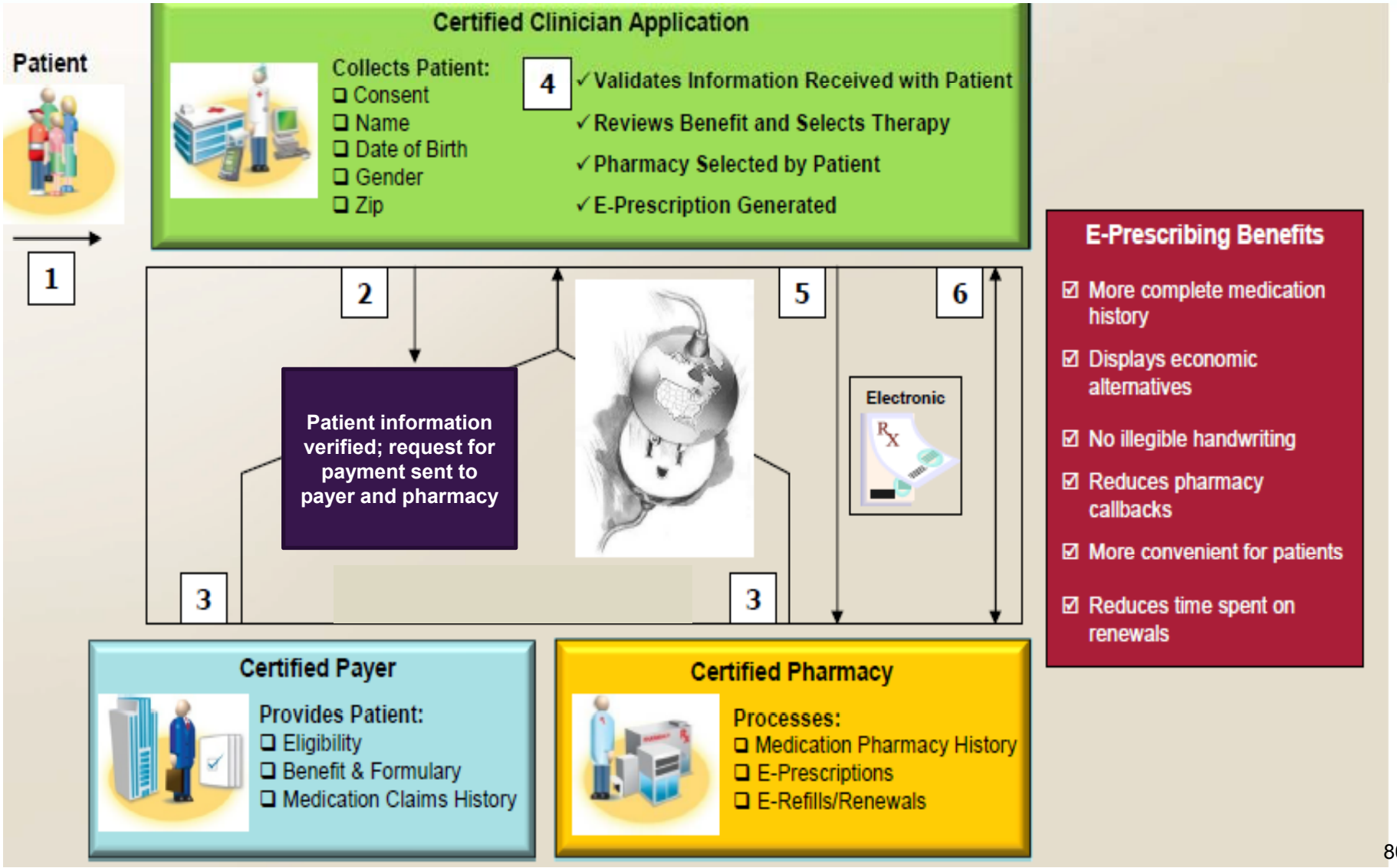
***p<.001 vs paper charts**

EMR=electronic medical record.

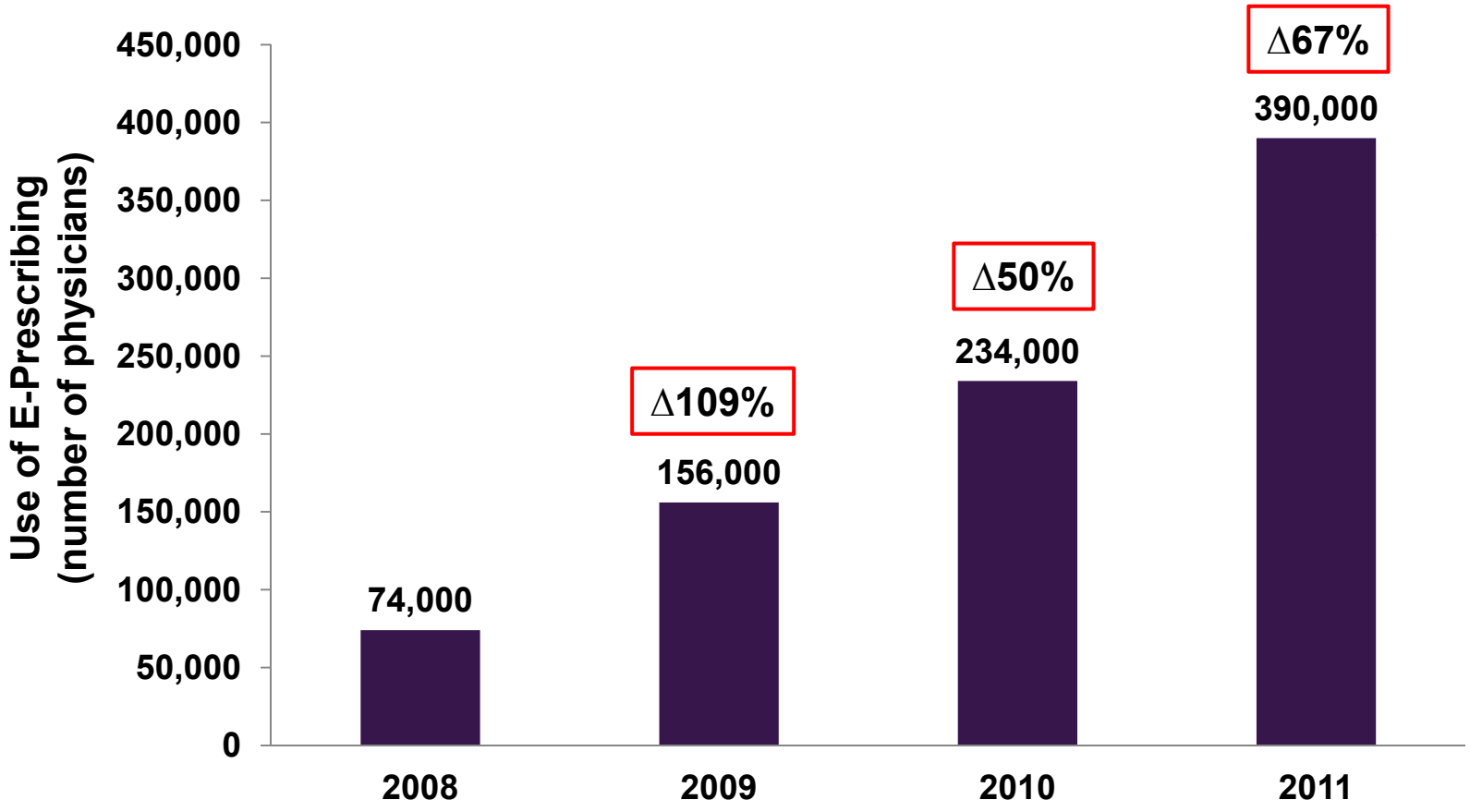
Harshberger CA, et al. *J Oncol Pract*. 2011;7:233-236.

E-Prescribing

How E-Prescribing Works

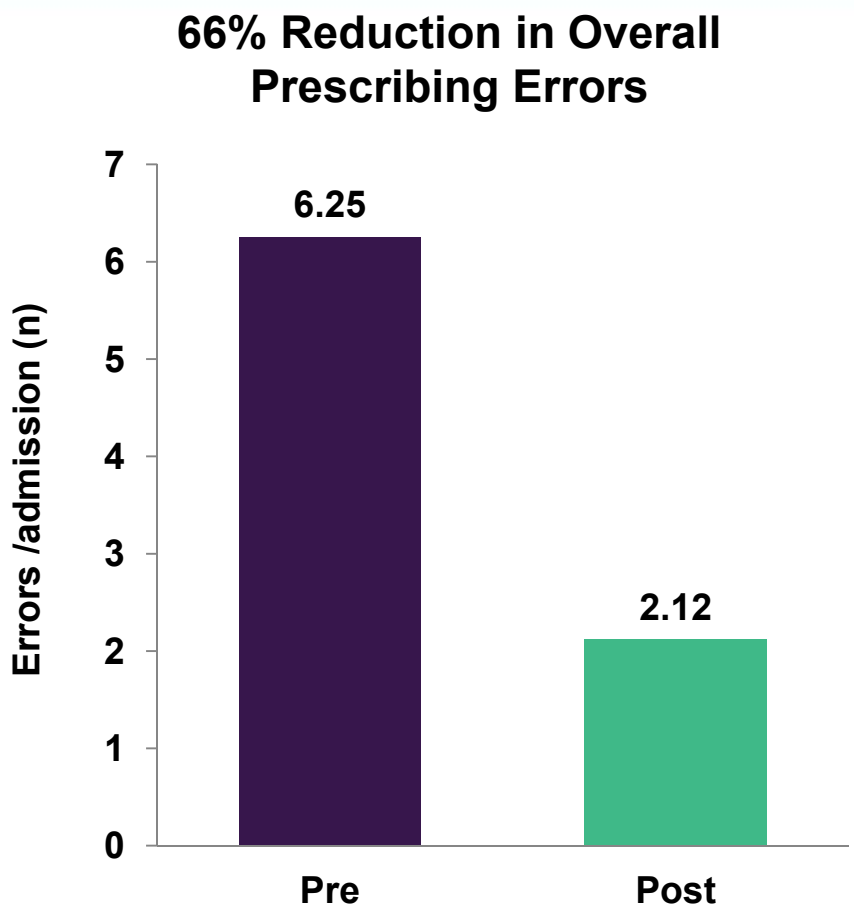


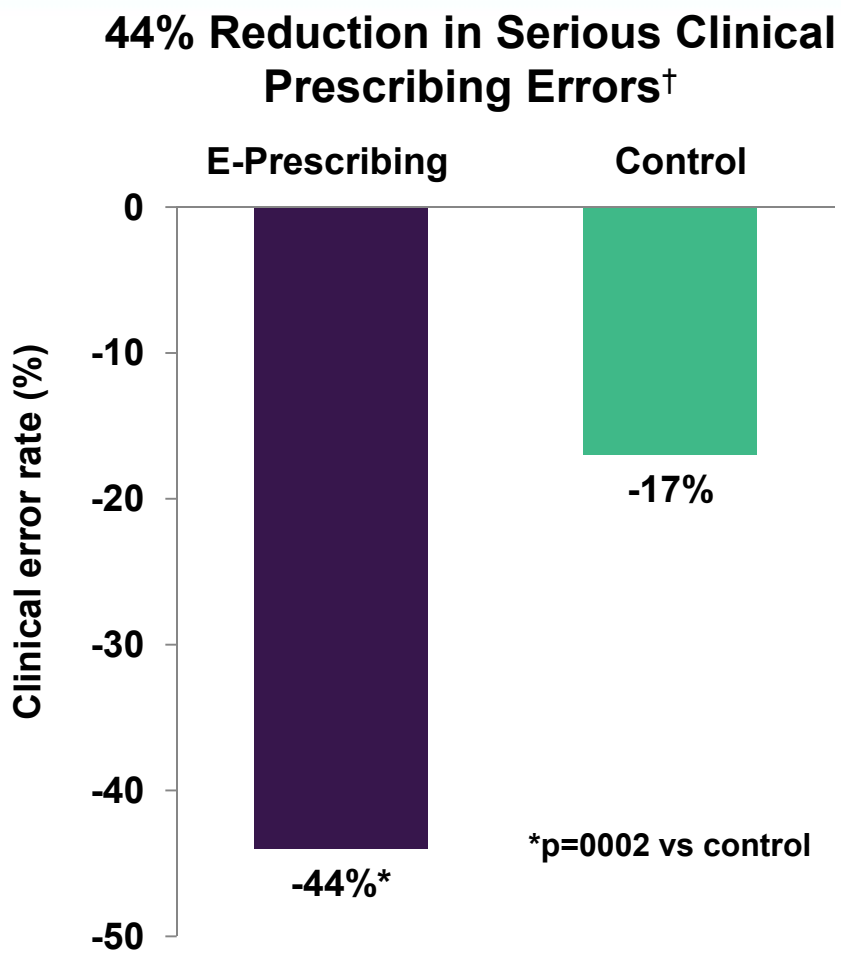
Use of E-Prescribing Increasing Rapidly



Data from CVS Caremark, Express Scripts, Medco Health Services, Prescription Solutions, Prime Therapeutics, and Walgreens. Surescripts.com/connected-pharmacies.html.

Use of E-Prescribing Reduces Medication Error Rate





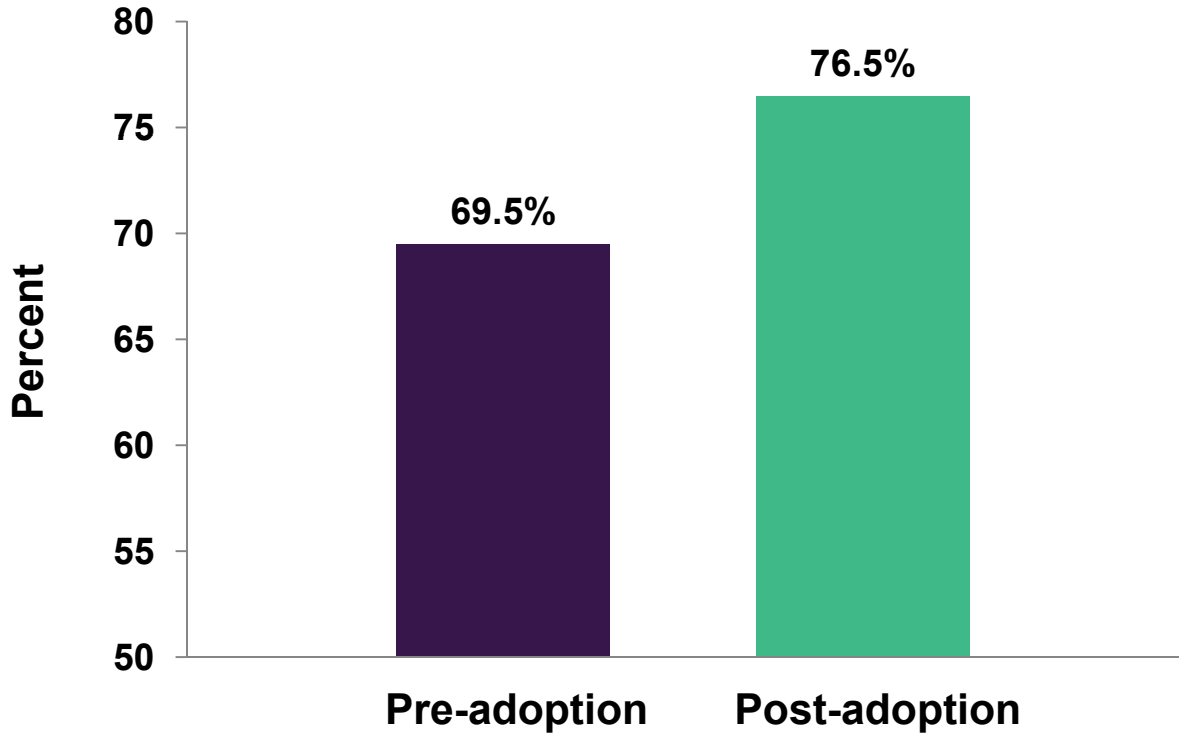
Data from a medication chart audit of 3,291 hospital admissions.

†Likely to lead to permanent reduction in bodily functioning, increased length of stay, surgical intervention, major permanent loss of function, or death.

Westbrook JI, et al. *PLoS Med*. 2012;9:e1001164.

E-Prescribing Led to a 10% Increase in First Fill Adherence

10% More Patients Picked Up Their Prescription Following Adoption of E-Prescribing by Their Physician



Retrospective, longitudinal study of 50,000 active prescribers from four different pharmacy and PBM organizations and >40 million prescription records.

Health Manag Technol. 2012;33(Apr):22-23.

Data Synthesis, Evaluation, and Application: Comparative Effectiveness Research

Evidence Gaps in Oncology

- National Comprehensive Cancer Network (NCCN) estimates ½ to ¾ of all cancer drugs are used off-label[1]
- Survey of oncologists identified at least 87 distinct oral anticancer therapies used outside labeled indications[2]
- Some argue that useful evidence is simply not being generated so compendia cannot synthesize evidence
- Data gaps include
  - Few comparative studies
  - Limited evidence on clinical or humanistic outcomes
  - Evidence is not always "patient-centered" nor "payer-applicable"
  - Review of the primary oncology compendia cited that they "*lack transparency, cite little current evidence, and lack systematic methods....*"[3]

1. Soares M. *J Oncol Practice*. 2005;1:102-105.
2. Goss T. Off-Label Use of Anticancer Therapies: Physician Prescribing Trends and the Impact of Payer Coverage Policy. 2007. Gaithersburg, MD: Covance Market Access Services.
3. Abernethy AP, Raman G, Balk EM et al. *Ann Intern Med*. 2009;150:336-343.

Filling the Evidence Gap

- It's important to fill the right gap/answer the right question
- Simultaneously "too little" and "too much" info

CER as a Decision Support Tool

- Clinical decision making is frequently impeded by incomplete data
- "Trial and error" approach to decision making often used due to lack of comparative data
- CER can fill data gaps
  - Comparison of drug therapies in the absence of head-to-head data
  - Applicable to a wide variety of practice settings and diversity of patients

CER=comparative effectiveness research.

Brixner DI, Oderda G. *J Manag Care Pharm*. 2012;18(Suppl. 4-a):S3-S4.

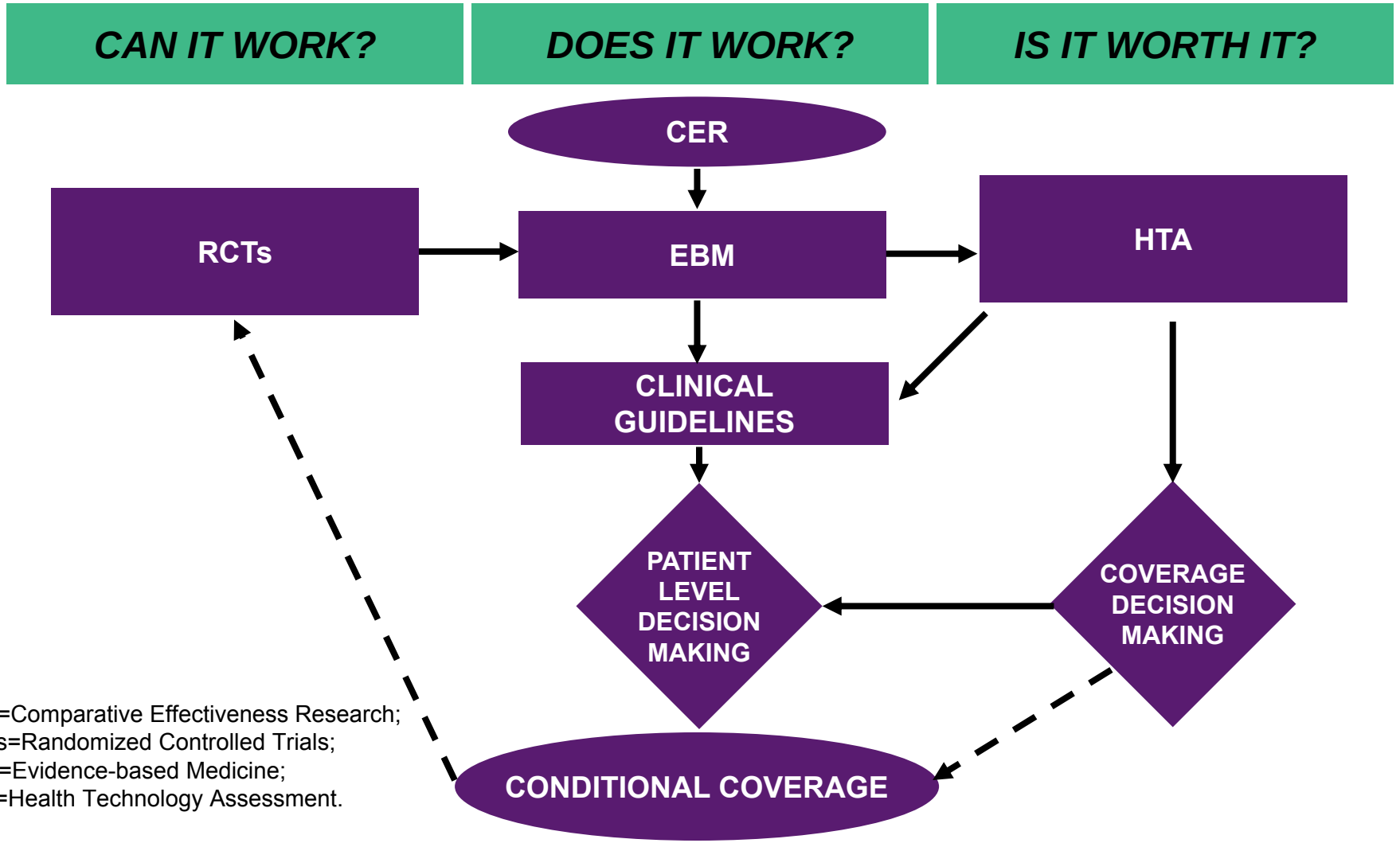
CER Provides Data to Enhance Clinical Decisions

- CER is defined as…
  - "Generation and synthesis of evidence that *compares the benefits and harms of alternative methods* to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care"
- CER results are used to…
  - "Synthesize existing evidence in order to *address knowledge gaps* and drive patient-focused clinical decisions and outcomes"
  - Compare relative merits of competing interventions

CER=comparative effectiveness research.

Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: The National Academies Press; 2009.

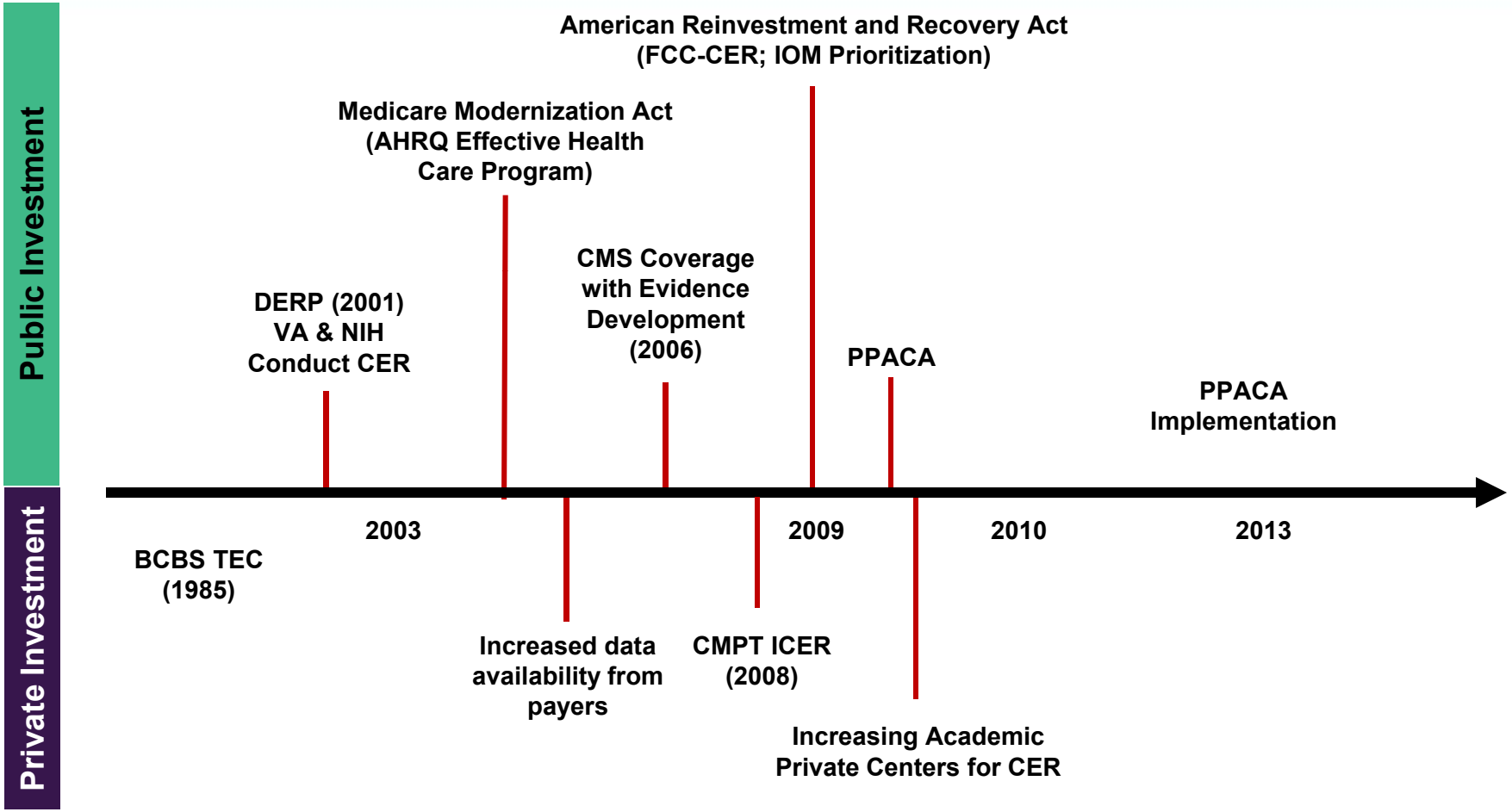
Addressing the Evidence Gaps and Uncertainty



CER=Comparative Effectiveness Research;
RCTs=Randomized Controlled Trials;
EBM=Evidence-based Medicine;
HTA=Health Technology Assessment.

Drummond MF, et al. *Int J Technol Assess Health Care*. 2008;24:244-258.

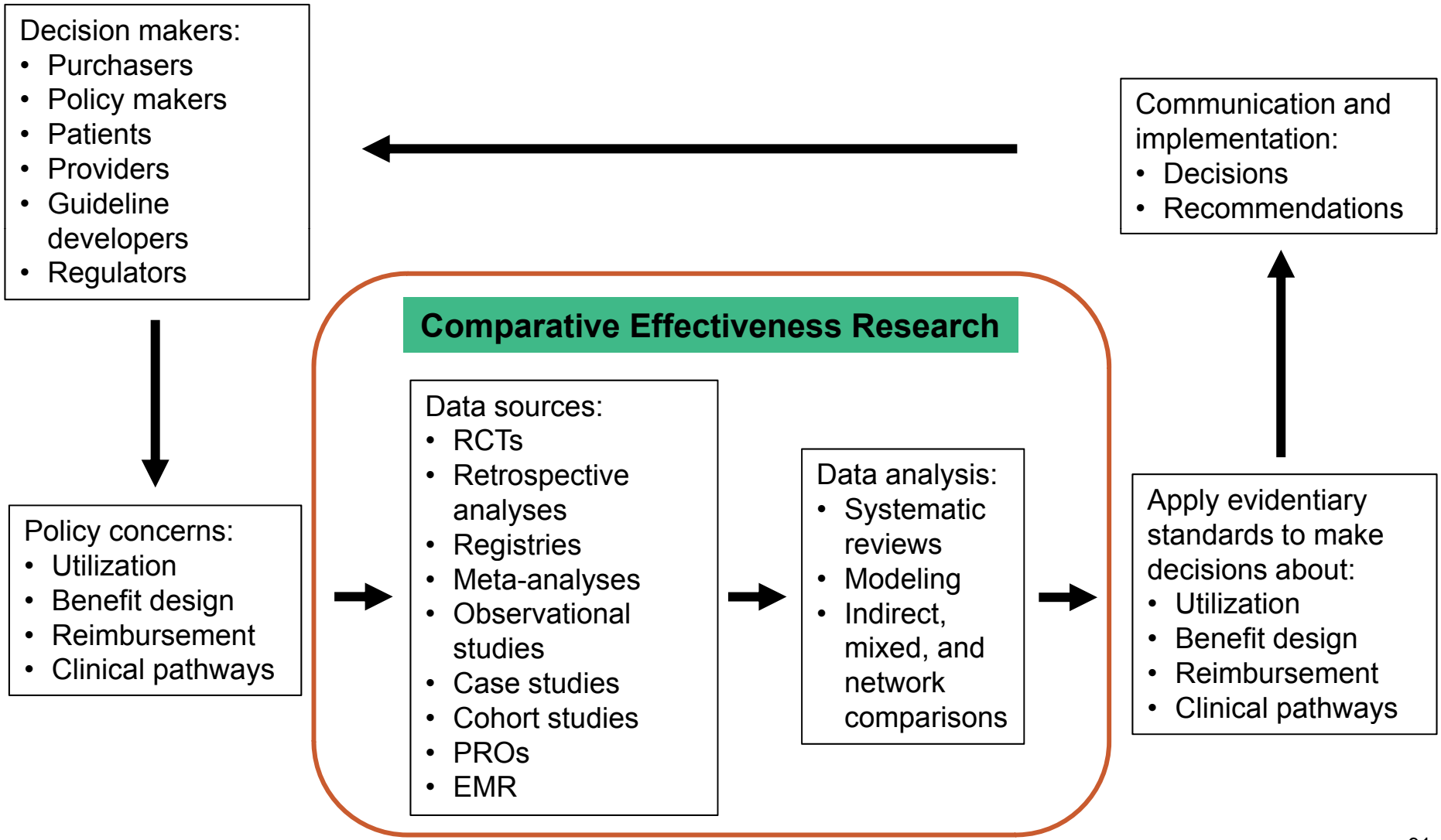
CER Has a Long History of Use in the US



CER=comparative effectiveness research; BCBS=BlueCross BlueShield; TEC=Technology Evaluation Center; DERP=Drug Effectiveness Review Program; AHRQ=Agency for Healthcare Research and Quality; CMS=Centers for Medicare & Medicaid Services; CMPT ICER=Center for Medical Technology Policy Institute for Clinical and Economic Review; FCC-CER=Federal Coordinating Council for Comparative Effectiveness Research; IOM=Institute of Medicine; PPACA=Patient Protection and Affordable Care Act .

Hochman M, McCormick D. *JAMA*. 2010:303;951-958; Clement FM, et al. *JAMA*. 2009;302:1437-1443.

CER Processes, Stakeholders, and Data Sources



CER Consolidates Evidence From Multiple Sources

Model Type	Description	Best Suited For
Decision tree	Diagrams the risk of events and states of nature over a fixed time horizon	Interventions for which the relevant time horizon is short and fixed
Markov	Simulates a hypothetical cohort of individuals through a set of health states over time	Modeling interventions for diseases or conditions that involve risk over a long time horizon and/or recurrent events
Microsimulation	Tracks the past health states of individual and models risk of future events	Modeling complex disease processes, when Markov models are too limiting
Discrete event simulation	Simulates time to an event and subsequent events, one individual at a time as well as interactions among individuals or within a health care system	Evaluating alternative health care systems

Sainfort F, et al. *Value Health*. 2013;16:133-139.
Ahmann A. *Am J Manag Care*. 2011;17(2 suppl):S41-S51.
Malone DC. *Am J Pharm Benefits*. 2010;2:301-303.

CER=comparative effectiveness research.

What is Being Compared in CER?

- Competing treatment alternatives
  - Novel vs current standard of care
  - Competing vs novel interventions
- Health or economic outcomes resulting from an intervention
  - Overall Survival
  - Cost-effectiveness
- Harms resulting from an intervention
  - Occurrence of adverse events among competing interventions
- Patient preferences for competing interventions

CER=comparative effectiveness research.

CER as an Oncology Decision Support Tool

- Guideline concordant care
  - Reduces variability in outcomes
  - Reduces variability in costs
  - Invests in patients' health & improves health outcomes
  - Reduces wasteful spending by reducing toxicities
- Translated for patients
- Translated for physicians
- Translated for payers

CER=comparative effectiveness research.

Evidence Needs for CER Evaluations of MM Treatments

- Few systematic comparative studies in MM
  - Few active comparator studies
  - Inconsistent methods, so indirect comparisons are a challenge
- CER can be used to address clinical and pharmaco-economic endpoints
  - Identify subgroups of responders
  - Include patient-centered outcomes
  - Examine the impact of patient cost-sharing on clinical outcomes

CER=comparative effectiveness research.

CER as a Decision Support Tool: Perspective

- CER is a valuable part of a larger effort to foster evidence-based medicine to promote and support high-quality health care
- Many CER studies sacrifice internal validity in order to increase generalizability, relevance, feasibility, and timeliness
- Striking the right balance involves patients, providers, payers, and other stakeholders
- Process to achieve this not yet well defined

CER=comparative effectiveness research.

Docteur E, Berenson R. Urban Institute. February 2010. Available at: http://www.urban.org/uploadedpdf/412040_comparative_effectiveness.pdf. Accessed March 4, 2013.

Some Questions Cannot Be Answered Without Asking The Patient

- Main objective of much of health care is improving how patient feels and functions
  - Reduction in pain
  - Improved functioning
- Patient is best judge
- Patient best observer of some events and health outcomes (ie, improvement in function or occurrence of complications)

Oncology CER to Oncology Patient-Centered Outcomes Research (PCOR)

- Capturing patient perspective vital to complete picture of treatment impact
- Strategies to accelerate development of useful evidence
  - Apply research-grade standardized questionnaires
  - Include more uniformity in clinical trials, registries
  - Integrate into EMRs
  - Incentivize addition of administrative data (eg, pay for collection; require for reimbursement)

CER=comparative effectiveness research; EMR=electronic medical record.

Patient-Centered Outcomes Research Institute. http://www.pcori.org/research-we-support/pcor/establishing-a-definition/. Accessed February 25, 2013.

Data Synthesis, Evaluation, and Application: Treatment Pathways

Decreasing Variability of Oncology Patient Care

- Goal
  - Reduce variability in oncology care[1]
- Approach
  - Utilize pathways programs that identify “preferred” options: either a single-treatment option per condition or a subset of treatment options per condition[1]
  - Equalize incentives so physicians choose the best treatment without considering revenue implications[2]
  - Oncologists who achieve a specified level of pathway compliance may receive additional compensation[2]

1. Danielson E, et al. *J Natl Compr Canc Netw*. 2010;8(Suppl 7):S28–S37.
2. Soper AM, et al. *Am J Manag Care*. 2010;16:e94-e97.

Pathway Development: Guiding Principles

- Driven by data and best practice
  - Primary literature
  - National guidelines (eg, NCCN, ASCO, ASH, etc)
  - Appropriately conducted CER
- Exhaustive enough to cover 90% of the eligible patients
- Designed to allow outliers
- Economics considered when equivalent therapies identified
- Physician has ultimate control of treatment decision at point of care
- Pathways routinely modified/updated

NCCN=National Comprehensive Cancer Network; ASCO=American Society of Clinical Oncology; ASH=American Society of Hematology; CER=comparative effectiveness research.

https://www.p4pathways.com/go/p4pathways/program/services/pathway-development.htm.

Integration of Clinical Data into MM Treatment Pathways

- Utilization of a consistent treatment regimen based upon a balance between outcomes, toxicity, and cost
- Features of treatment pathways
  - Based upon the scientific and clinical literature
  - Provide a standard approach to the patient (eg, reduce misuse, hospitalizations)
  - Decrease variability of regimens utilized, including “off label” indications
  - Clearly define treatment endpoints and treatment milestones
- Benefits of treatment pathways will lead to
  - Reduced variability of care
  - Optimal outcomes
  - Minimizing and better management of toxicities
  - Allowing for a greater predictability of treatment cost

https://www.p4pathways.com/go/p4pathways/program/services/pathway-development.htm.

NCCN Treatment Guidelines Provide Evidence-based Direction to MM Care

- NCCN guidelines outline standards for the diagnosis, prognosis, treatment, and appropriate follow-up of patients with MM
  - Comprehensive guidance across the natural history of the disease
  - Identifies primary treatment modalities
  - Includes supporting references, background information, and discussion of ongoing controversies
  - Integrates clinical data and expert judgment to incorporate real-world clinical experience
- Uses an evidence-based approach when evidence is available
  - Evidence-based expert consensus when high-level evidence is lacking

NCCN=National Comprehensive Cancer Network.

Benson AB III, Brown E. *Am Health Drug Benefits*. 2008;1:28-33.

Engaging Oncology Providers Through Pathways Programs

- Key to the successful management of a high-cost disease is collaboration with the provider network on clinical pathways
  - Provides shared ownership of treatment outcomes
  - Acts as a vehicle to achieve buy-in from the general network
  - Encourages greater consensus between payer and providers
- Collaborative development of clinical pathways programs and performance metrics
  - Provide a process for evaluating new therapies and regimens
  - Pay-for-Performance initiatives in cancer remain uncommon, although some consider pathways programs to be a Pay-for-Performance model
  - Enables development of a more comprehensive program such as a patient-centered medical home (PCMH) or accountable care organizations (ACOs)

Danielson E, et al. *J Natl Compr Canc Netw*. 2010;8(Suppl 7):S28–S37
Wong W. Available at: http://www.valuebasedcancer.com/myeloma/article/are-pathways-effective-tool-controlling-costs. Accessed March 7, 2013.

United Healthcare Pay-for-Performance (P4P)

- Adherence to National Comprehensive Cancer Network (NCCN) Clinical Practice guidelines for chemotherapy administration
- Episode-of-care payment pilot initiated in 2009 and involving
  - 5 practices (n=158 oncologists)
  - 19 stages/types of breast, lung, and colon cancer
- Practices provided up-front lump sum payment to incentivize adherence to the appropriate clinical pathways
  - Drug costs reimbursed separately
- Covers all aspects of care as dictated by the disease stage and patient status
- Outcomes are compared and contrasted

Goozner M. *J Natl Cancer Inst*. 2011;103:8-10.

Leveraging the Features of an Accountable Care Organization (ACO)

ACO opportunities for cancer care

- Reduce treatment variation and optimize costs in "3 big-ticket areas":
  1. Treatment decision-making and therapeutic intervention
  2. Identification and management of side effects
  3. Delivery of end-of-life palliative care
- Opportunity with plans and cancer centers to tie service payments to benchmarks for quality, outcomes, and patient safety
- Potential savings will be driven by the design of incentive structures
  - The more oncologists are allowed to provide cost-effective care, the more likely they will be to participate

Summary

Summary

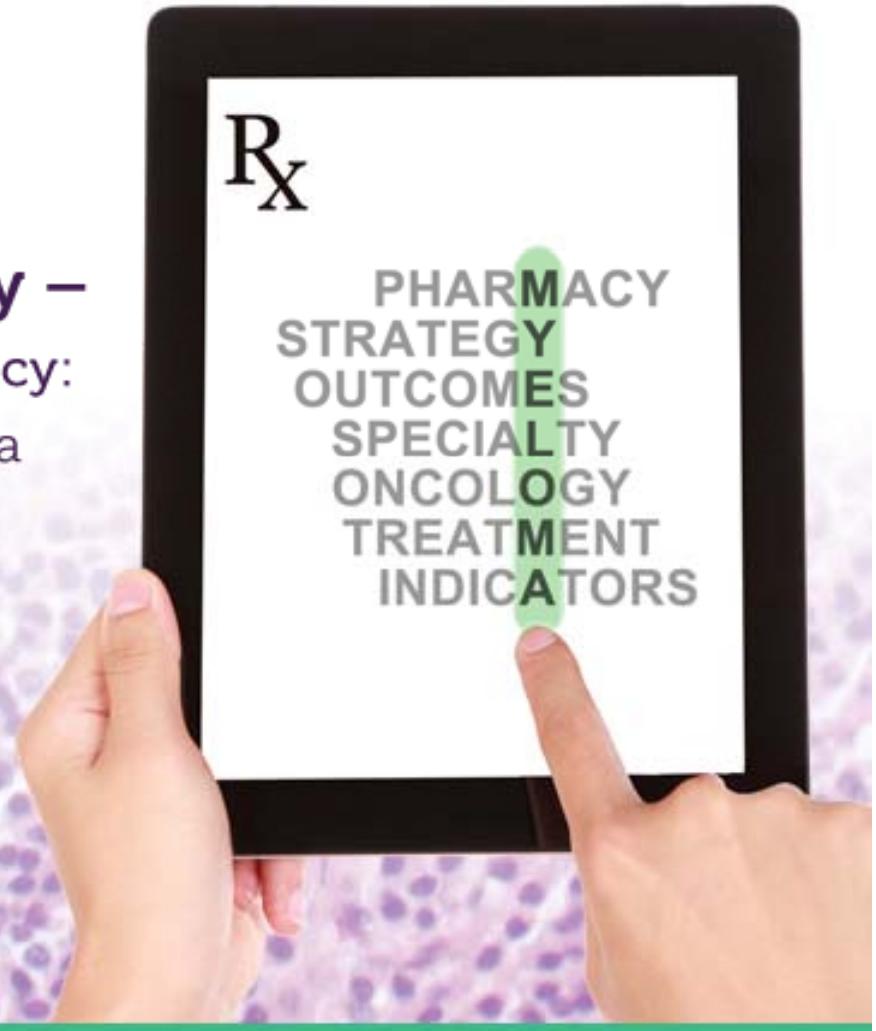
- Delivery of high-quality care requires access to state-of-the-art clinical knowledge
- Decision support tools provide health plans and affiliated clinicians with patient-specific assessments or recommendations to improve decision making and reduce treatment variability
- EMRs and e-prescribing provide a technology platform to integrate all aspects of patient care and reduce errors
- CER minimizes knowledge gaps to drive patient-focused clinical decisions and outcomes
- Treatment pathways can decrease variability of regimens with clearly defined treatment endpoints and treatment milestones

EMR=electronic medical record; CER=comparative effectiveness research.

Applying a Congruent Oncology Pharmacy Strategy –

From Guidelines to Specialty Pharmacy:

Steps for Success with Multiple Myeloma



Jointly sponsored by: PIM Postgraduate Institute for Medicine; Impact Education, LLC

This activity is supported by educational grants from Celgene Corporation, Millennium: The Takeda Oncology Company, and Onyx Pharmaceuticals.

ONYX Celgene Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

Collaborating to Improve Supportive Care Outcomes for Patients with Multiple Myeloma

Sandra Kurtin, RN, MS, AOCN®, ANP-C

University of Arizona Cancer Center

Disclosures

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Sandra Kurtin, RN, MS, AOCN®, ANP-C

  – *Consulting Fees*: Onyx Pharmaceuticals, Celgene Corporation, and Millennium: The Takeda Oncology Company

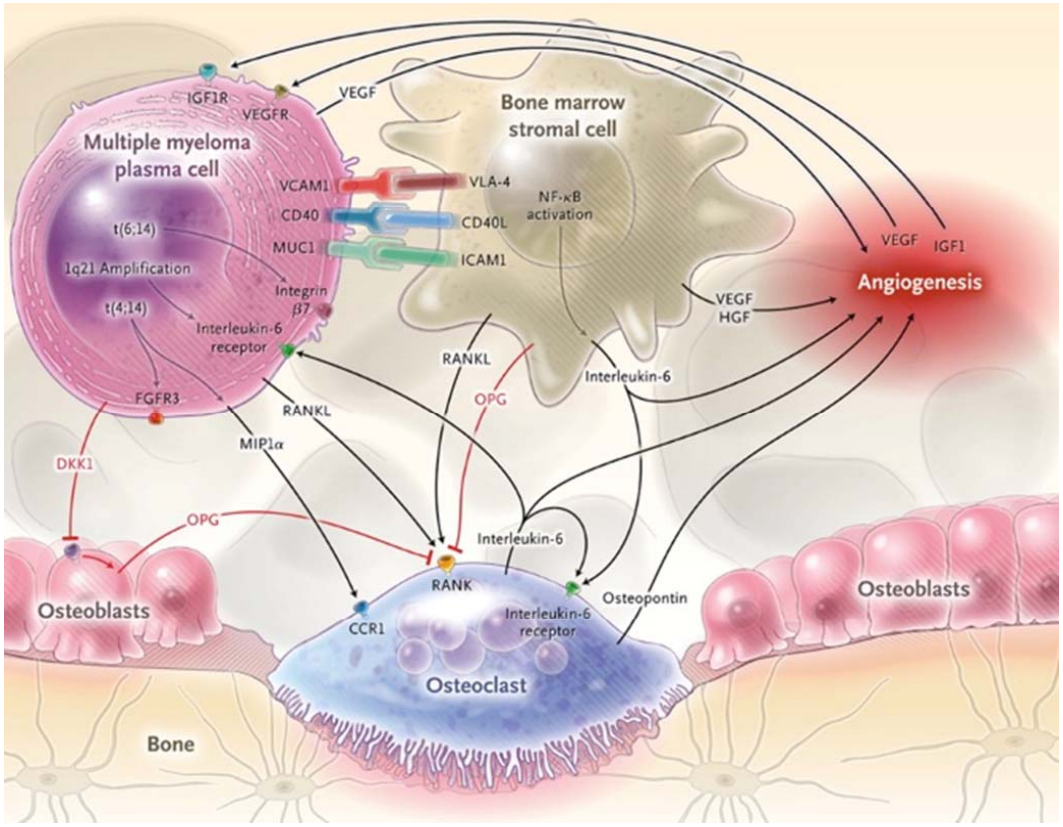
  – *Fees for Non-CME/CE Services*: Onyx Pharmaceuticals, Celgene Corporation, and Millennium: The Takeda Oncology Company

Outline

- Pathobiology of multiple myeloma
  - Common signs and symptoms
- Review of treatment options
  - Relationship of treatment to supportive care requirements
- Areas of supportive care including
  - Anemia
  - Infections
  - Thrombosis
  - Bone health and disease
  - Renal dysfunction
  - Neuropathy
- Summary

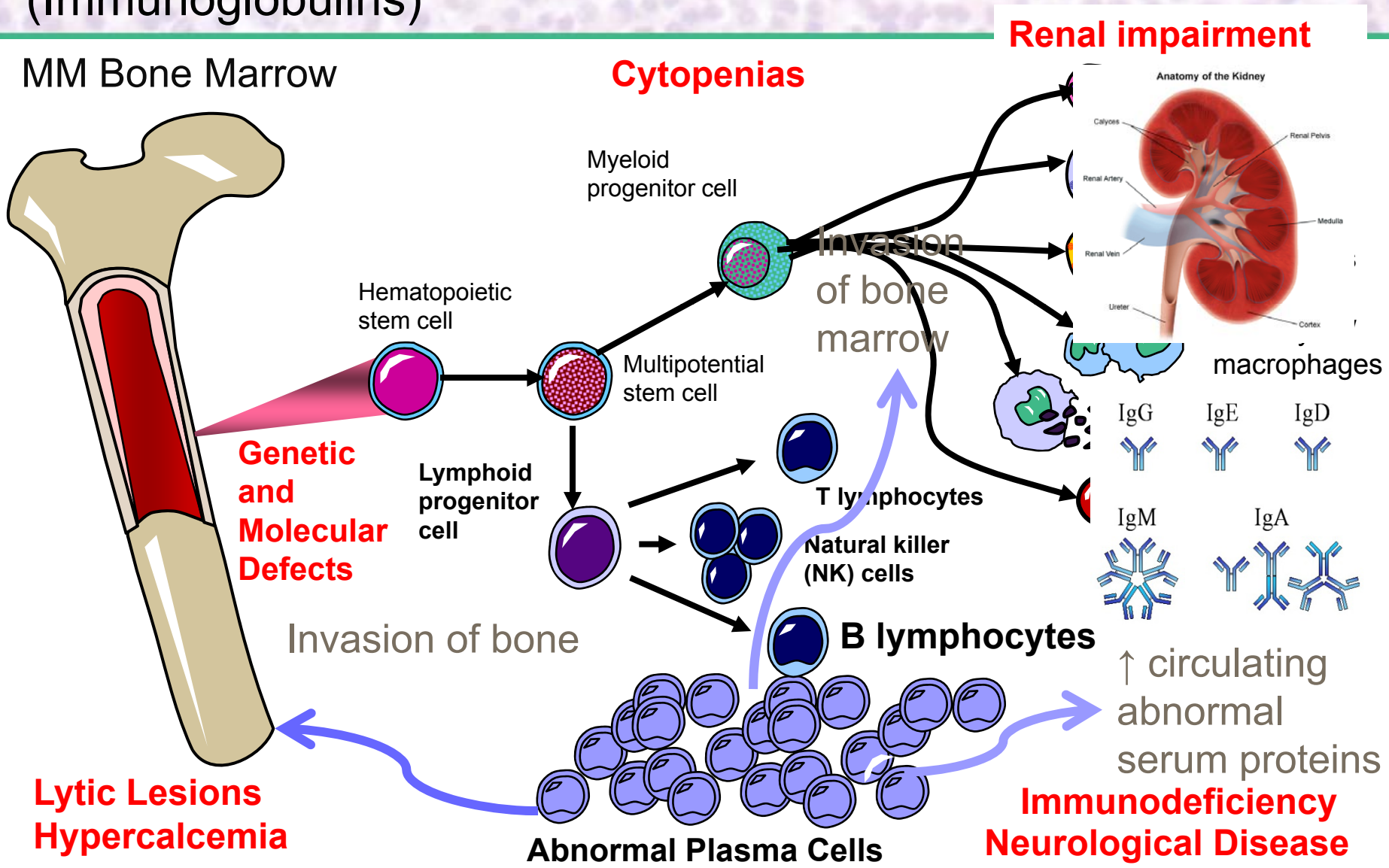
Pathobiology

- Clonal (lymphoid) plasma cell malignancy
- Complex interaction
  - Malignant progenitor cells
  - Bone marrow stroma
    - Stromal dysregulation
  - Bone marrow microenvironment
    - Cytokine abnormalities
    - Oncogene dysregulation
- These attributes are key to the presenting signs and symptoms and current approach to treatment



Richardson PG, et al. *Oncology*. 2010;24(suppl 2):2-32.
Siegel DS, Bilotti E. *Community Oncol*. 2010;6(suppl 3):22-30.
Palumbo A, Anderson KC. *N Engl J Med*. 2011;364:1046-1060.

Genetic and Molecular Defects Lead to Overproduction of Abnormal Plasma Cells and Associated Serum Proteins (Immunoglobulins)



Stem cell basics. NIH Stem Cell Information Available at: http://stemcells.nih.gov/info/basics/basics4.asp. Accessed March 21, 2013.

Common Presenting Signs and Symptoms

- **Most common complaint at presentation is bone pain and fatigue**
- **Signs and symptoms result from an overproduction of immunoglobulins with secondary processes**

Disease Process	Symptoms	Clinical Findings
Plasma cell invasion of the bone	• **Bone pain (58%)** • **Hypercalcemia**	• **Lytic lesions (66%)** • **Compression fractures or other skeletal fractures** • **Hypercalcemia (13%)** • **Osteoporosis, Osteopenia** • **Cord compression**
Bone marrow involvement	• **Fatigue (32%)** • **Infections** • **Bleeding**	• **Anemia (73%)** • **Neutropenia** • **Thrombocytopenia**

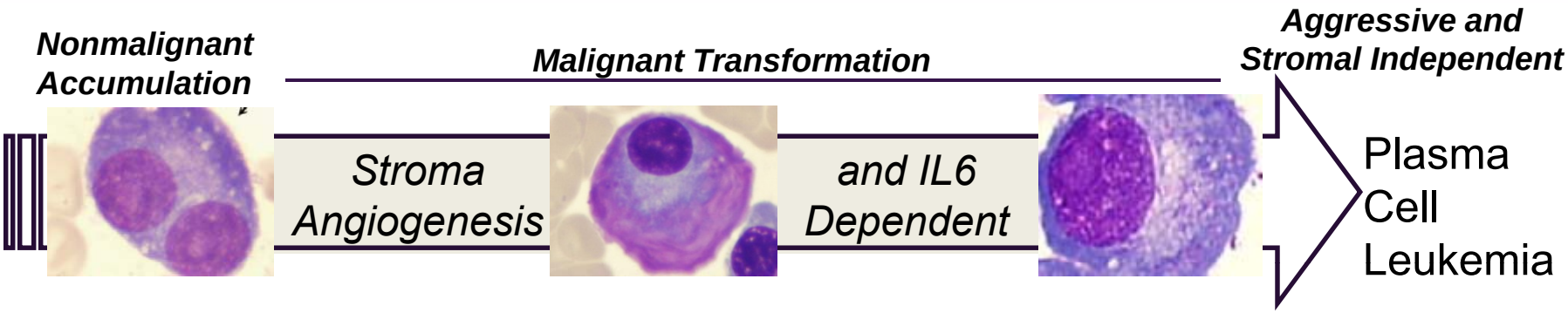
Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33.

Common Presenting Signs and Symptoms (2)

Disease Process	Symptoms	Clinical Findings
Renal injury	• Fatigue • Oliguria (late finding) • Hematuria	• Elevated creatinine (19%) • Acute renal failure (ARF) Chronic renal insufficiency (CRI) • Chronic renal failure • Anemia • Hypercalcemia • Hyperviscosity • Urate nephropathy
Abnormal immunoglobulin function	• Fever • Infections	• Hypogammaglobulinemia • Infections • Neurological disease
Hyperviscosity	• Pain • Paresthesia • Immobility	• Peripheral neuropathy (5%) • Strokes

Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33.

Disease Trajectory

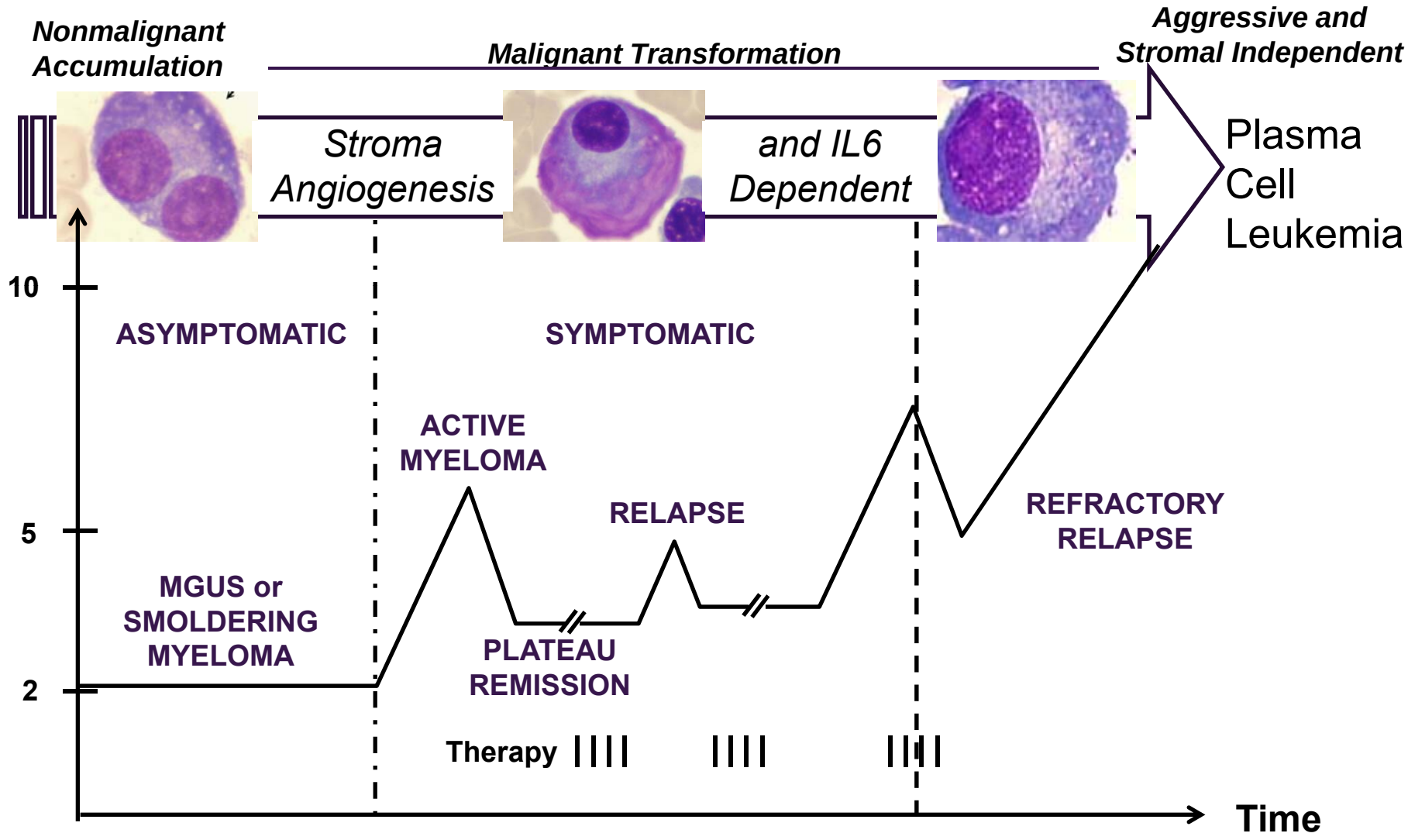


MGUS	Smoldering Myeloma	Multiple Myeloma
< 3 g M protein **< 10% clonal BMPC** **No MM-related end-organ damage**	**≥ 3g M protein** **< 10% clonal BMPC** **No MM-related end-organ damage**	**≥ 10% clonal BMPC** **M protein in serum and/or urine** **≥ 1 CRAB features of disease related organ damage** **C**: Calcium elevation > 11.5 mg/L or ULN **R:** Renal dysfunction serum creatinine > 2 mg/dL **A:** Anemia Hb < 10 g/dL or 2 g < normal **B:** Bone disease lytic lesions or osteoporosis

BMPC=bone marrow plasma cells; Hb=hemoglobin; MGUS=monoclonal gammopathy of unknown significance; M protein=myeloma protein; IL6=interleukin-6; ULN=upper limit of normal

Kuehl WM, Bergsagel PL. *Nat Rev Cancer*. 2002;2:175-187.
Vacca A, Ribatti D. *Leukemia.* 2006;20:193-199.
Siegel DS, Bilotti E. *Community Oncol*. 2009;6:12(suppl 3):22-29.
Durie BG, et al. *Hematol J*. 2003;4:379-398.
Adapted with permission from Kurtin SE. *JAdPrO,* 2010;1:19-29.

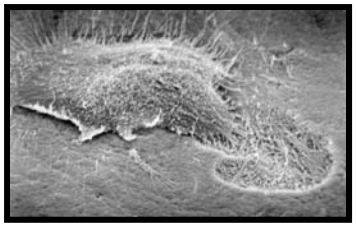
Disease Trajectory (2)



Kuehl WM, Bergsagel PL. *Nat Rev Cancer*. 2002;2:175-187; Vacca A, Ribatti D. *Leukemia.* 2006;20:193-199; Siegel DS, Bilotti E. *Community Oncol*. 2009;6:12(suppl 3):22-29; Durie BG, et al. *Hematol J*. 2003;4:379-398; Adapted with permission from Kurtin SE. *JAdPrO,* 2010;1:19-29.

Beyond the CRAB Criteria: Myeloma Defining Event

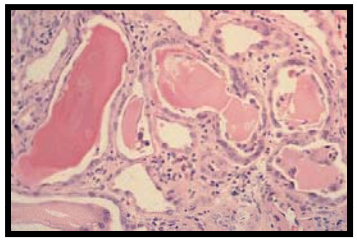
Calcium (either):



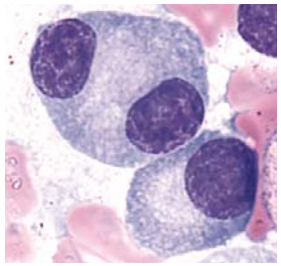
osteoclast

> 11mg/dl OR
≥ 1mg/dL above ULN

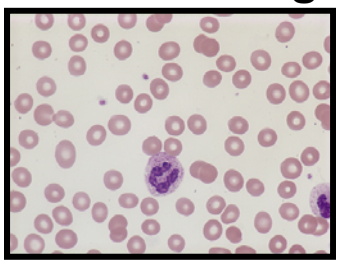
Renal: creatinine >2mg/dL



OR (at at least one):
eGFR ≤ 50
eGFR ↓ ≥35% in 1y
Biopsy confirmation

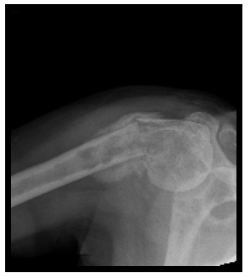


Anemia: HgB <10g/dL OR



2g/dL below LLN)

Bone - lytic lesions on bone survey

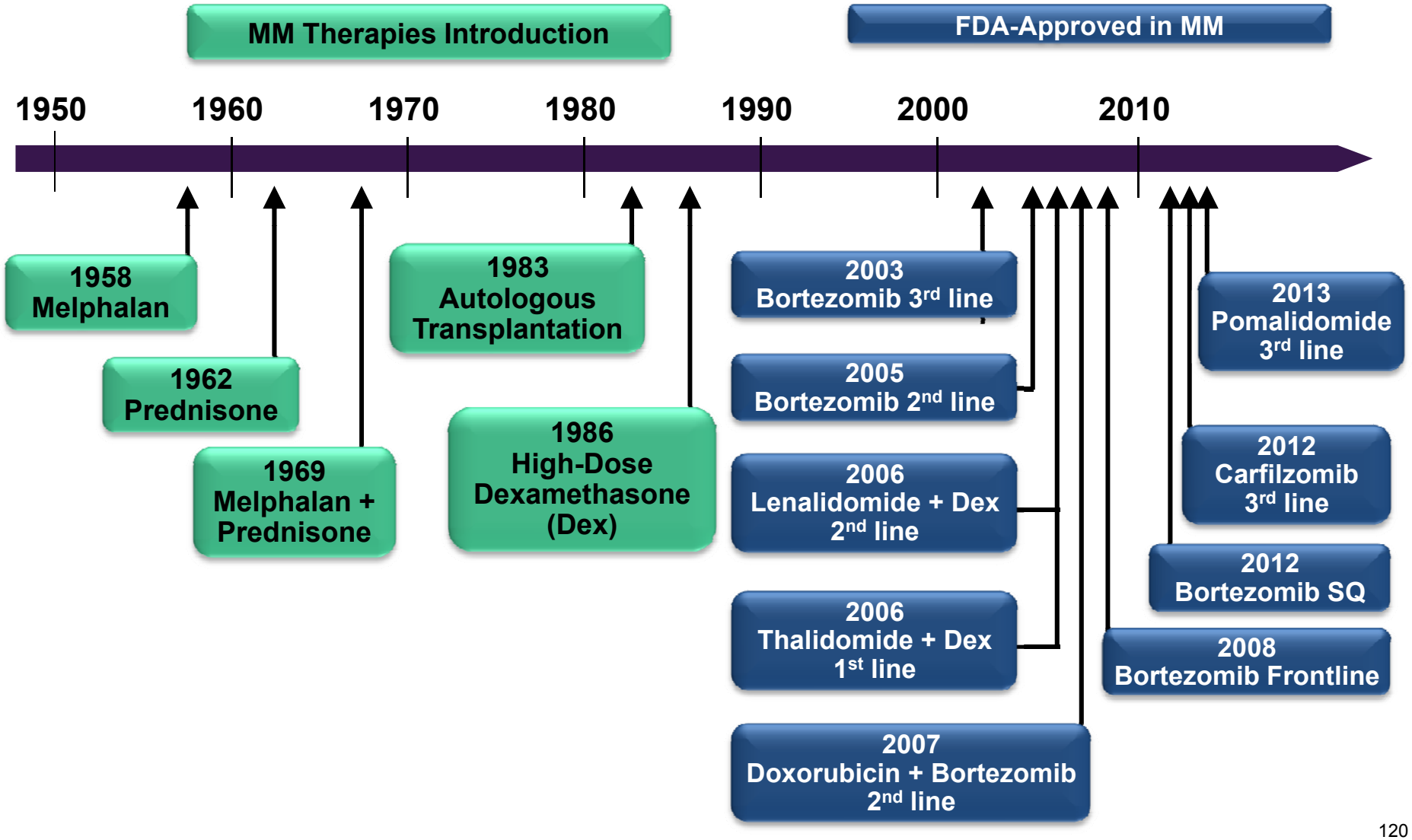


Or, if x-rays negative -either:
≥ 3 hyperintense MRI foci
≥ 1 "large" MRI lesion
≥ 1 lytic lesion > 1cm PET/CT
≥ 3 small lytic PET/CT)

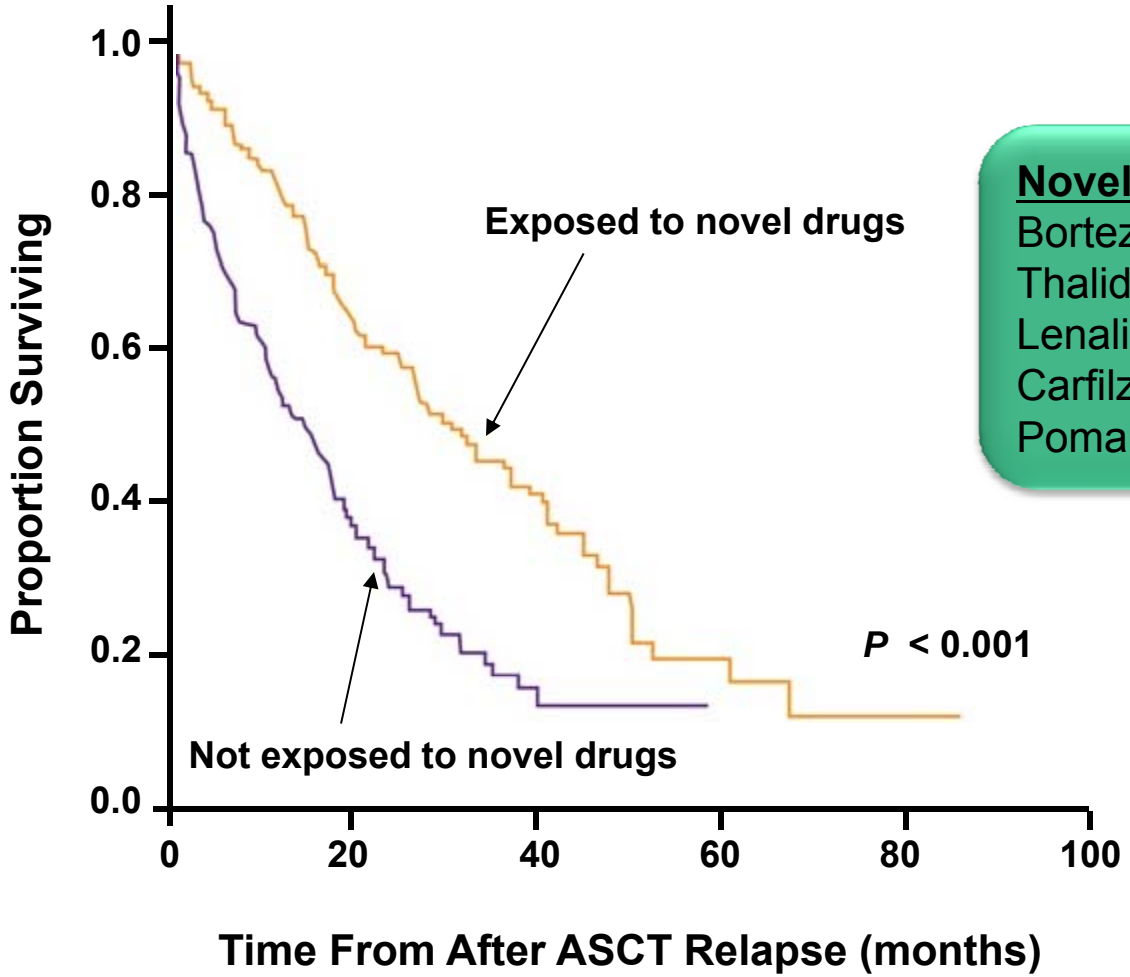
IMWG. *Br J Haematol*. 2003; 121:749–57.
Update in: Durie BG,et al. *Leukemia*. 2006;20:1467-73.
Kyle RA, Rajkumar SV. *Leukemia*. 2009;23:3–9.
Update Paris, 2011. Available at: http://myeloma.org/pdfs/XIV-06_Panel2.pdf. Accessed March 21, 2013.

Arnett T. www.brsoc.org.uk/gallery/arnett_osteoclast.jpg. Accessed March 21, 2013.
Maslak P. ASH Image Bank. 2004; 2004:101227.
Chapel H, et al. Essentials of Clinical Immunology 5th Ed., Blackwell Publishing.
Maslak P. ASH Image Bank. 2008; 2008: 8-00095.
Alexander et al. *Eye*. 2008;22:1089-1092.

Treatment Options Have Greatly Increased in the Past Decade



Novel Drugs Are Key for Improved Survival



Novel therapy	Approval
Bortezomib	2003
Thalidomide	2006
Lenalidomide	2006
Carfilzomib	2012
Pomalidomide	2013

ASCT=autologous stem cell transplant

Kumar SK, et al. *Blood*. 2008;111:2516-2520; ONS NLB Presentation 2010.

Drugs Used to Treat Multiple Myeloma

	Abbreviation	Drug Class	Brand
Bortezomib	btz	Proteasome inhibitor	VELCADE®
Carflizomib	car	Proteasome inhibitor	KYPROLIS®
Lenalidomide	len	Immunomodulatory agent	REVLIMID®
Thalidomide	thal	Immunomodulatory agent	THALOMID®
Pomalidomide	pom	Immunomodulatory agent	POMALYST®
Melphalan	mel	Alkylating agent	ALKERAN®, ALPHALAN®
Cyclophosphamide	CTX	Alkylating agent	CYTOXAN®
Prednisone	P, pred	Corticosteroid	DELTASONE®
Dexamethasone	D, d, Dex, DXM	Corticosteroid	DECADRON®
Pamidronate	pmd	Bisphosphonate	AREDIA®
Zoledronic Acid	zol	Bisphosphonate	ZOMETA®

- **In addition to new therapeutic options, combination and supportive care has also improved including use of bisphophonates, antibiotics, and reduced doses of steroids**
- **Improving quality of life and survival has become an important goal of treatment**

Common Dosing Regimens for Novel Therapies

Agent/Class	Dosing and Route of Administration
Bortezomib[1] **Proteasome inhibitor**	• **1.3 mg/m^2 IV or SC days 1,4,8,11, every 21 days x 2 cycles, then weekly dosing 3 weeks on/1 week off** • **Variable dosing in combination regimens** • **Dose modification for neuropathy, cytopenias**
Carfilzomib[2] **Proteasome inhibitor**	• **20 mg/m2 IV (cycle 1), 27mg/m2 (cycle #2-12) days 1,2,8,9,15,16, every 28 days** • **Dose modifications for cytopenias, cardiopulmonary symptoms**
Lenalidomide[3] **Immunomodulatory agent**	• **25 mg/d by mouth for induction** • **Variable dosing in combination regimens** • **Dose modification based on renal function, cytopenias**
Pomalidomide[4] **Immunomodulatory agent**	• **4 mg/d days 1-21 using a 28 day cycle** • **Dose modifications for cytopenias**
Thalidomide[5] **Immunomodulatory agent**	• **200 mg/d by mouth at bedtime** • **Variable dosing in combination regimens** • **Dose modification for neuropathy, cytopenias**

1. Velcade [bortezomib]. Prescribing information. Millenium Pharmaceuticals, Inc. Cambridge, MA. 2012; 2. Kyprolis [carfilzomib]. Prescribing Information. Onyx Pharmaceuticals, Inc. S. San Francisco, CA. 2012; 3. Revlimid [lenalidomide]. Prescribing Information. Celgene Corporation. Summitt, NJ. 2013; 4. Pomalyst [pomalidomide]. Prescribing Information. Celgene Corporation. Summitt, NJ. 2013; 5. Thalomid [thalidomide]. Prescribing Information. Celgene Corporation. Summitt, NJ. 2013.

Common Adverse Events for Proteasome Inhibitors Used to Treat MM

Adverse Event All grades Grade 3 /4	Proteasome Inhibitor Agents	
	Bortezomib	Carfilzomib Relapsed/Refractory
Thrombocytopenia and Neutropenia	Thrombocytopenia (cyclic):36% (29%) Neutropenia: 17%; (12%)	Thrombocytopenia: (cyclic): 36.3% (23.4%) Neutropenia: 20.7% (10.3%)
Peripheral Neuropathy	Twice weekly IV: 53% (16%) Weekly IV: 41% (16%) Weekly SC: 24% (6%)	Overall: 14% (1% grade 3, no grade 4)
Fatigue	Overall: 64% (16%)	Overall: 55.5% (7.6%)
Gastrointestinal	Diarrhea: Overall: 52% (8%) Nausea: 57% (8%)	Constipation: 20.9% (0.2 %) Diarrhea: 32.7% (1.0%) Nausea: 44.9% (1.3 %)
Cardiopulmonary	Dyspnea: 11%, Hypotension: 13% Congestive Heart Failure (CHF): 5% Peripheral edema: 11%	Dyspnea: 34.6% (4.9%)✦ Hypertension: 14.3% (3.2%) Peripheral edema: 24.0% (0.6%)
Infectious complications	Varicella Zoster: 13-20%	Varicella Zoster: 2% Pneumonia: 12.7% (10.5%)
Renal dose modification	No renal dose adjustment required	Renal dose adjustment recommended for creatinine $\geq$ 2 x baseline
Thromboembolic Events	Not reported*	Not reported*
Rash	Not reported*	Not reported*

Based on clinical trials to date with incidence >5-10%; prescribing information for each agent (Palumbo A, Anderson K. *N Engl J Med*. 2011;364:1046-1060).
*Data not available or incidence was below threshold for reporting.
Kurtin SE, Bilotti E. *JAdPrO*. 2103 (accepted for publication).

Common Adverse Events for Immunomodulatory Agents Used to Treat MM

Adverse Event All grades Grade 3 /4	Immunomodulatory Agents		
	Lenalidomide (with dexamethasone)	Thalidomide (with dexamethasone)	Pomalidomide 4mg * (with dexamethasone) Relapsed/Refractory
Thrombocytopenia and Neutropenia	Thrombocytopenia: 21% (12%) Neutropenia: 42% (33%)	Thrombocytopenia:23% Neutropenia: 31%	Thrombocytopenia: 23% (19%) Neutropenia: 47% (38%)
Peripheral Neuropathy	Not significant	All Grades: 54% (3-5%) ↑ with higher doses and prolonged therapy	Overall: 7% (0)
Fatigue	Overall: 43% (6%)	Overall: 81% (17%)	Overall: 63% (13%)
Gastrointestinal	Constipation: 40% (3%) Diarrhea: 38.5% (2%) Nausea: 26% (1%)	Constipation: 56% (8%) Nausea: 29& (5%)	Diarrhea: 33% (0) Anorexia: 35% (0) Nausea: 22% (0)
Cardiopulmonary	Dyspnea: 23% (not reported) Hypotension: 7% (not reported)	Dyspnea: 41% (13%) Peripheral edema: 57% (6%) Bradycardia reported	Dyspnea: 45% (13%) Peripheral edema: 16% (0)
Infectious complications	Pneumonia: 14%	Pneumonia: 35%	Pneumonia: 29% (23%)
Renal dose modification	Requires renal dose adjustment	No dose modification required	Dose modification of creatinine >3.0 should be considered – clinical trial in renal impairment under way
Thromboembolic Events	Overall: 9.3%	Overall: 23%	Not reported*
Rash	Overall: 21%	Overall: 30%	Overall: 16%

Based on clinical trials to date with incidence >5-10%; prescribing information for each agent. (Palumbo A, Anderson K. *N Engl J Med*. 2011;364:1046-1060).
*Data not available or incidence was below threshold for reporting.
Kurtin SE, Bilotti E. *JAdPrO*. 2103 (accepted for publication).

Factors Associated with High Risk for Chemotherapy-Induced Myelotoxicity

Host related Factors	Disease and Treatment Related Factors
Age > 65	High tumor burden/extensive disease
Female gender	Previous history of chemotherapy or radiation
ECOG PS >1	Pre-existing cytopenias
Malnutrition	Bone marrow involvement with tumor
Immunosuppression	Type of chemotherapy
Comorbidities: COPD, diabetes, renal impairment, liver disease	Dose intensity of chemotherapy
Open wounds or recent surgery	Elevated lactate dehydrogenase (LDH)
Active infection or pre-existing fungal infections	Hypoalbuminemia
Drug-drug Interactions	Hyperbilirubinemia
	Hematological malignancy
	Hospitalization

ECOG PS=Eastern Cooperative Oncology Group performance status

Scripture CD, et al. *Curr Neuropharmacol*. 2006;4:165-72; Daniel D, Crawford J. *Semin Oncol*. 2006;33:74-85; Aapro M, et al. *Ann Oncol*. 2011;22:257-267; Schwenkglenks M, et al. *Support Care Cancer*. 2011;19:483-490; Kurtin SE, Bilotti E. *J Adv Pract Oncol*. 2103 (accepted for publication).

Management of Anemia in MM

Assessment of Risk

Patients at high risk for more serious complications of anemia include:

- **Cardiopulmonary disease, progressive or rapid decline in Hgb with or without recent chemotherapy or radiation, Sustained symptom: tachycardia, tachypnea, chest pain, dyspnea, syncope, debilitating fatigue**

General Principle of Treatment

- **Establish the underlying cause(s):**
  - **Bleeding, nutritional, inherited, renal insufficiency, treatment, chronic disease, hemolysis**
- **Treatment of the underlying cause(s)**
- **Evaluate symptoms of anemia with consideration of individual patient characteristics**
- **Weigh the risks and benefits of each treatment approach (PRBC transfusion, ESA administration)**

ESA=erythropoiesis-stimulating agent; PRBC=Packed Red Blood Cell

Kurtin S. *J Adv Pract Oncol*. 2012;3:209–224.

Management of Anemia: Transfusion of PRBCs

Requires informed consent

General Guidelines:

- Asymptomatic patients: transfuse to maintain Hgb 7-9 g/dL
- Symptomatic with hemorrhage: transfuse to maintain hemodynamic stability
- Symptomatic with Hgb < 10g/dL – transfuse to maintain Hgb 8-10g/dL
- Acute coronary syndromes with anemia – transfuse to maintain Hgb > 10g/dL

Benefits: Rapid increase in Hgb, may improve fatigue in some patients

Risks

- Viral transmission: HIV: 3.1/100,000, Hepatitis C: 5.1/100,000, Hepatitis B: 3.41-3.43/100,000
- Transfusion related acute lung injury (TRALI): 0.81/100,000
- Transfusion associated circulatory overload (TACO):1-6% - ↑ in ICU and post-operative settings
- Fatal Hemolysis: 1.3-1.7/million transfused units
- Febrile non-hemolytic reactions: 1.1 - 2.15%

PRBC=Packed Red Blood Cell

Kurtin S. *J Adv Pract Oncol*. 2012;3:209–224.

Management of Anemia: ESA Administration

- **Benefits: Avoidance of transfusions**
- **Risks**
  - Inferior survival and decreased time to progression—most notably with target Hgb > 12g/dL
    - http://www.fda.gov/cder/drug/infopage/RHE/default.htm
  - Thrombosis—increased with risk with history of coagulopathy, obesity, coronary artery disease, thrombocytosis, hypertension, immobilization, hospitalization, selected hormonal therapies, immunomodulatory agents
    - http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive
  - Hypertension/Seizures
  - Pure red cell aplasia (rare)
- **Administration of ESAs: FDA approved agents:**
  - Aranesp® (darbepoetin alfa), Procrit® (epoetin alfa), Epogen® (epoetin alfa)
  - Not indicated in patients receiving chemotherapy with curative intent
  - Requires REMS compliance and training for providers (ESA APPRISE Oncology Program)
    - https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp
  - Requires informed consent for patients
  - Goal is to administer the lowest dose necessary to avoid PRBC transfusion not to exceed a Hgb of 10g/dL
  - If Hgb rises > 1g/dL in any 2-week period dose reductions are required – see prescribing information
    - https://www.esa-apprise.com/ESAAppriseUI/ESAAppriseUI/default.jsp

ESAs=Erythropoiesis Stimulating Agents

Kurtin S. *J Adv Pract Oncol*. 2012;3:209–224.

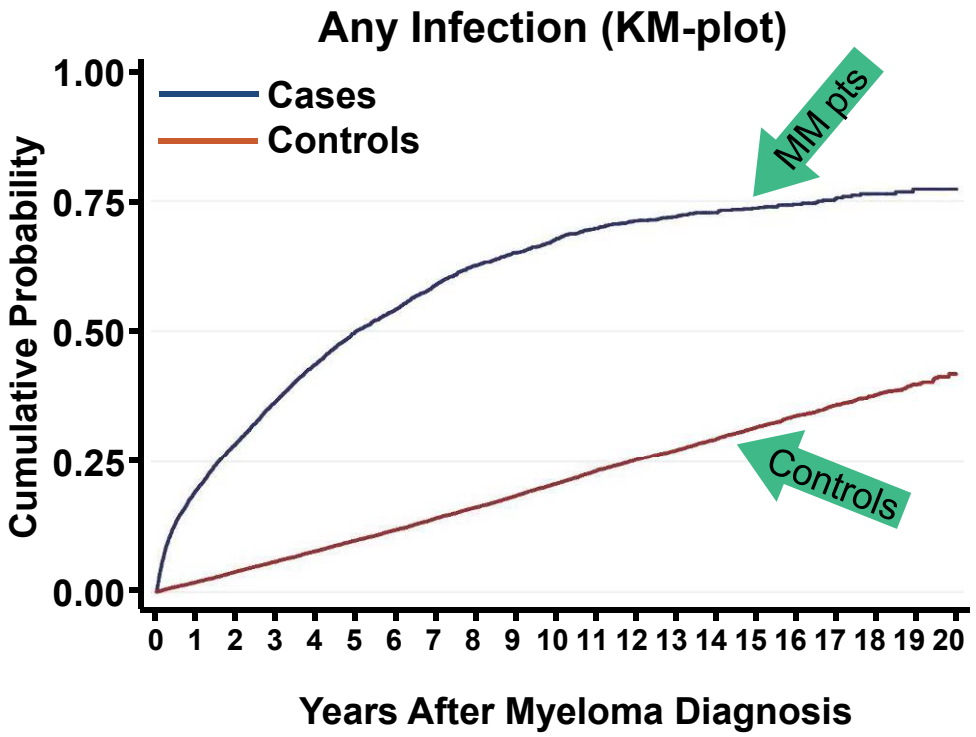
MM Patients at Risk for Developing Infections

Study

- Goal: assess the risk of infections in MM patients (pts)
- All 9,610 MM pts in Swedish Cancer Registry 1988-2004 compared to 4 age matched controls (37,718 controls)

Results

- Increased risk for bacterial infection was 6-fold (HR=5.9; 95%; CI=5.6-6.1)
- Increased risk for viral infections was 9-fold (HR=9.0; 95% CI=8.0-10.1)
- Risk of specific infections like pneumonia, and septicemia >10 times higher in pts than in controls during first year after MM diagnosis



Myeloma patients have a high risk (6X or greater than controls) of developing infections

HR=hazard ratio; CI=confidence interval

Blimark C, et al. Presented at the American Society of Hematology Annual Meeting. 2012. Abstract 945.

Common Infectious Pathogens in Neutropenic Patients

- Initial infections are primarily bacteria; subsequent infections are primarily antibiotic-resistant bacteria, yeast, other fungi, and viruses
- Infection from Candida species occurs later in the course of neutropenia, often as a consequence of GI mucositis
- Aspergillus species and other filamentous fungi are causes of morbidity and mortality with severe and prolonged neutropenia

Wood SK, Payne JK. *J Adv Pract Oncol*. 2011;2:356–371.

Common Infectious Pathogens in Neutropenic Patients

Major Gram-Positive Pathogens	Major Gram-Negative Pathogens	Initial Viral Pathogens
• Coagulase-negative staphylococci • Staphylococcus aureus, including methicillin-resistant strains • Enterococcus species, including vancomycin-resistant strains • Viridans group streptococci • Streptococcus pneumoniae • Streptococcus pyogenes	• Escherichia coli • Klebsiella species • Enterobacter species • Pseudomonas aeruginosa • Citrobacter species • Acinetobacter species • Stenotrophomonas maltophiliata	• Herpes simplex virus • Respiratory syncytial virus • Parainfluenza • Influenza A & B

Wood SK, Payne JK. *J Adv Pract Oncol*. 2011;2:356–371.

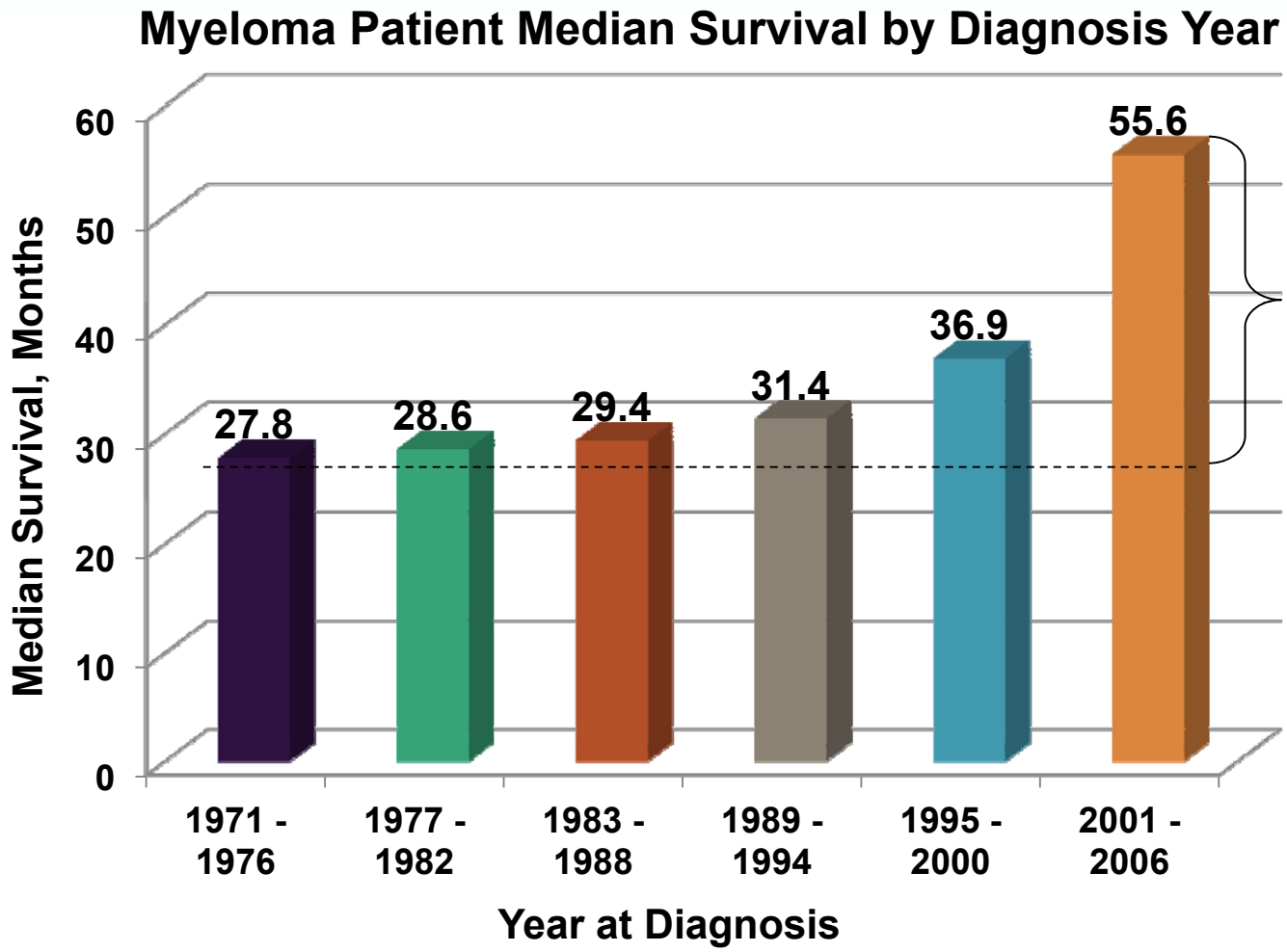
Disease and Treatment Related Side Effects: Infections

- **Leading cause of death in myeloma patients**
  - Risk further increased by cytotoxic therapy, transplant, and glucocorticoids
- **Immunoglobulin levels decreased**
  - Hyporesponsive to antigen stimulation
  - Deficient antibody production
- **Infiltration of bone marrow by plasma cells**
- **Interventions**
  - Prompt reporting of symptoms and institution of treatment
  - IVIG for serum IgG<500
  - Poor response to pneumococcal and influenza vaccines (STILL GIVE)
  - No ZOSTAVAX; give herpes zoster oral prophylaxis (bortezomib, carfilzomib)
  - Treatment for fungal infections using azoles based on response and tolerance

IVIG= Intravenous immunoglobulin; IgG=immunoglobulin G

Wood SK, Payne JK. *J Adv Pract Oncol*. 2011;2:356–371.

Multiple Myeloma Patients Are Living Longer



OS = 4.6 yrs

Patients live twice as long with MM*

OS improved to 7.3 yrs in 1 subgroup when a newer agent (len, thal, or btz) was used

***Prior to recent agent approvals; survival may be longer now**

Kumar SK, et al. Presented at ASH. 2012. Abstract 3972; Kumar SK, et al. *Blood*. 2008;111:2516-2520.

OS=median overall survival

Dose Adjustments for Age/Frailty

Drug	Age		Frailty*
	65-75 Years	>75 Years	for >75 yrs of age
Lenalidomide**	25 mg days 1-21	15 mg days 1-21	mild to severe with no risk factors
Bortezomib	1.3 mg/m^2 biweekly	1.3 mg/m^2 weekly	mild or moderate and up to one risk factor
Dexamethasone	40 mg weekly	20 mg weekly	mild to severe with no risk factors
Melphalan	0.25 mg/kg days 1-4	0.18 mg/kg days 1-4	mild to moderate and up to 1 risk factor
Thalidomide	200 mg per day	100 mg per day	mild to severe with no risk factors

*** Patients grouped from very fit to severely frail, depending upon need for help and level of activity. Risk factors include comorbidities.**
**** Lenalidomide plus melphalan starting dose 10 mg/d.**

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

Management of Chemotherapy-Induced Thrombocytopenia

Assessment of risk

- CTCAE risk and WHO bleeding grades
  1. Petechiae, ecchymosis, occult blood in body secretions, mild vaginal spotting
  2. Evidence of gross hemorrhage not requiring red blood cell transfusion over routine needs: epistaxis, hematuria, hematemesis
  3. Hemorrhage of one or more units of PRBCs/day
  4. Life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (eg, intracranial, pericardial, or pulmonary hemorrhage)
- Evaluate symptoms and underlying disease
- Determine chronicity
- Consider individual characteristics of the patients, including proximity to treatment center, concomitant anti-coagulation therapy or antiplatelet drugs, prior response to platelets, concurrent inflammatory process/infection, CNS disease

CTCAE=Common Terminology Criteria for Adverse Events

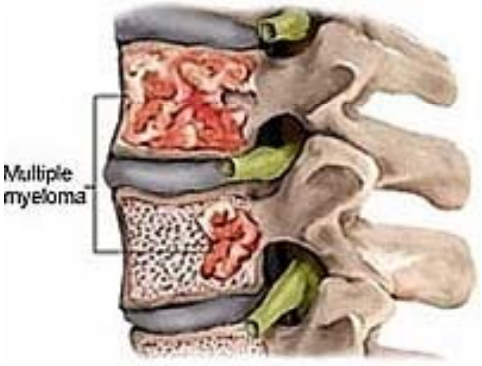
Management of Chemotherapy-Induced Thrombocytopenia (2)

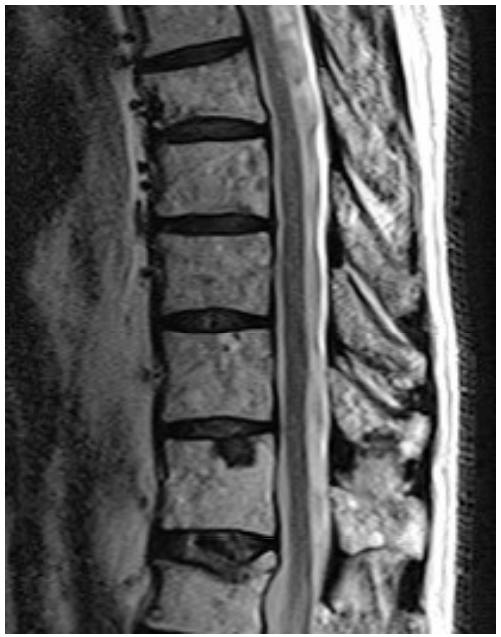
Prevention

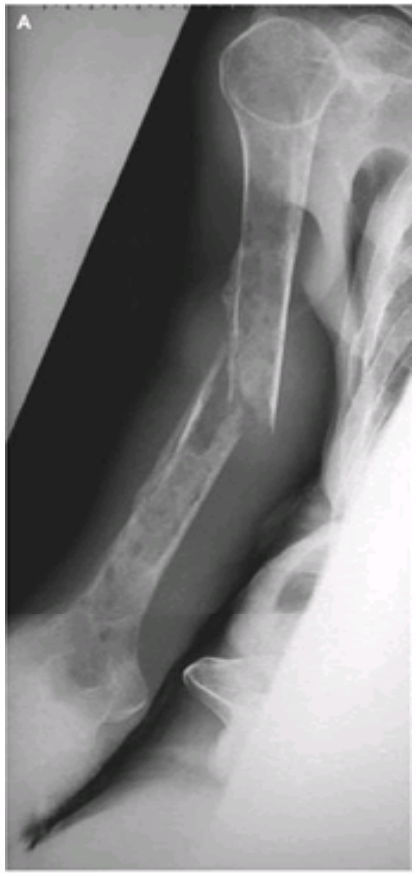
- Evaluate bleeding risk
- Establish plan of care for monitoring blood counts and follow-up
- Maintain a current type and screen blood identification band for patients requiring frequent transfusions
- Hold anticoagulation therapy for platelet count < 50,000/µL
- Educate the patient and caregivers about bleeding precautions and reportable signs and symptoms

Bone Disease

- Myeloma cells produce cytokines
- Increase osteoclast differentiation
- Suppress osteoblast maturation
- Inhibit new bone
- Results
  - Infiltrate and destroy bone
  - Cause
    - Osteolysis
    - Bone pain
    - Pathological fractures
    - Hypercalcemia







Niesvizky R, Badros AZ. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20.
Drake MT. *Oncology*. 2009;23(14 suppl 5):28-32.

Imaging Techniques for Assessing Bone Disease

Technique	How it Works	When to Use	Limitations to Use
MBS (skeletal survey)	• Series of x-rays of axial and appendicular skeleton	• Baseline & relapse	• Insensitive; bone lesions only seen >30% bone loss occurs
MRI	• Three sequence approach (T1, STIR, post-gadolinium) detects MM activity in bone marrow • Highly sensitive	• Verify solitary plasmacytomas; non-secretory disease • Assess spinal cord compression	• Lack of specificity reflects marrow infiltration not specifically bone deterioration • Expense & time
CT	• Multiple computerized x-ray images from different angles • Highly sensitive	• Soft-tissue disease; non-secretory disease	• Does not differentiate between active & inactive lesions • Higher levels of radiation exposure
PET	• FDG tracer illuminates metabolically active cells • Highly sensitive	• Assess extra-medullary disease; response	• Lack of specificity of findings may result in false-positive results; expense
CT/PET Fusion	• Fusion of CT/PET imaging • Highly sensitive	• Assess active disease & areas of bone destruction that are not active	• Expense
DEXA (bone densitometry)	• Measurement of osteopenia or osteoporosis	• If comorbid conditions exist for osteoporosis	• Does not measure osteolytic disease
Technetium-99 Sestamibi Scan (Bone Scan)	• Measure osteoblast activity	• Not appropriate for evaluating MM	• Underestimates osteolytic lesions found in MM

MBS=metastatic bone survey; STIR=short tau-inversion recovery; FDG=^{18}F-deoxyglucose.

Roodman GD. *Hematology Am Soc Hematol Educ Program*. 2008:313-319 ; Durie BG, et al. *Leukemia*. 2006;20:1467-1473; Tariman JD. *Clin J Oncol Nurs*. 2004;8:318-320; Guise TA, Mundy GR. *Endocr Rev*. 1998;19:18-54; Gralow JR, et al. *J Natl Compr Canc Netw*. 2009 ;7 (Suppl 3):S1-32; Dimopoulous M, et al. *Leukemia.* 2009; 23:1545-1556.

Management of Bone Disease

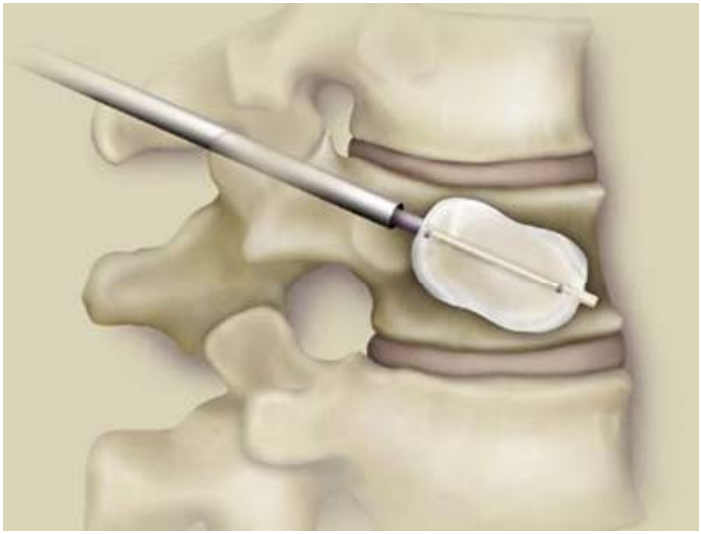
Treat the myeloma

- Novel therapies have benefit:
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoclast stimulation
- Radiotherapy (low dose)
  - Impending fracture
  - Cord compression
  - Plasmacytomas
- Orthopedic consultation
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability

Niesvizky R, Badros AZ. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20.
Drake MT. *Oncology*. 2009;23(14 suppl 5):28-32.

Management of Bone Disease: Supportive Care

- Bisphosphonates (category 1)
  - Pamidronate
  - Zoledronic acid
  - Both require monitoring
    - Renal function
    - Osteonecrosis of jaw
- Kyphoplasty/vertebroplasty
- Home safety evaluation
- Pain management
- Use of spinal support (braces) may be indicated
- Ongoing evaluation of bone health



Kyphoplasty uses a “balloon” to create a cavity for bone cement to reduce vertebral fracture and pain

Niesvizky R, Badros AZ. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20; Drake MT. *Oncology*. 2009;23(14 suppl 5):28-32; Miceli TS, et al. *Clin J Oncol Nursing*. 2011;15(suppl):9-23; Coleman RE. *Br J Cancer*. 2008;98(11):1736-1740; Morgan GJ, et al. ASH 2010 #311; Witzig T, et al. ASH 2010 #3053. Berenson J, et al. *Lancet Oncol*. 2011;12:225-235; Images: Medtronic, Kyphon Products Division.

Guidelines for Bisphosphonates

- Guidelines for bisphosphonate use published by IMWG, ASCO, and NCCN
- All patients with MM related bone disease should be started on zoledronic acid or pamidronate IV using standard dosing.
- Symptomatic patient without documented bone disease should be considered for zoledronic acid
- Patients with age-related osteoporosis and smoldering MM can be treated using dosing for osteoporosis
- Duration of therapy:
  - Recommend patients on primary MM therapy receive bisphosphonates for up to 2 years
  - Patient with active disease may continue beyond 2 years on Zoledronic acid
- Upon relapse and evidence of new bone involvement, additional bisphosphonate use recommended
- In patients with renal impairment, bisphosphonates recommended with monitoring, dose adjustment, and discontinuation for severe impairment
- Bisphosphonates not recommended for patients with smoldering MM except in a clinical trial

IMWG=International Myeloma Working Group; ASCO=American Society of Clinical Oncologists; NCCN=National Cancer Center Network

Durie BGM. *Mayo Clin Proc.* 2007;82:516-522,[letter]; Lacy MQ, et al. *Mayo Clin Proc.* 2006;81:1047-1053; Kyle RA. *J Clin Onc.* 2007;24:2464-2472; NCCN Multiple Myeloma Guidelines v 1.2013; Terpos E, et al. *Blood*. 2013 Feb 13. [Epub ahead of print].

Zoledronic Acid Prolongs PFS, OS vs Clodronate (EU) in Newly Diagnosed MM in Combination With Chemotherapy

- Newly diagnosed stage I-III MM patients (n = 1960)—MRC Myeloma IX trial with or without baseline bone disease
  - Randomized to concurrent clodronate (n = 979) EU approved vs zoledronic acid (n = 981)
  - Variety of regimens: CVAD, C-TD, MP—included thalidomide maintenance in some patients
- Median follow-up 3.8 years
  - 5.5-month improvement in OS in zoledronic acid arm (*P* = .04)
  - **Reduction in disease-related bone disease (fractures, cord compression, new disease) and OS in favor of zoledronic acid irrespective of bone disease status at baseline**
  - Best outcomes seen in patients with thalidomide-based regimens in combination with zoledronic acid

Morgan GJ, et al. *Blood*. 2010;116. Abstract 311.
Morgan GJ, et al. *Lancet Oncol.* 2011;12:743-752.

OS=median overall survival; PFS=progression-free survival

Bisphosphonate Use in MM: Adverse Events

Flu-like symptoms

- Fever, myalgias, arthralgias
- Occurs usually 12-48 hours following infusion; lasts 6-24 hours
- Occurs in minority of patients (10%-20%)
- Generally reduced with continued dosing
- Slow rate of infusion and use of steroids and antihistamines may help reduce intensity

Pamidronate: Use in Renal Patients

Creatinine clearance (mL/min)	Dosing (mg) 90 mg/500 mL NS IV
>30	2-4 hours
<30	Not recommended

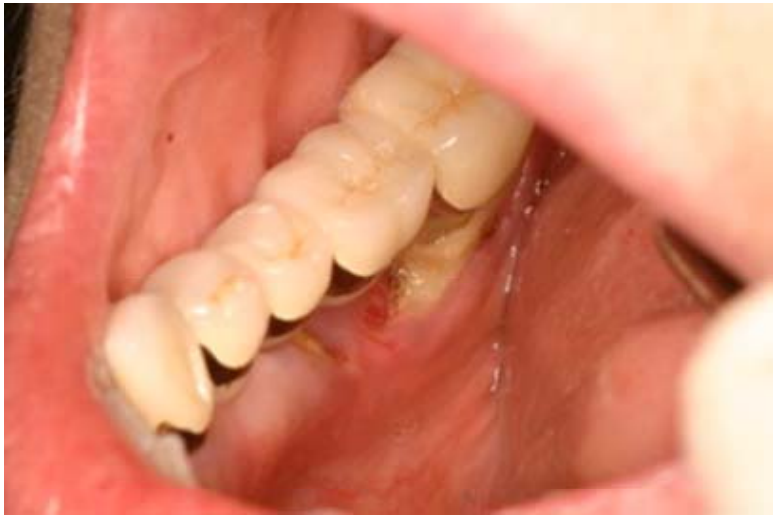
Zoledronic Acid: Use in Renal Patients

Creatinine clearance (mL/min)	Dosing (mg)
>60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

Durie BGM. *Mayo Clin Proc.* 2007;82:516-522,[letter]; Lacy MQ, et al. *Mayo Clin Proc.* 2006;81:1047-1053; Kyle RA. *J Clin Onc.* 2007;24:2464-2472; NCCN Multiple Myeloma Guidelines v 1.2013; Terpos E, et al. *Blood*. 2013 Feb 13. [Epub ahead of print].

Osteonecrosis of the Jaw

- Excellent oral hygiene is best prophylaxis
- Limit alcohol and tobacco use
- Patients starting IV BPs should have a dental assessment first
- Dental procedures (extensive) should be done prior to starting IV BPs if possible
- Avoid unnecessary dental procedures once IV BPs start
- There is no standard treatment
- Consider supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day



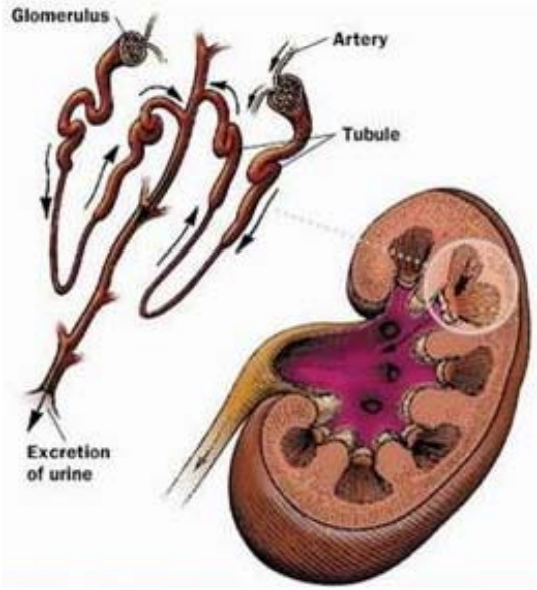
Osteonecrosis of the jaw can be a consequence of bisphosphonates

MRI=magnetic resonance imaging; IU=international units; IV=intravenous; PO=orally.
Kyle RA, et al. 2007; Faiman B, et al, 2008; Faiman B, et al, 2013 *in press*.

Renal Disease in Multiple Myeloma

Multiple Myeloma Factors

- 2%-40% of patients
- Cast nephropathy
- Hypercalcemia
- Hyperviscosity
- Light chain deposition
- Amyloidosis



Contributing Factors

- Dehydration
- Hyperuricemia
- Medications
  - Loop diuretics
  - NSAIDs
  - Contrast media
  - Active therapies for MM
  - Bisphosphonates

Measure of Renal Disease in MM

- Serum creatinine > 2 mg/dL
- Calcium levels > 12 mg/dL
- Elevated free light chains
- Uric acid

Treatment of the multiple myeloma is often the best strategy to improve renal function

Mulkerin D, et al. *Blood*. 2007;110. Abstract 3477.
Niesvizky and Badros. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20.

Strategies to Improve Renal Function

- **Treatment of hypercalcemia**
  - Hydration
  - Dexamethasone
  - Diuretics
  - Bisphosphonates
- **Treatment of hyperviscosity**
  - MM therapy
  - Plasmapheresis
- **Avoidance of aggravating factors**
  - Dehydration
  - Diabetes
  - Hypertension (HTN)
  - Medications (NSAIDs, loop diuretics)
  - IV Contrast
- **Coordination with dialysis schedule**
- **Effect of novel therapies**
  - **Thalidomide**
    - No dose adjustment required
    - May be associated with hyperkalemia
  - **Bortezomib**
    - No dose adjustment required
  - **Lenalidomide**
    - Excreted substantially by the kidney
    - Dose adjustments required
    - Adverse events (AEs) may be increased with renal impairment
  - **Pomalidomide**
    - No dose adjustment required based on current trials
  - **Carfilzomib**
    - No dose adjustment required

Mulkerin et al. *Blood*. 2007;110. Abstract 3477.
Niesvizky R, Badros AZ. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S13-S20.

Improving Renal Function With Novel Agents

Background

- 30% to 40% have elevated serum creatinine at presentation
- <10% have severe renal failure at presentation

Study:

- 112 newly diagnosed MM patients with renal impairment
- Received thalidomide-based regimen, bortezomib-based regimen, or lenalidomide-based regimen
- Complete renal responses (CRR) or partial renal responses (PRR) determined by GFR

Results:

Regimen	Renal response		Median time to first renal response
	Complete	Complete + Partial	
Bortezomib-based	**70%***	**80%***	**0.85 months***
Thalidomide-based	**53%***	**55%***	**1.5 months***
Lenalidomide-based	**34%**	**38%**	**5.5 months**

**P*<0.05 vs. lenalidomide-based regimen

Conclusions:

- Novel MM agents can improve renal function
- Bortezomib and thalidomide-based regimens statistically better for improving renal function

GFR=glomerular filtration rate; CRR=sustained increase in baseline eGFR of <15 mL/min to >60 mL/min; PRR=sustained increase from baseline to 30-50 mL/min

Dimopoulos MA, et al. Presented at ASH. 2011. Abstract #3961; Faiman B, et al. *Clin J Oncology Nursing.* 2011;15:66-76.

Risk Factors for Thromboembolism

Individual Factors

- General
  - Age
  - Obesity or diabetes
  - Cardiovascular or renal disease
  - Acute infection
- Inherited thrombophilic abnormalities
  - Protein C, protein S deficiency, factor V Leiden mutation
  - Elevated homocysteine levels
- Central venous catheter use
- Prior DVT, PE, or superficial vein thrombosis

Disease-Related Factors

- Diagnosis of MM
- Anesthesia, surgery, trauma, or hospitalization
- Immobilization, sedentary lifestyle, extremity paresis
- Other malignant neoplasm
- Hyperviscosity

Treatment-Related Factors

- High-dose dexamethasone
- Thalidomide, lenalidomide
- Adjuvant doxorubicin for other cancer
- Multi-agent chemotherapy
- Erythropoietin use

Palumbo AV, et al. *Leukemia*. 2008;22:414-423.
PEP Group. *Lancet*. 2000;355:1295-1302.
Pal S, et al. *Blood*. 2010;115:605-614.
Palumbo AV, et al. *Blood*. 2009;114. Abstract 492.
Rome S, et al. *Clin J Oncol Nurs*. 2008;12(suppl 3):21-28.

DVT=deep venous thrombosis; PE=pulmonary embolism

Prevention of Thrombosis

- Low risk
  - None or 1 risk factor
  - Thromboprophylaxis
    - Low-dose aspirin (81-100 mg/d) is effective if used consistently
- High risk
  - ≥ 2 risk factors
  - High-dose dexamethasne (≥ 480 mg/month)
  - Doxorubicin
  - Multiagent chemotherapy
  - Thromboprophylaxis:
    - LMWH or warfarin with therapeutic dosing (INR 2-3)

LMWH=low-molecular-weight heparin

Palumbo AV, et al. *Leukemia*. 2008;22:414-423.
Wiley KE. *Clin J Oncol Nurs.* 2007;11:847-851.
Rome S, et al. *Clin J Oncol Nurs*. 2008;12(suppl 3):21-28.

Thromboembolic Events: Prophylaxis

- Mechanical
  - Ambulation, exercise is the most effective prophylactic strategy
  - Sequential compression devices
  - Anti-embolism stockings—questionable
- Steroid dose reduction
  - Decreased risk of venous thromboembolism in ECOG trial
  - Dexamethasone reduced dosing 40 mg weekly
    - Deep vein thrombosis: 26% RD vs 12% Rd (*P*=0.0003)
    - Infection/Pneumonia: 16% vs 9% (*P*=0.04)

Rome S, et al. *Clin J Oncol Nurs*. 2008;12(suppl 3):21-28.
Rajkumar SV, et al. *Lancet Oncol*. 2010;11:29-37.

Treatment Recommendations for Venous Thromboembolism

Initiate therapy with LMWH (Use unfractionated heparin in renal failure patients)		
	Once daily	Twice daily
Dalteparin	200 U/kg	100 U/kg
Enoxaparin	1.5 mg/kg	1 mg/kg
Nadroparin	171 U/kg	86 U/kg
↓		
Start oral anticoagulation within 2 hours (if concomitant thrombocytopenia risk is low)		
↓		
Administer LMWH for a minimum of 5 days, do not stop treatment until INR is 2.0–3.0 for 2 consecutive Days		
↓		
Briefly discontinue IMID until full anticoagulation has been established		
↓		
Optimal treatment duration is unknown; extended LMWH treatment should be considered based on cost/benefit analysis		

Sullivan E, et al. *J Adv Pract Oncol*. 2013;4:37–46.

Neuropathy

General Considerations

- Endocrine disorders
  - Hypothyroidism
  - Diabetes
- Nutritional disease
- Connective tissue disease
- Vascular disease
- Medications
- Herpes zoster

Most Common Symptoms

- Sensory deficits
- Neuropathic pain

Disease- and Treatment-Related Factors

- Hyperviscosity syndrome
- Hypergammaglobulinemia
- Incidence of peripheral neuropathy in untreated patients: 39%
- Incidence of grade 3/4 CIPN with novel agents:
  - Bortezomib: 26%-44%
    - ↓ with weekly vs twice weekly dosing
    - ↓ with SC administration
  - Thalidomide: 27.5%-41%
    - ↑ with higher doses and prolonged therapy
  - Carfilzomib: overall 14%

Wickham R. *Clin J Oncol Nurs*. 2007;11:361-375.
Tariman JD, et al. *Clin J Oncol Nurs*. 2008;12(3 suppl):29-36.
Hausheer FH, et al. *Semin Oncol*. 2006;33:15-39.
Gleason C, et al. *J Natl Compr Cancer Netw*. 2010;7:971-979.

CIPN=chemotherapy-induced peripheral neuropathy

Management of Neurotoxicity Symptoms

- Baseline and ongoing evaluation
  - Include high-risk comorbidities
- Dose reduction, delay, or omission of drug
  - Agent-specific guidelines
- Use of various supplements
  - Avoid green tea or vitamin C with bortezomib administration
  - Daily doses of B6 should not exceed 100 mg
- Emollient creams (eg, cocoa butter, menthol and eucalyptus-based)
- Physical therapy
- Stress reduction
- Cognitive behavioral therapy
- Acupuncture
- Pain also may be treated with gabapentin, tricyclic antidepressants, or other agents helpful in relieving neuropathic pain

Hausheer FM, et al. *Semin Oncol*. 2006;33:15-39.
Agafitei RD, et al. *J Clin Oncol.* 2004;22(suppl 14). Abstract 3600.
Saif MW. *J Appl Res*. 2004;4:576-582.
Tariman D, et al. *Clin J Oncol Nurs*. 2008;12(3 suppl 1);29-35.

Common Supplements Used to Treat Peripheral Neuropathy

Vitamin/Supplement	Dosing Regimen
Multi-B complex vitamins (with B1, B6, B12, folic acid and other)	B6 should be approximately 50 mg daily, not to exceed 100 mg per day Folic acid should be 1 mg per day
Vitamin E	400 IU daily
Vitamin D	400-800 IU daily
Fish oils (omega-3 fatty acids [EPA and DHA])	1-2 capsules daily with food (1 capsule is usually 1 g)
Magnesium	Suggested doses include: 250 mg twice a day May cause diarrhea in larger doses
Potassium	Either as provided by the treating physician or foods rich in potassium (eg, bananas, oranges, potatoes)
Tonic water (Seltzer water)	Drink 1 glass in evening and any other time cramping occurs
Acetyl-L-carnitine	500 mg twice a day with food Can take up to 2000 mg a day
Alpha-lipoic acid	300 mg to 1000 mg a day with food
Glutamine	1 g up to 3 times a day with food

Opportunities to Collaborate

- **Devise safety nets to help patients adhere to long-term oral therapies**
  - Ample monitoring and safety checks
    - Drug utilization reporting of premature or delayed prescription refills
- **Communication among cancer care team, PCP, specialty pharmacy**
  - Implement an efficient process to share treatment plan and goals
- **Integrated patient education and support**
  - Electronic health record (EHR) after visit instructions
    - Med self management
      - Proper use
      - Who to call for what
      - Handle cytotoxic meds
      - Disposal of cytotoxic meds
- **Continuous evaluation of outcomes, including patient experience**

Bennett MP, et al. *J Nurse Practitioner*. 2012;8:112-16.

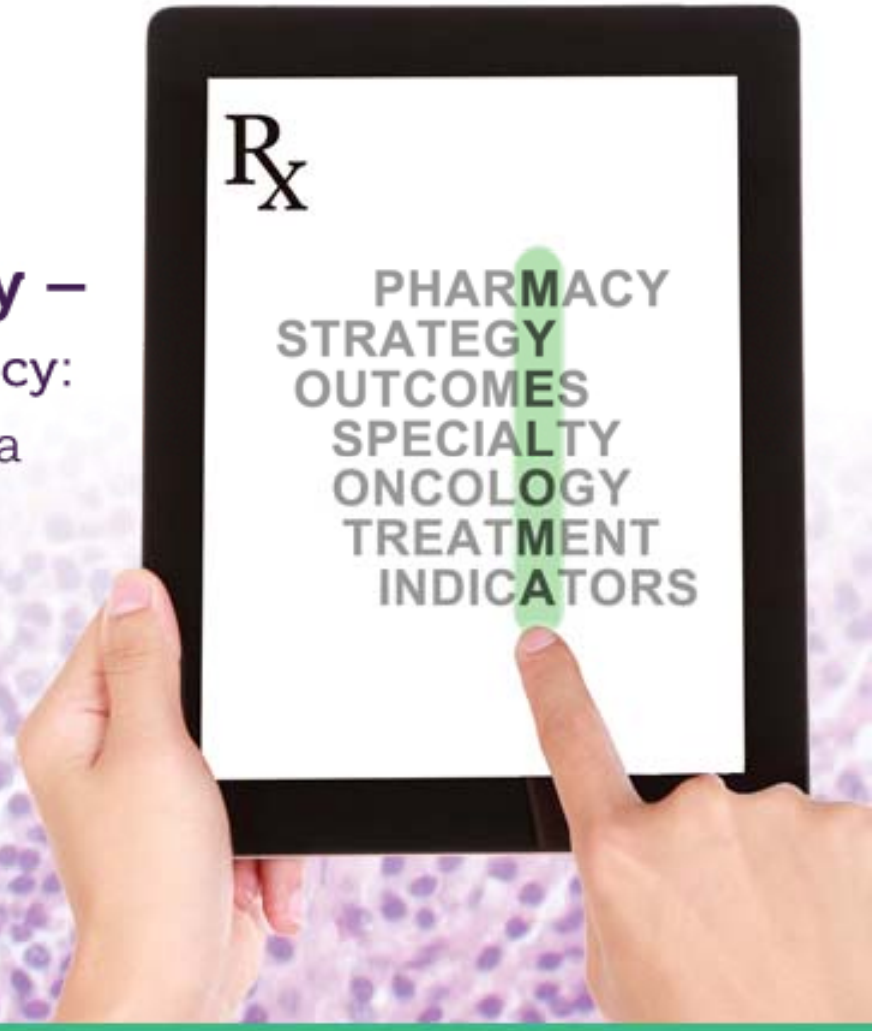
Summary

- Although currently not curable, median overall survival has improved dramatically over the last decade
  - Understanding of the pathobiology of the disease will improve the rationale of supportive care requirements
  - Identification of new therapeutic targets
- Improved long-term survival if the goal
  - Early depth of response → sustained response with an acceptable level of toxicity
- Many new agents are on the way, most will be oral
- Collaborative clinical management together with patient and caregiver empowerment will promote the best outcomes and preserve future treatment options

Applying a Congruent Oncology Pharmacy Strategy –

From Guidelines to Specialty Pharmacy:

Steps for Success with Multiple Myeloma



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ONYX Celgene Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY

Oncology Pharmacy Benefit Models and Specialty Management Services

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Disclosures

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Atheer Kaddis, PharmD

  – *No financial interest/relationships relating to the topic of this activity*

Outline

- Trends in oncology/multiple myeloma pharmacy
- Oncology benefit design considerations
- Specialty pharmacy and oncology drug management
- Summary

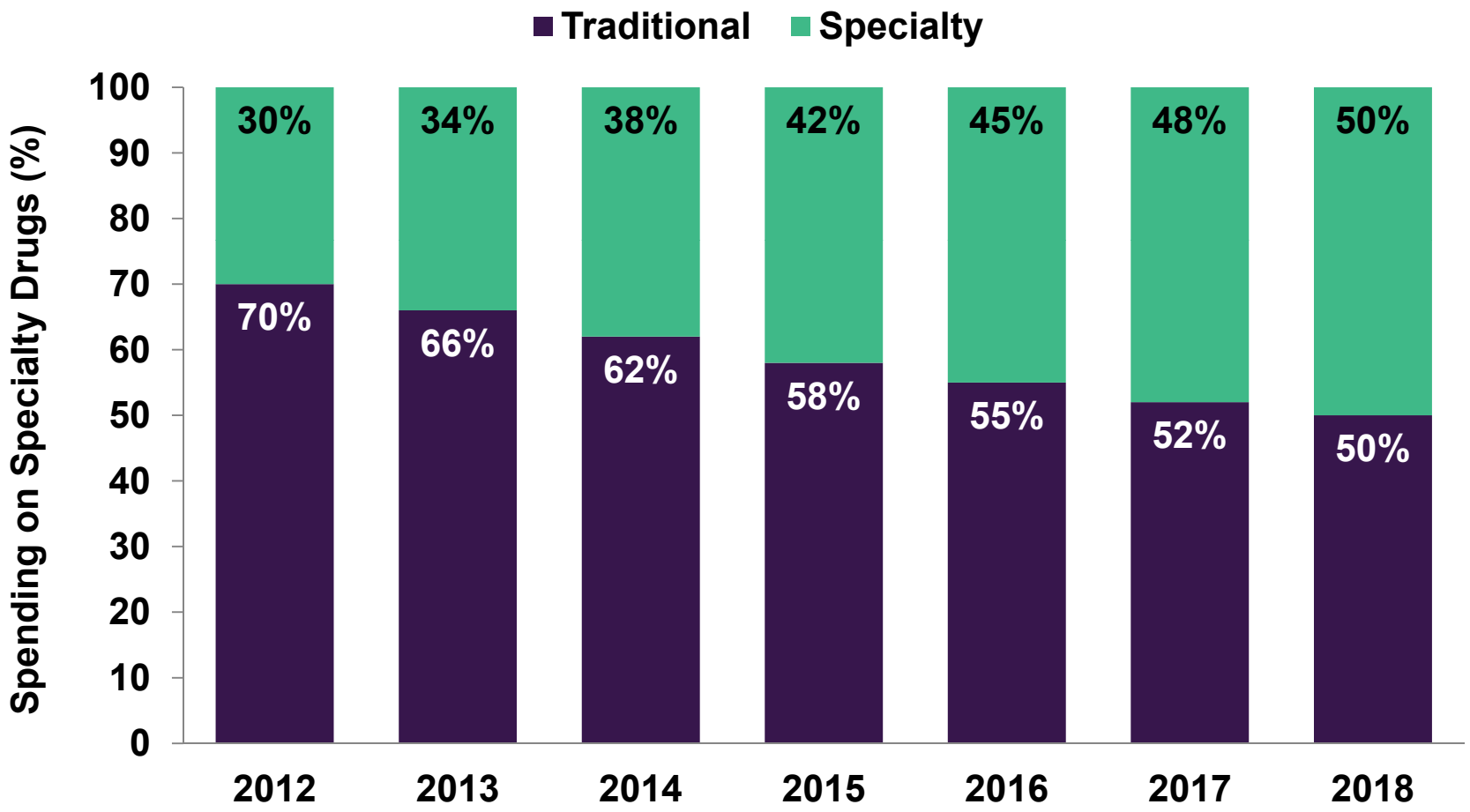
Trends in Oncology/Multiple Myeloma Pharmacy

Cost of Multiple Myeloma Care is Disproportionately High

- Multiple myeloma represents ~1% of all cancers, but its financial burden is disproportionately high[1]
- Cost drivers include[1,2]
  - Natural history of relapse and remission
  - Intensive chemotherapy regimens
  - Novel drugs (eg, immunomodulators, proteasome inhibitors) used as add-on therapies to chemo regimens
  - Stem cell transplants
  - Diagnostics to measure disease progression and response to therapy
  - Treatment of complications (eg, lytic bone disease, infection, anemia)
  - Supportive care

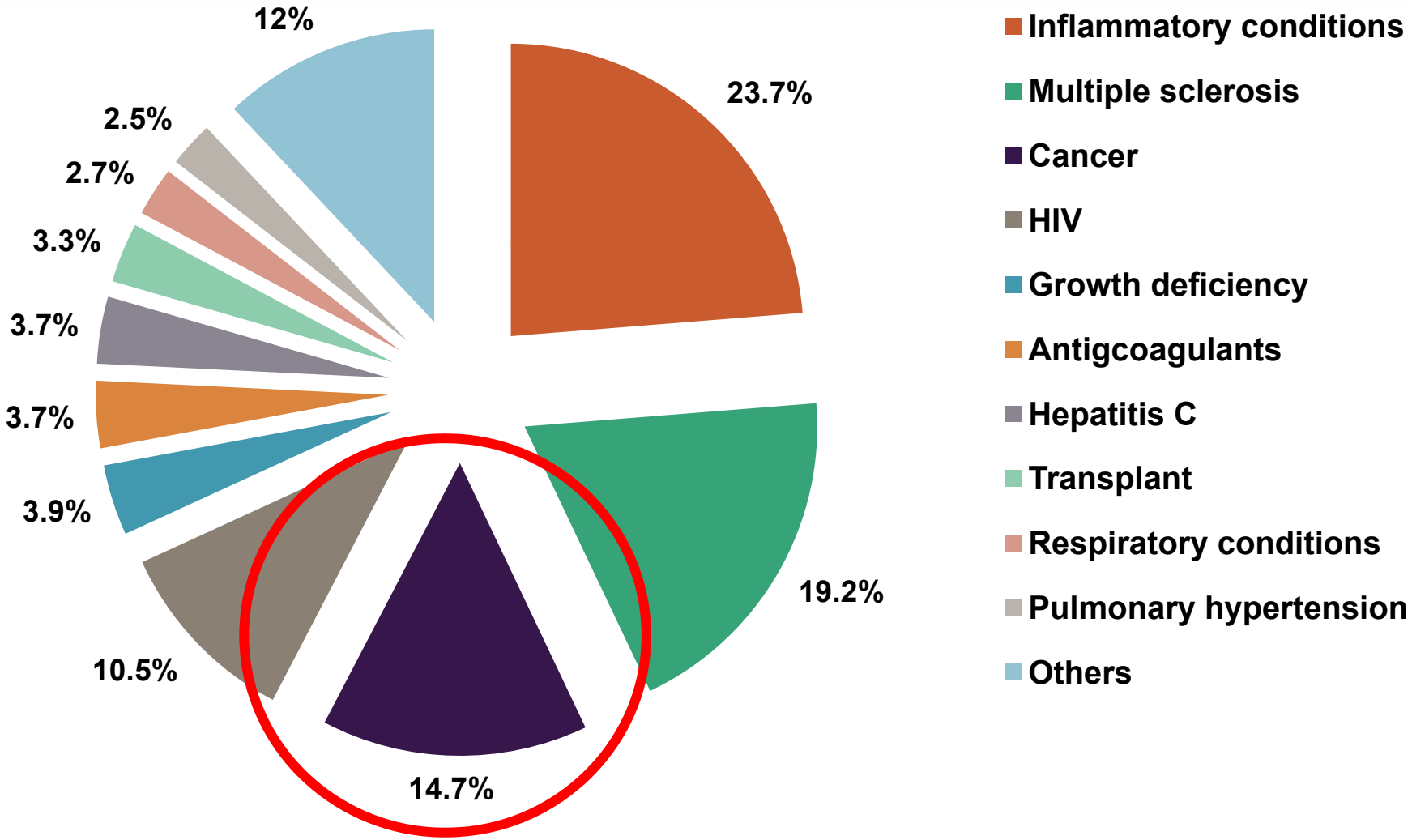
1. Cook R. *J Manag Care Pharm*. 2008;14(suppl S):S18-S11.
2. Klein IM. Available at: http://www.valuebasedcancer.com/myeloma/article/information-technology-solution-management-chronic-disease. Access March 3, 2013.

Proportion of the Prescription Drug Spend Utilized on Specialty Pharmacy Continues to Rise



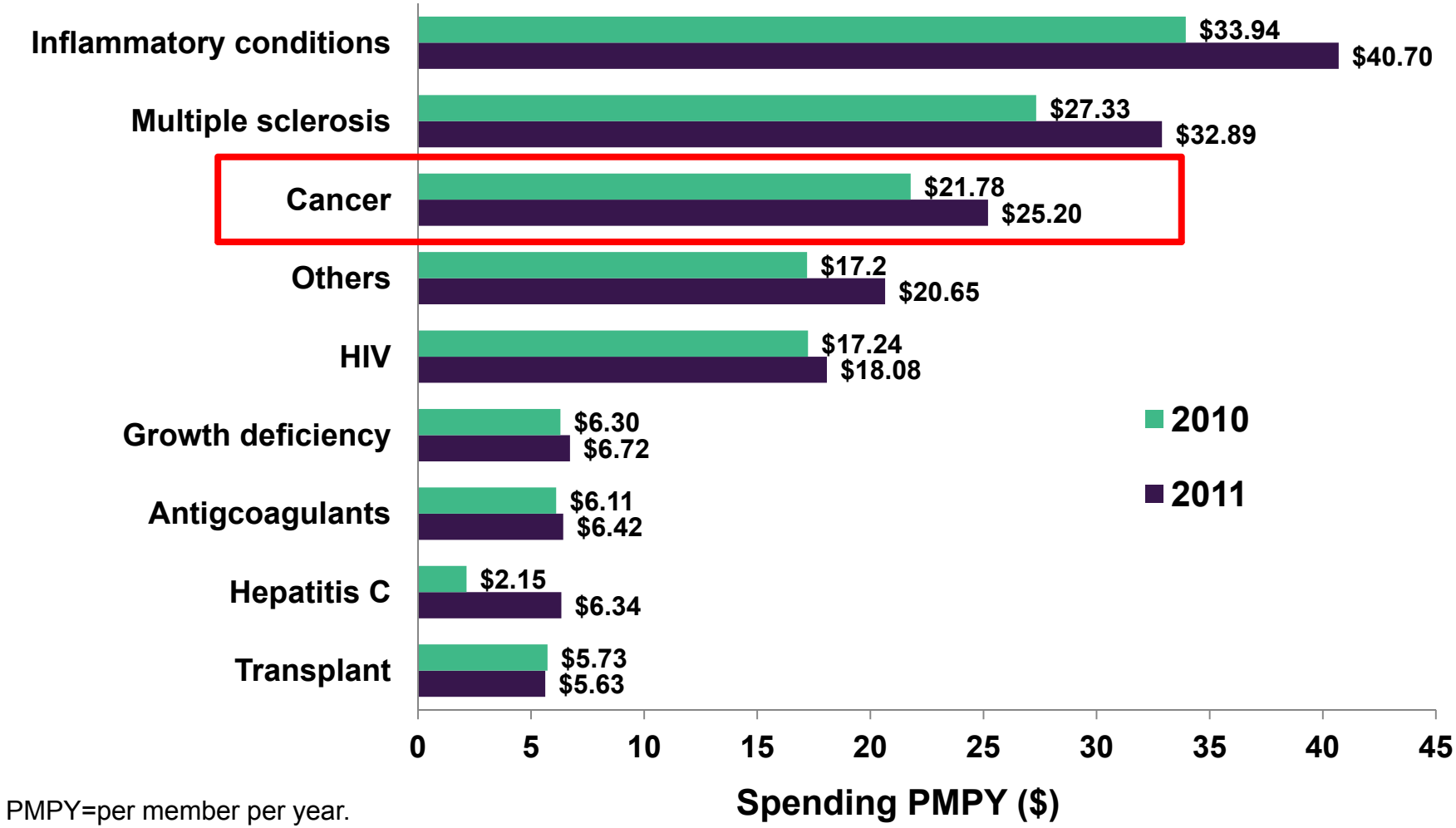
Artemetrx. Specialty drug trends across the pharmacy and specialty benefit. 2013. Available at: http://www.artemetrx.com/docs/ARTEMETRX_Specialty_Trend_Rpt.pdf. Accessed March 3, 2013..

Oncology Represents the 3rd Largest Component of the Specialty Spend



2011 Drug Trend Report. Express Scripts. Available at: http://www.express-scripts.com/research/research/dtr/archive/2012/dtrFinal.pdf. Accessed March 3, 2013.

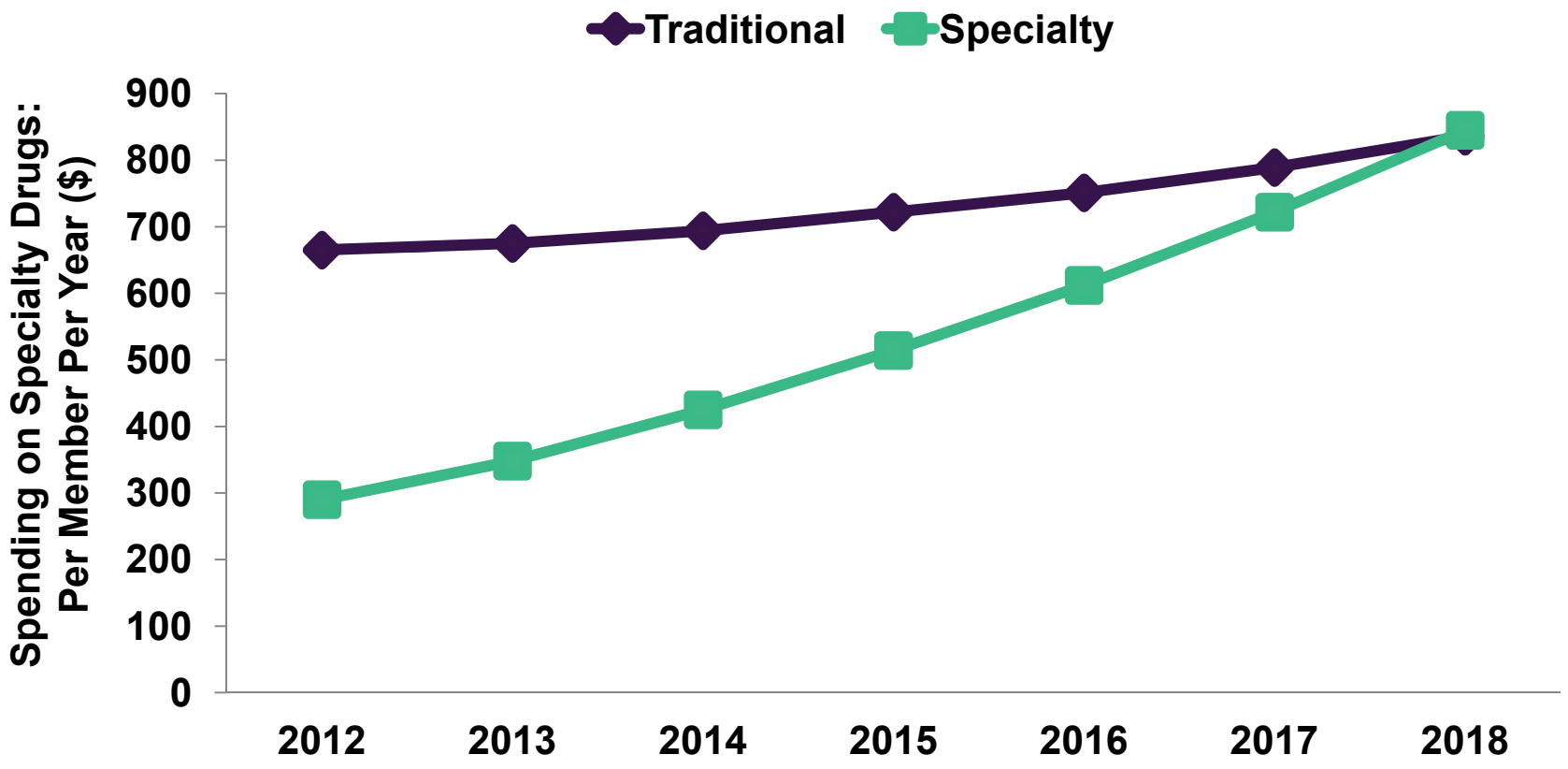
PMPY Spending on Oncology Specialty Drugs in the Pharmacy Benefit Rose ~16% from 2010 to 2011



PMPY=per member per year.

2011 Drug Trend Report. Express Scripts. Available at: http://www.express-scripts.com/research/research/dtr/archive/2012/dtrFinal.pdf. Accessed March 3, 2013.

Trend of Specialty Drug PMPY Spending is Increasing Rapidly



PMPY=per member per year.

Artemetrx. Specialty drug trends across the pharmacy and specialty benefit. 2013. Available at: http://www.artemetrx.com/docs/ARTEMETRX_Specialty_Trend_Rpt.pdf. Accessed March 3, 2013..

Emergence of Oral Anticancer Drugs

- Sales of oral oncolytics have increased every year since 2005
- Novel oral medications comprise ~25% of the oncology drug development pipeline
- Rapid emergence of oral oncology drugs and decreasing use of buy-and-bill is driving more drugs into the pharmacy benefit
- Coverage with the pharmacy benefit facilitates use of traditional utilization management strategies and coverage rules including prior authorization and tiered copays

Wang L, et al. Trends in Oncology Market Access. Campbell Alliance. 2012.
Hernandez R. *Specialty Pharm Times*. July 5, 2012.

Example of a Recently Approved Oral Specialty Drug for the Treatment of Multiple Myeloma

Name (generic/trade)	Pomalidomide (POMALYST) capsules
Manufacturer	Celgene Corporation
Approval date	February 8, 2013
Means of administration	Oral
Indication	Treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy
Comments	• Accelerated approval based on results of the Phase II CC-4047-MM-002 trial • Pomalidomide is available only through a restricted distribution program called the POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program

Pomalyst [prescribing information]. Celgene Corporation. Summit, NJ: February 2013.

Oncology Benefit Design Considerations

Oncology Benefit Design: Current Challenges

- No single standard in the marketplace
- Most plans use traditional cost-management methods applied to other chronic diseases
  - Adaptation of existing tiered formulary methodology
  - Demand management through cost-sharing and other barrier to access
- Most current designs have no consideration on patients' total out-of-pocket burden
- Is oncology a "value-based" disease state?

Stern D, et al. *J Manag Care Pharm*. 2008;14(suppl S):S12-S16.
Mullins CD, Dunn JD. *J Manag Care Pharm*. 2012;18(suppl 8a):S13-S19.

Benefit Design Goal: Providing Access to All Appropriate Therapeutic Options

- Benefit should not hinder access to available and appropriate treatment options
- Approach
  - Select therapies from evidence-based clinical oncology guidelines including
    - National Comprehensive Cancer Network (NCCN)
    - American Society of Clinical Oncology (ASCO)
- Align incentives with the implementation of practice patterns that meet established benchmarks

Danielson E, et al. *J Natl Compr Canc Netw*. 2010;8(Suppl 7):S28–S37.

Benefit Design Goal: Reducing Variability of Care

- Reducing variability in care delivery can improve treatment outcomes
- Approach
  - Utilize clinical pathways that identify “preferred” treatment options
    - Either a single-treatment option per condition or a subset of treatment options per condition
  - Equalize incentives to encourage physicians to select the most appropriate therapy independent of the revenue implications
  - Align incentives with achievement of specified levels of compliance with the approved clinical pathway

Soper AM, et al. *Am J Manag Care*. 2010;16:e94-e97.
Danielson E, et al. *J Natl Compr Canc Netw*. 2010;8(Suppl 7):S28–S37.

Benefit Design Goal: Minimizing Patient Out-of-Pocket Expenses

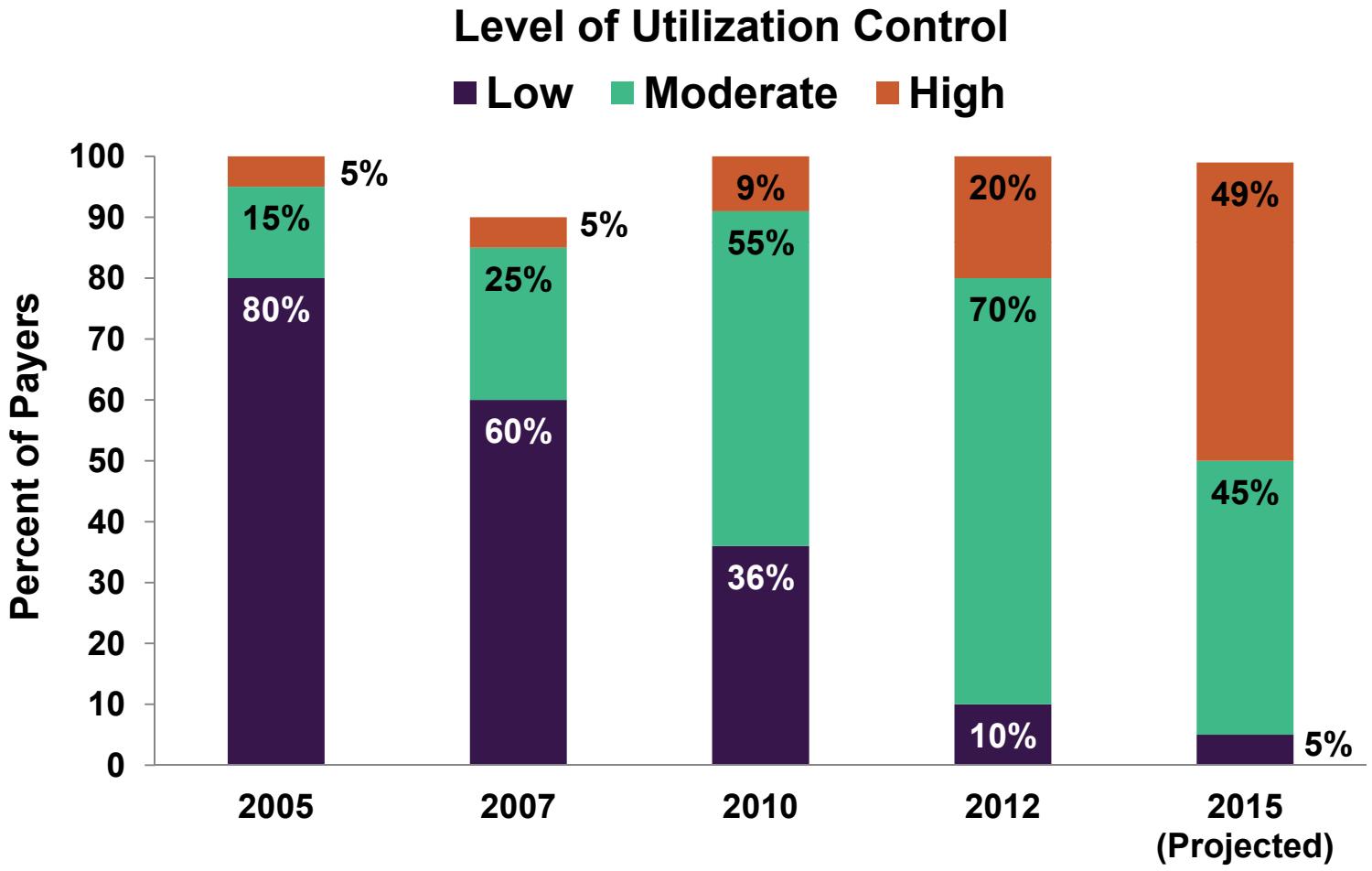
- Ensure copayments, coinsurance, and other out-of-pocket expenses will not compromise compliance with therapy
- Approach
  - Require home delivery of certain drugs
  - Implement reminder programs
  - Use specialty pharmacy to counsel patients on treatment costs

Danielson E, et al. *J Natl Compr Canc Netw*. 2010;8(Suppl 7):S28–S37.

Benefit Design Goal: Establishing a Balance Between Cost-Shifting and Compliance

- Member decision factors
  - Cost-sharing
  - Compliance to prescribed regimens
  - Monitoring efficacy/tolerability
- Benefit design factors
  - Medical vs pharmacy
  - Copay vs coinsurance
  - Specialty tiers

Payers are Increasingly Implementing More Aggressive Oncology Drug Management



The Zitter Group. Oncology Business Review. May 2010.

Anticipated Oncology Management Tactics*

Tactic	Not Utilized (%)	Currently Utilized (%)	Likely to be Utilized in the Next 2 Years (%)
NCCN/ASCO Guidelines	10	76	14
Pharmacy benefit classification	21	65	14
ASP-level payments	21	58	21
Biomarker testing for appropriate therapy selection	10	52	38
Quality initiatives	28	41	31
Episode of care payments	55	17	28
Oncology formulary with preferred bands	45	17	38

NCCN=National Comprehensive Cancer Network; ASCO=American Society of Clinical Oncology; ASP=average sales price.

*Survey of 57 medical and pharmacy directors from US national and regional health plans and PBMs responsible for 151 million lives enrolled in commercial and Medicare plans; all respondents were formulary decision makers for oncology coverage.

Greenapple R. *Am Health Drug Benefits.* 2012;5:242-253.

Characteristics of Oral Multiple Myeloma Drugs

- High cost
  - Costs vary, but the average monthly prescription cost is >$4,000
- High complexity
  - Cytotoxic agents with the potential to cause side effects
- High touch
  - Regular follow-up and monitoring
  - Patient education
  - Assessment of compliance

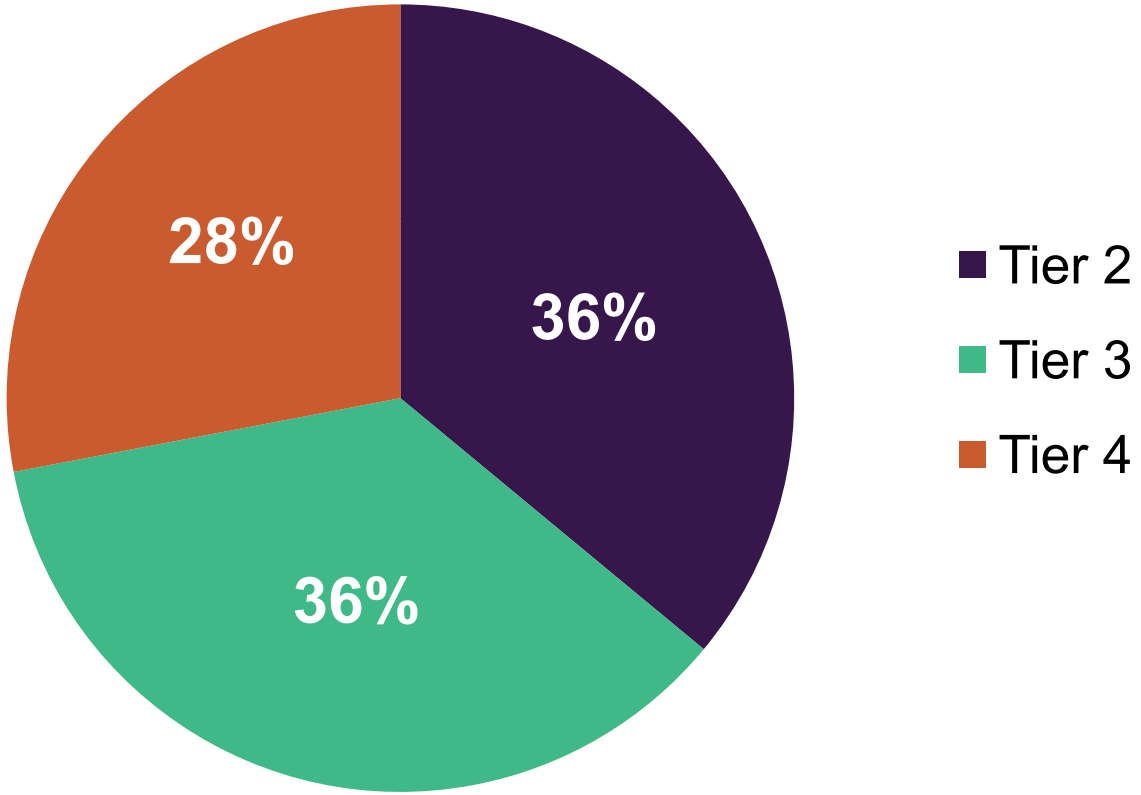
Correia RJ. Oral Oncology therapies: specialty pharmacy's newest challenge. *Spec Pharm Times*. Available at: http://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2011/may-2011/Oral-Oncology-Therapies-Specialty-Pharmacys-Newest-Challenge-. Accessed March 3, 2013.

Payers, But Not Necessarily Patients or Physicians, Prefer Oral Agents

Payers	Providers	Patients
Minimize/eliminate infusion costs	Eliminates buy and bill profits	Ease of use
Maximizing cost-sharing contribution collection	Reduces/eliminates reimbursement for supportive care and administrative duties	High out-of-pocket expense can lead to non-adherence
Enhancing spend transparency	Removes provider from the patient feedback loop	
Enabling more robust utilization management	Increase in patient convenience may enhance adherence	
High oral drug cost-sharing pushes many patients toward infusible products	Encourage patients toward infused drugs to minimize cost-sharing burden	

The Zitter Group. *Oncology Business Review*. May 2011.
Wang L, et al. Trends in Oncology Market Access. Campbell Alliance. 2012.

Most Oral Oncolytics are Placed on Formulary Tiers 2 and 3



n=36 commercial managed care payers

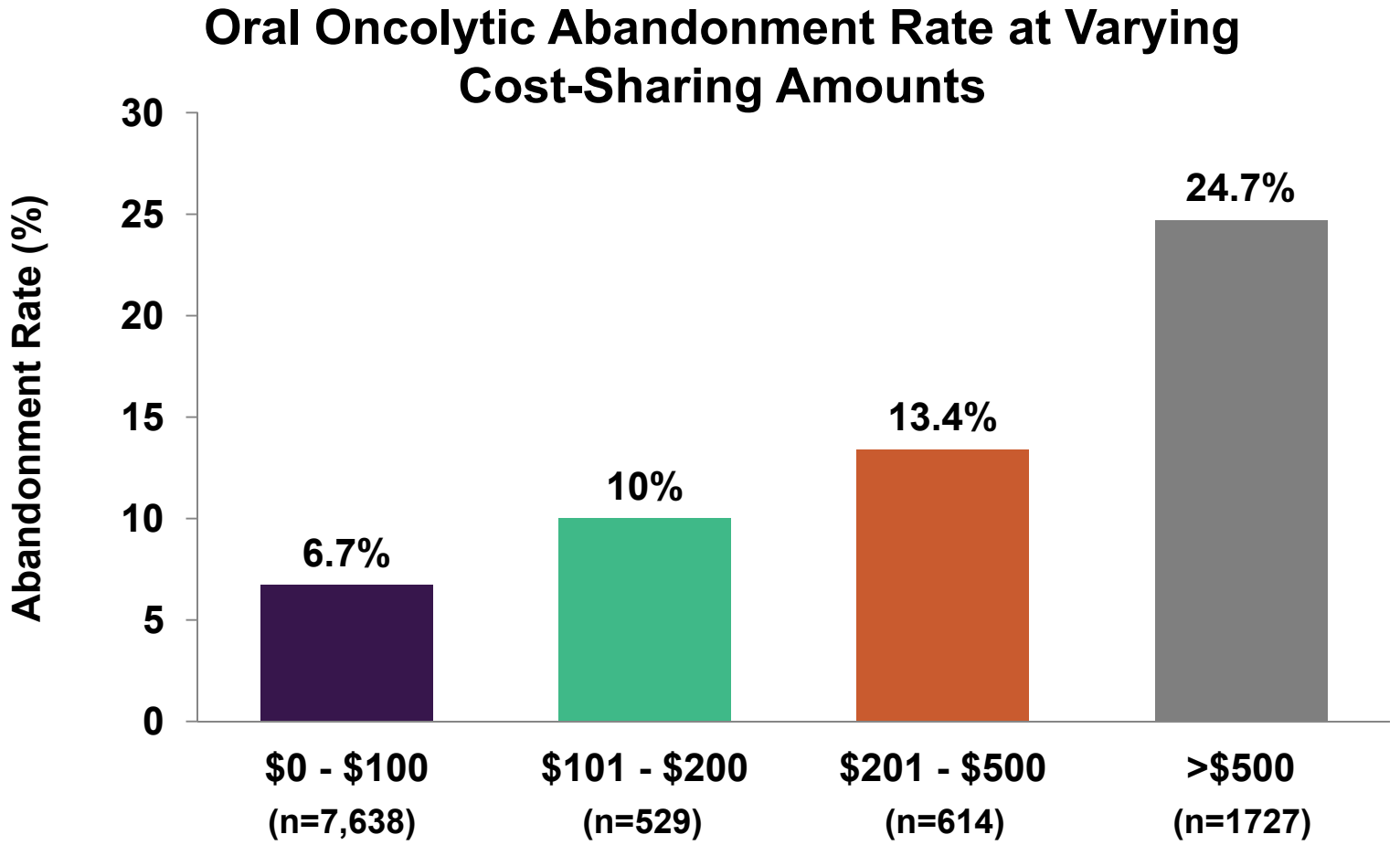
Wang L, et al. Trends in Oncology Market Access. Campbell Alliance. 2012.

Utilization of Oral Drugs Managed Through Cost-Shifting

- Increasingly, payers are shifting costs to patients[1]
  - Oral drugs increasingly covered under the pharmacy benefit and frequently placed in a higher formulary tier
- Although the intent is to reduce the payer's financial risk, cost-shifting can make therapies unaffordable for many patients[2,3]
- Large variation in the willingness of patients to pay for their drugs[2,3]
  - Out-of-pocket (OOP) cost changes have little effect on ongoing treatment[2]
  - However, compliance declines once OOP costs reach $1,000[3]

1. Butcher L. *Manag Care*. April 2008.
2. Goldman DP. *Health Serv Res*. 2010;45:115-132.
3. Willey VJ. *Health Aff*. 2008;27:824-834.

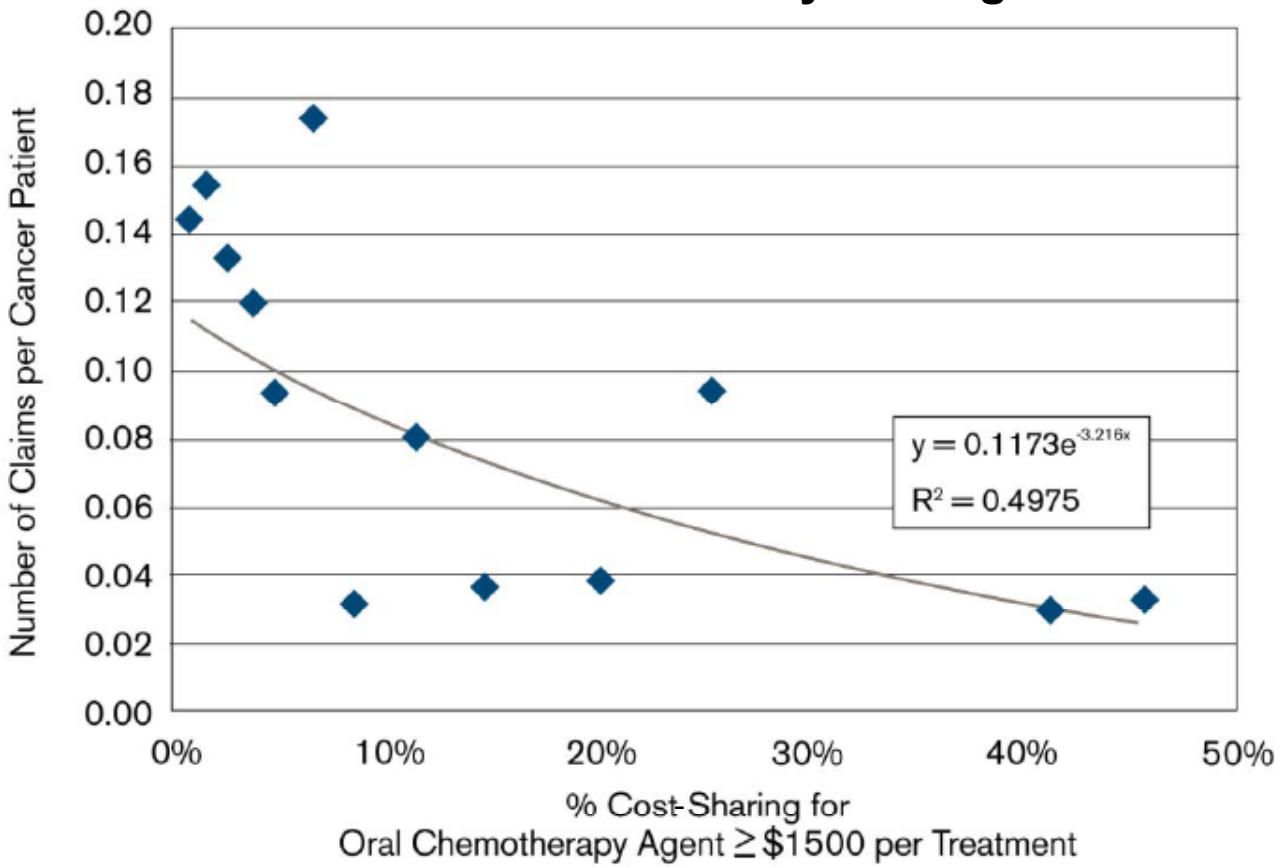
Higher Cost-Sharing Leads to Greater Prescription Abandonment



Streeter SB, et al. *Am J Manag Care*. 2011;17(5 Spec No.):SP38-SP44).

Higher Cost-Sharing Decreases Utilization of Oral Oncolytics

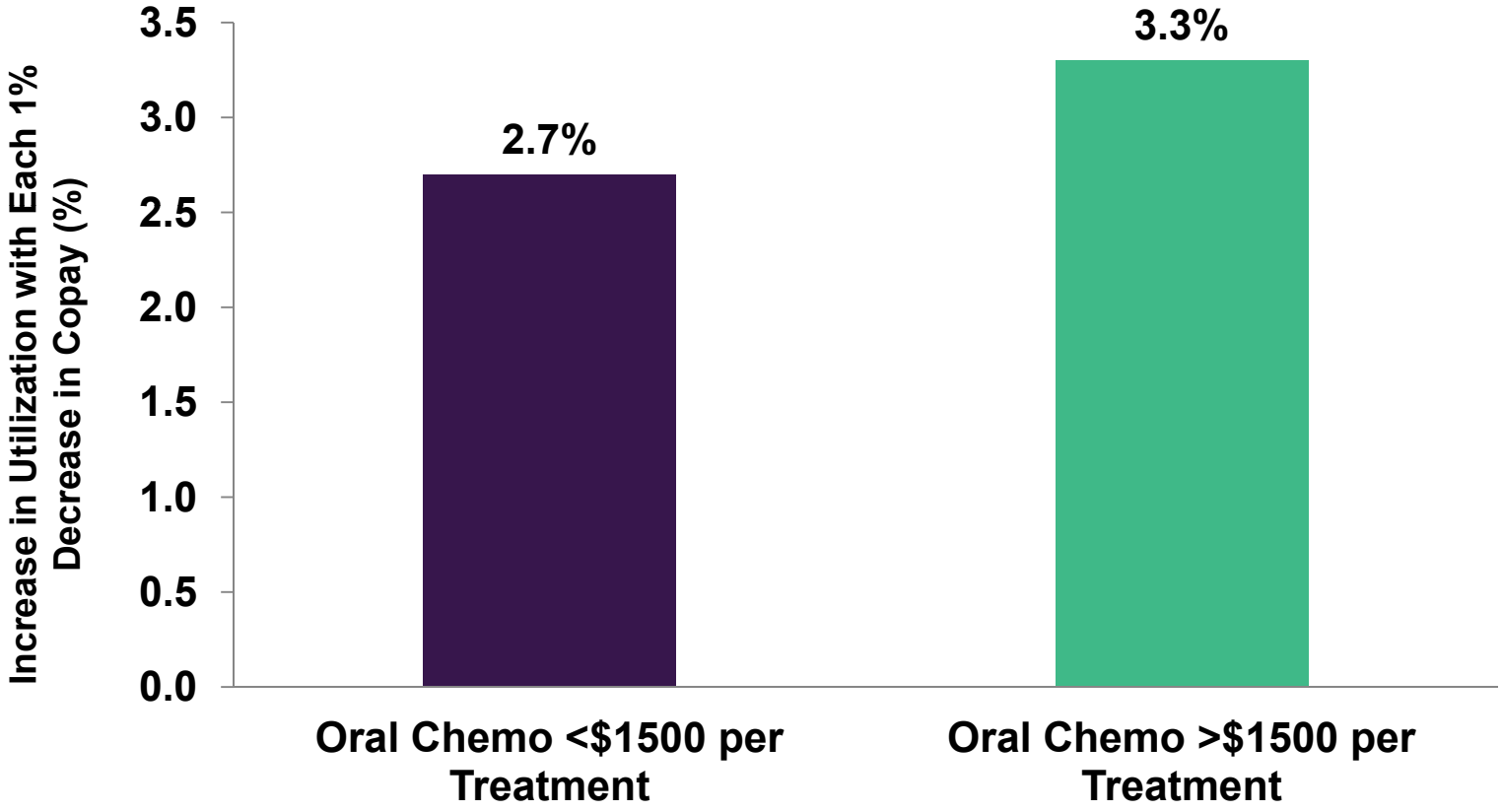
Relationship Between Cost Share and Number of Claims for Oral Oncolytic Drugs



n=24,474 cancer patients, 20–69 years of age.

Milliman Inc., Parity for oral and intravenous/injected cancer drugs. January 25, 2010. Available at: http://publications.milliman.com/research/health-rr/pdfs/parity-oral-intravenous-injected.pdf. Accessed March 3, 2013.

1% Reduction in Cost-Sharing Can Increase Utilization of Oral Oncolytics Up to 3.3%



n=24,474 cancer patients, 20–69 years of age.

Milliman Inc., Parity for oral and intravenous/injected cancer drugs. January 25, 2010. Available at: http://publications.milliman.com/research/health-rr/pdfs/parity-oral-intravenous-injected.pdf. Accessed March 3, 2013.

As Multiple Myeloma Care Evolves, Payers are Changing Their Management Approach

- Multiple myeloma is increasingly viewed as a chronic disease with long-term cost implications
- Payers are adapting management techniques used in other chronic diseases for use in oncology[1]
  - Greater cost-shifting to patients
  - Increased operational efficiency
  - Appropriate utilization
- Goal is to identify a consistent therapeutic approach, reduce variation, decrease costs, engage providers, and increase quality[2,3]

1. Stern D, et al. *J Manag Care Pharm*. 2008;14(suppl S):S12-S16.
2. Kenney JT. *Am Health Drug Benefits*. 2012;5:S10-S12.
3. Holcombe D. *J Oncol Pract*. 2011;7:e46s-e49s.

Specialty Pharmacy and Oncology Drug Management

Why Use Specialty Pharmacy Services?

- In 51% of HMO plans when the oncology drug falls under the pharmacy benefit, use of a specialty pharmacy provider is mandatory[1]
- Specialty pharmacy shifts distribution to specialty pharmacy vendors and sends payment through the pharmaceutical benefit[2]
  - Increases payer control over drug utilization
- Potential issues[2]
  - Increased fragmentation of care between the specialty pharmacy and the oncology care team
  - Logistic procedures may be different for each drug/drug class
  - Reliance on integrated information-sharing technology to facilitate communication between the specialty pharmacy and other providers

1. Edwards AM. *Community Oncol*. 2010;7:309-313.
2. Schwartz RN, et al. *J Natl Comp Canc Netw*. 2010;8(suppl 4):S1-S12.

When does it Make Sense to Consider a Specialty Pharmacy Provider?

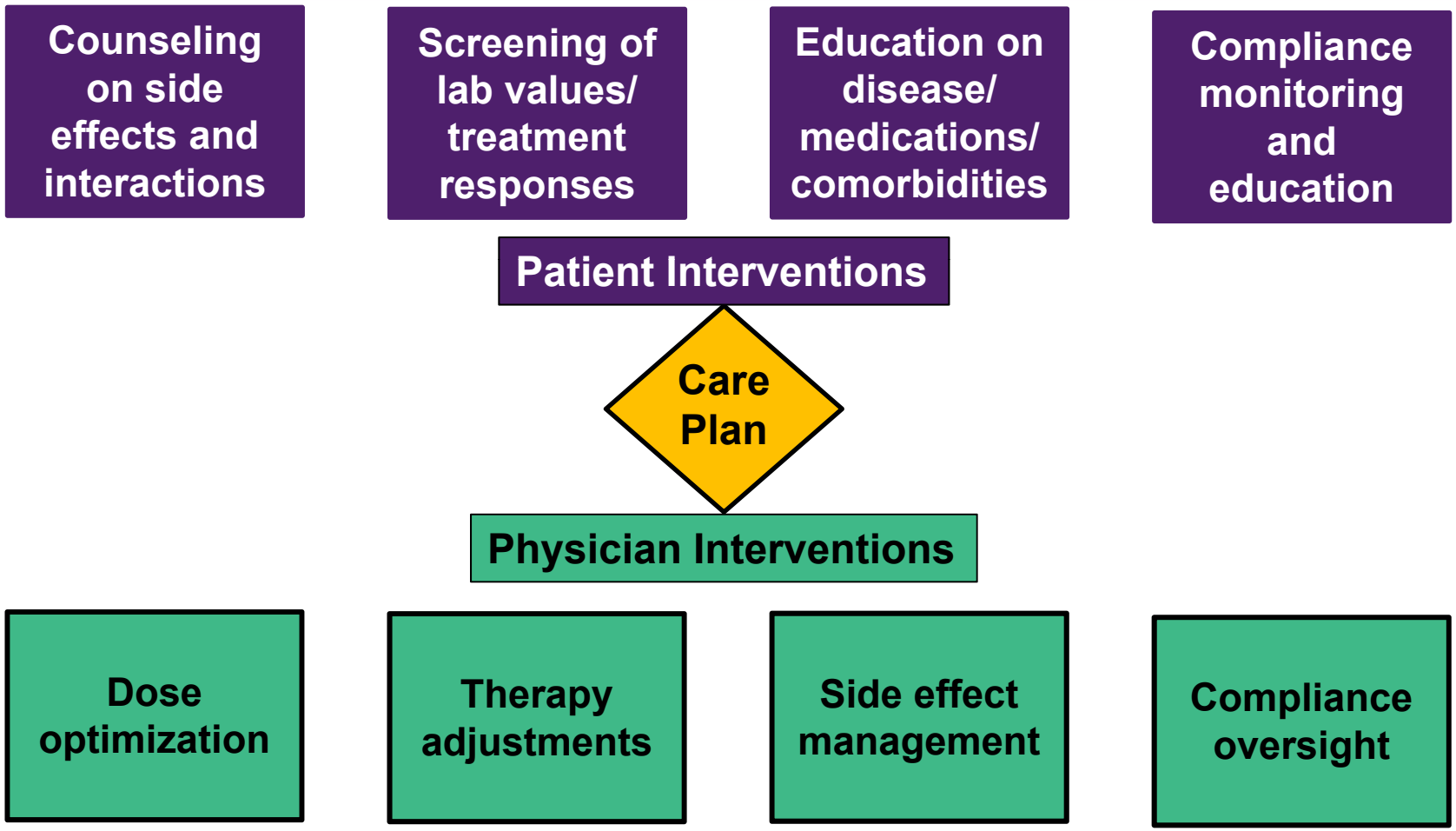
- Situations where specialty pharmacy providers add value:
  - Diseases with limited prescription volume
  - Diseases with low prevalence
  - Presence of frequent copay issues
  - Need for patient education
  - When prior authorization is commonly needed
  - When appeal of coverage denial is necessary
  - Management of treatment-related side effects
  - When quality data is needed
  - When rapid response and transparency are necessary
  - Need to improve/maintain compliance to prescribed therapy

Role of Specialty Pharmacy in Multiple Myeloma Care

- Reduce variability in care delivery
- Provide medication oversight (eg, coordinate medication ordering, delivery, storage, reconstitution, minimize wastage, etc)
- Manage dosing and limit unwarranted use of medication
- Identify and monitor management of comorbid conditions
- Support patient adherence to therapy
- Educate and reinforce patient self-care
- Coordinate or provide nursing care
- Provide patient education
- Communicate and collaborate with other care providers
- Provide reimbursement consultation

Tschida S, et al. J *Manag Care Pharm.* 2013;19:26-41.

Specialty Pharmacy Positioned to Implement Multiple Elements of the Care Plan



Correia RJ. Oral Oncology therapies: specialty pharmacy's newest challenge. *Spec Pharm Times*. Available at: http://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2011/may-2011/Oral-Oncology-Therapies-Specialty-Pharmacys-Newest-Challenge-. Accessed March 3, 2013.

Measuring Success of Specialty Pharmacy Services

- Patient
  - Improved clinical/humanistic outcomes
  - Enhanced compliance with therapeutic regimen
- Payer
  - Reduced pharmacy costs
  - Reduced direct medical costs
- Provider
  - Appropriate coverage under benefit
  - Ease of process for office and patient

Summary

Summary

- Oncology specialty drug spending is increasing rapidly with the introduction of novel biologic agents
- Oncology represents the 3rd largest category within the specialty budget
- A standardized specialty oncology drug benefit has yet to be established
- An ideal oncology specialty drug benefit
  - Provides access to all appropriate therapies
  - Includes cost-sharing requirements that support patient compliance to their prescribed regimen
- High copay requirements negatively affect compliance to oral oncolytics
- Specialty pharmacy providers can contribute to delivery of a consistent therapeutic approach, reduce variation, decrease costs, engage providers, and increase quality of care