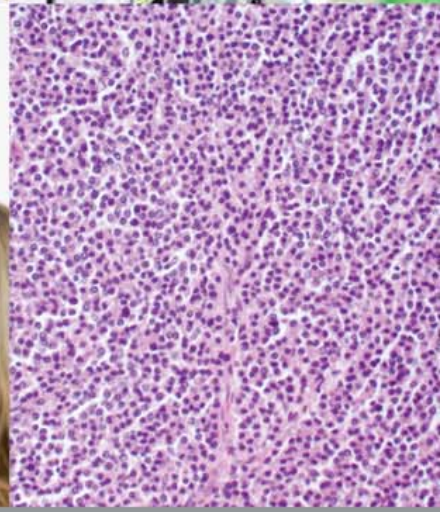
MCRB™



An Analysis of the Latest Treatments, Economic Value, and Benefit Designs for Multiple Myeloma

MANAGED CARE REVIEW BOARD™

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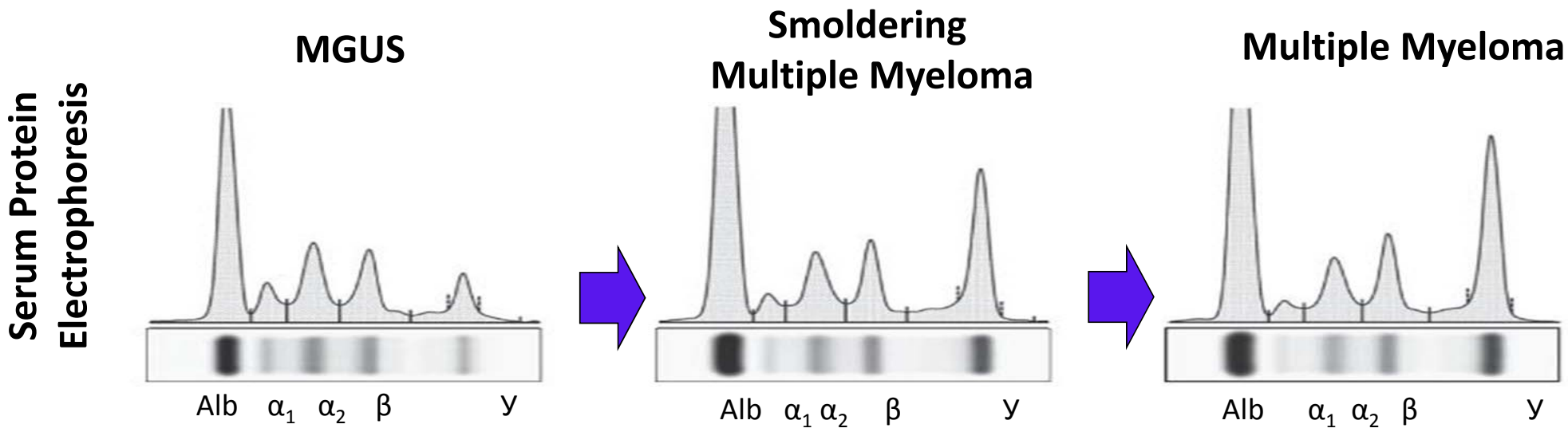
PIM Postgraduate Institute for Medicine

This activity is supported by independent educational grants from Celgene Corporation, Novartis Pharmaceuticals Corporation, and Takeda Oncology.

Evolving Treatment Options and Clinical Benefits Update in MM

Shaji Kumar, MD
Professor of Medicine
Division of Hematology
Mayo Clinic

The Natural History of MM



Bone Marrow	**<10% Plasma cells**	**≥ 10% Plasma cells**	**≥ 10% Plasma cells**
Clinical Picture	**Asymptomatic No end-organ damage**	**Asymptomatic No end-organ damage**	**Symptomatic End-organ damage present**
Therapy	**Observation only**	**Observation only**	**Therapy required**

Kyle RA, et al. *NEJM*. 2007;356:2582-2590.

A Stepwise Approach to Treatment of MM

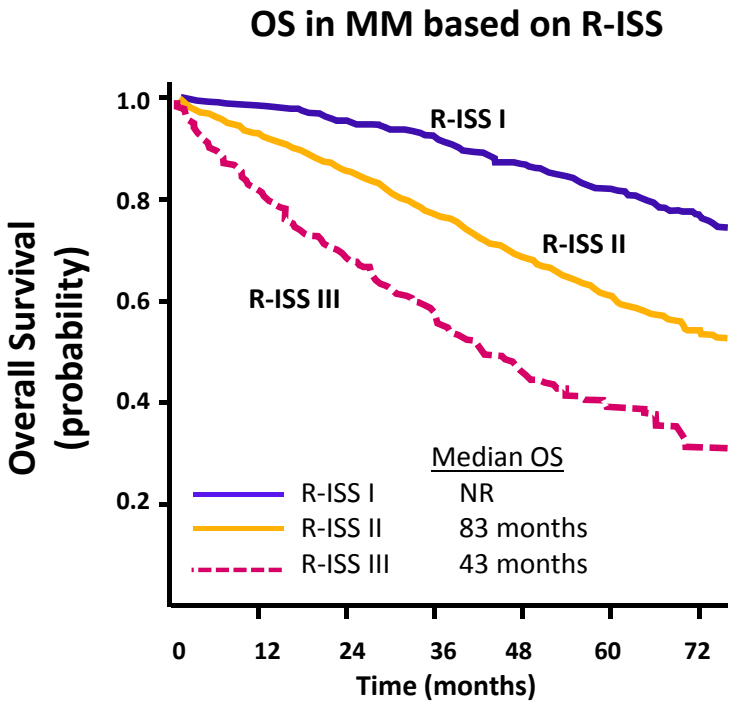
1. Risk stratification
2. Initial disease control/reverse complications
3. Consolidate initial response
4. Maintain response
5. Effective treatment at relapse

Supportive care at every stage

Revised International Staging System for MM

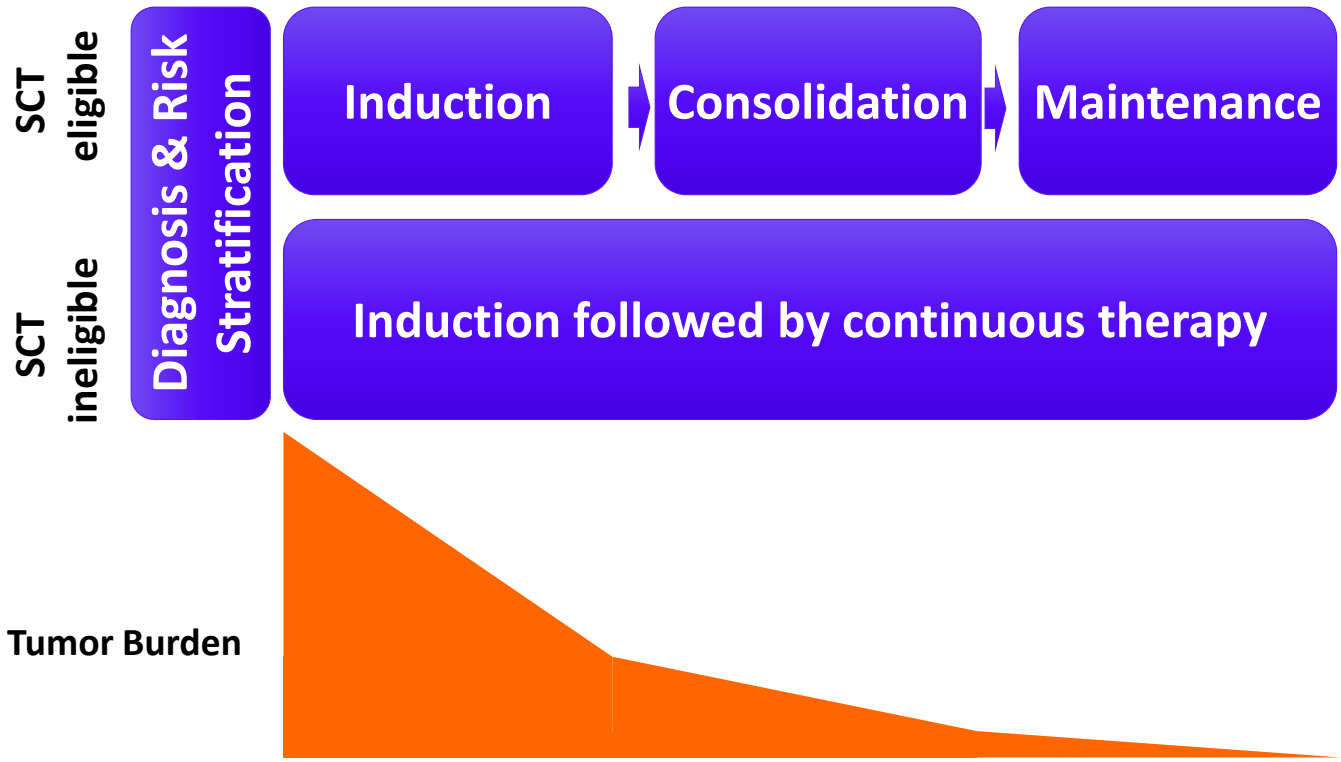
Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-macroglobulin < 3.5 mg/L, serum albumin ≥ 5.5 mg/L
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
New model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS state I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH



CA=chromosomal abnormalities; iFISH=interphase fluorescent in situ hybridization; ISS=International Staging System; LDH=lactate dehydrogenase; MM=multiple myeloma; R-ISS=revised International Staging System.

MM Treatment Paradigm



SCT=stem cell transplant

Initial Therapy for MM

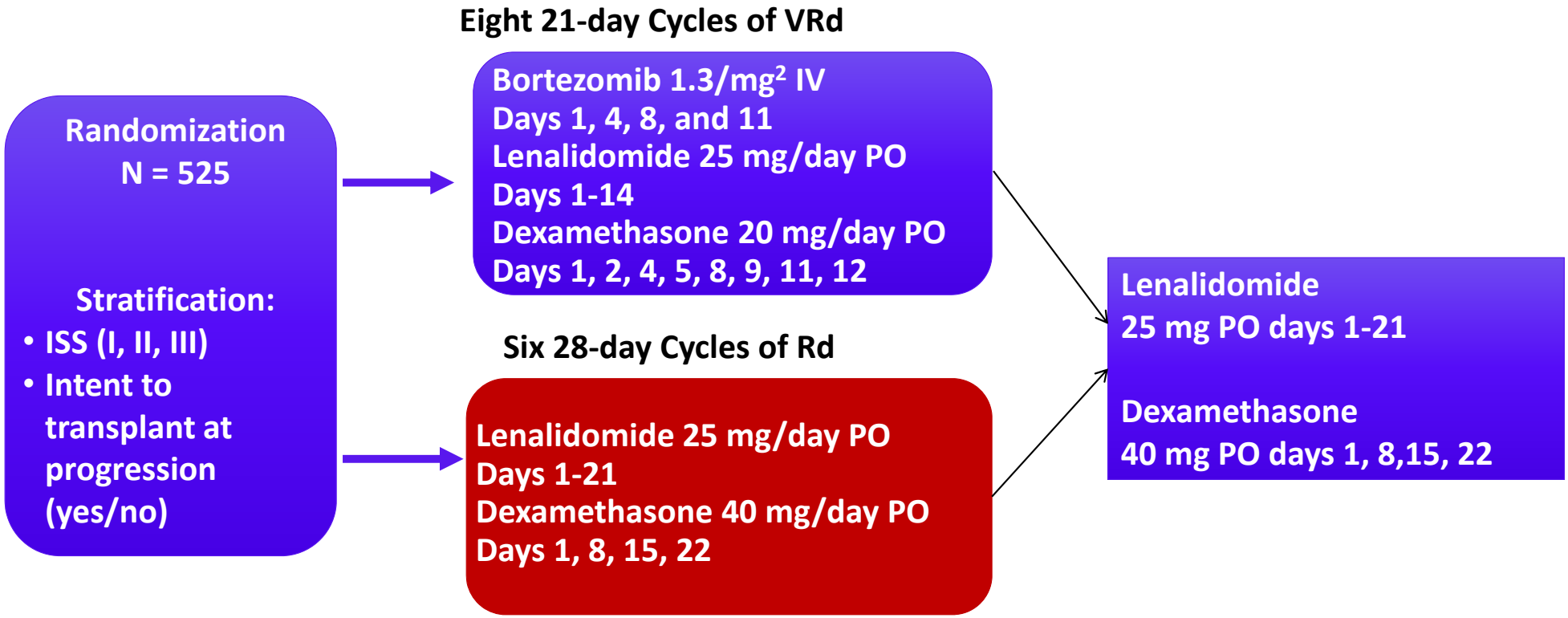
The ideal initial therapy should:

- Rapidly and effectively control disease
- Reverse disease-related complications
- Decrease the risk of early death
- Be easily tolerated with minimal/manageable toxicity
- Not interfere with the ability to collect stem cells for transplantation

Treatment options include:

- Immunomodulatory drugs
  - Thalidomide, lenalidomide
- Proteasome inhibitors
  - Bortezomib
- Traditional chemotherapy
  - Cyclophosphamide, doxorubicin

SWOG S0777: VRd vs Rd in Newly-Diagnosed MM

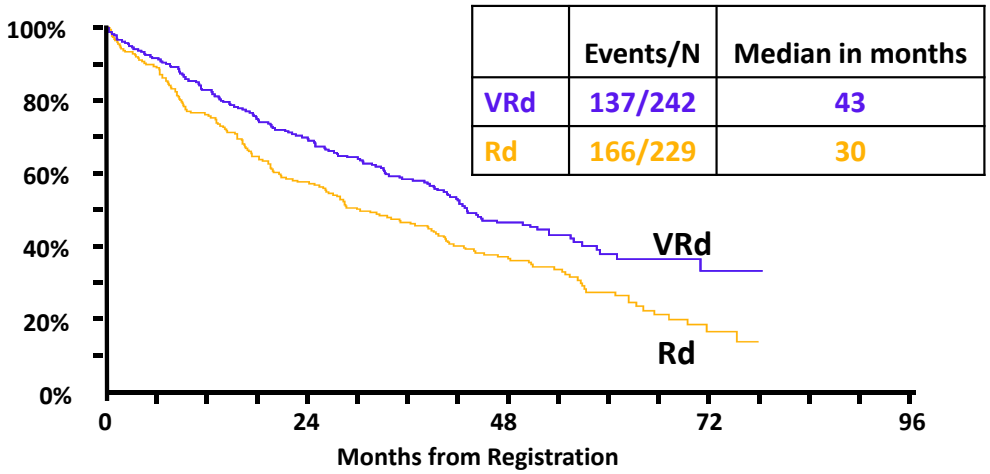


Rd=lenalidomide+dexamethasone;
VRd=bortezomib+lenalidomide+dexamethasone.

Durie B, et al. ASH 2015. Abstract 25.

SWOG S0777: PFS and OS Superior for VRd vs Rd

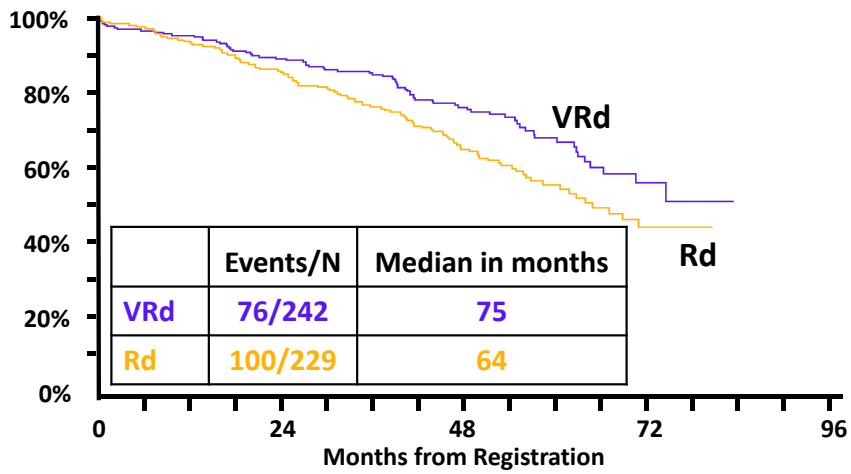
Progression-Free Survival (PFS)
by assigned treatment arm



	Events/N	Median in months
VRd	137/242	43
Rd	166/229	30

HR = 0.712 (0.560, 0.906)*
Log-rank P value = 0.0018 (one sided)*

Overall Survival (OS)
by assigned treatment arm



	Events/N	Median in months
VRd	76/242	75
Rd	100/229	64

HR = 0.709 (0.516, 0.973)*
Log-rank P value = 0.0250 (two sided)*

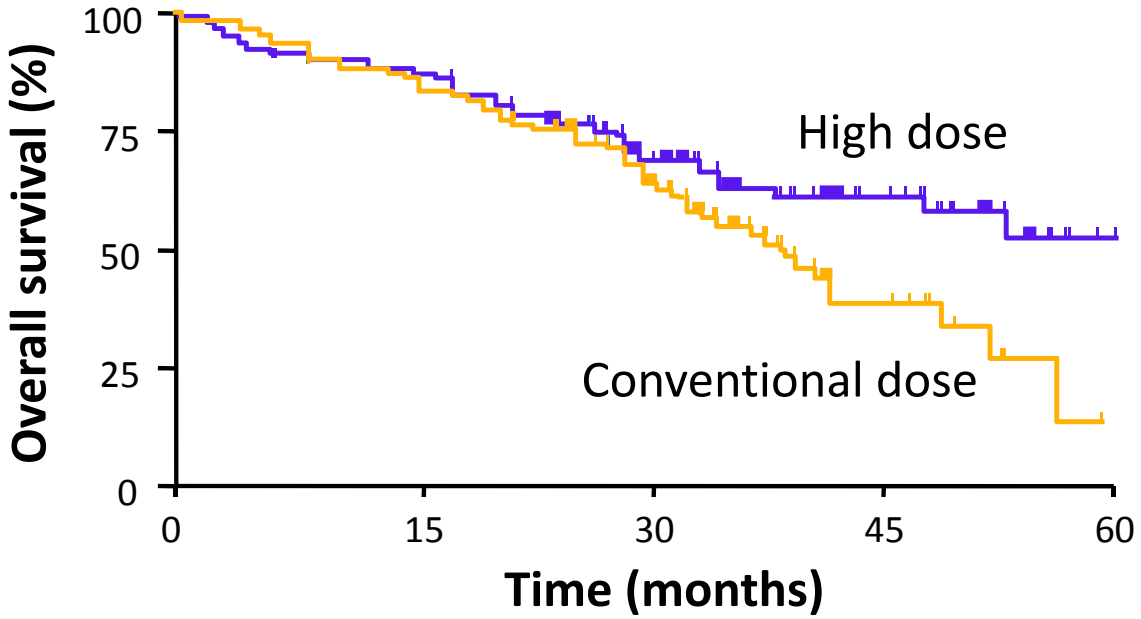
Rd=lenalidomide+dexamethasone;
VRd=bortezomib+lenalidomide+dexamethasone.

Durie B, et al. ASH 2015. Abstract 25.

***Stratified**

Consolidation: High- vs Conventional-Dose Chemotherapy

High-dose chemotherapy combined with transplantation improves response rates, event-free survival, and overall survival compared with conventional-dose chemotherapy in patients with MM



Patients Alive at Each Time Point % (95% CI)			
Conventional dose	63 (53–73)	35 (22–50)	12 (1–40)
High dose	69 (58–78)	61 (50–71)	52 (36–67)

Attal M. *N Engl J Med*. 1996;335:91-97.

IFM 2009: Auto SCT in the Era of New Drugs

TRIAL DESIGN

Registration

RVD cycle 1
Lenalidomide + Bortezomib + Dexamethasone

Randomization (stratified on ISS and FISH)

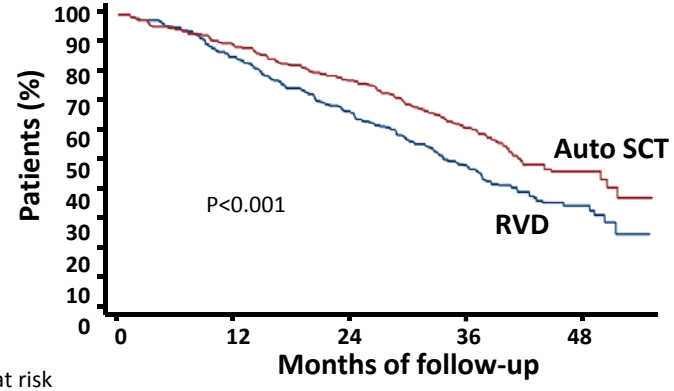
Arm A: RVD	Arm B: Auto SCT
RVD cycles 2 and 3	RVD cycles 2 and 3
PBSC Collection (cyclophosphamide and G-CSF)	PBSC Collection (cyclophosphamide and G-CSF)
RVD cycles 4 through 8	ASCT HDM 200 mg/m^2
Lenalidomide Maintenance 12 months (10-15 mg/d)	RVD cycles 4 and 5 (consolidation)
	Lenalidomide Maintenance 12 months (10-15 mg/d)

Attal M, et al. ASH 2015. Abstract 391.

IFM 2009: Auto SCT Enhances Response Rate and PFS

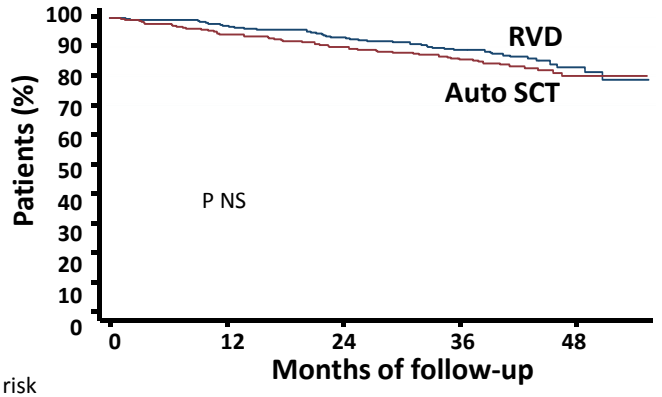
Response Parameter	RVD N=350	Auto SCT N=350	P-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by flow, n (%)	228 (65%)	280 (80%)	0.001

PFS
by assigned treatment arm



N at risk					
AutoSCT	350	309	261	153	27
RVD	350	296	228	128	24

OS
by assigned treatment arm



N at risk					
AutoSCT	350	328	309	226	55
RVD	350	338	320	144	56

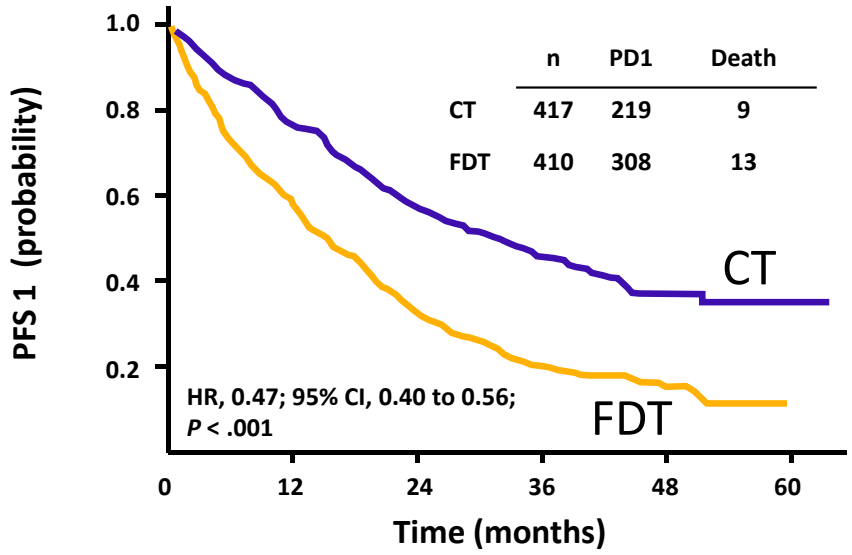
Attal M, et al. ASH 2015. Abstract 391.

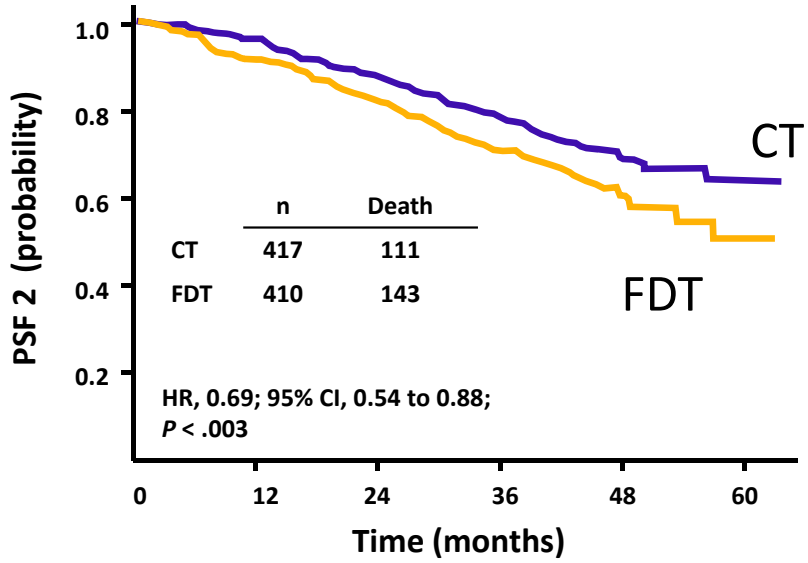
CR=complete response; FCM=flow cytometric detection; MRD=minimal residual disease; PR=partial response; VGPR=very good partial response.

Maintenance Therapy for MM

- Ongoing debate surrounding duration of maintenance therapy
  - Lenalidomide or bortezomib are considered most frequently
- Maintenance therapy improves PFS, but effect on OS is inconsistent
- Increased toxicity with maintenance therapy, especially over long term
- Quality of life impact
- Cost of care implications

Pooled Analysis of Continuous Therapy vs Fixed-Duration Therapy in Patients Newly-diagnosed with MM



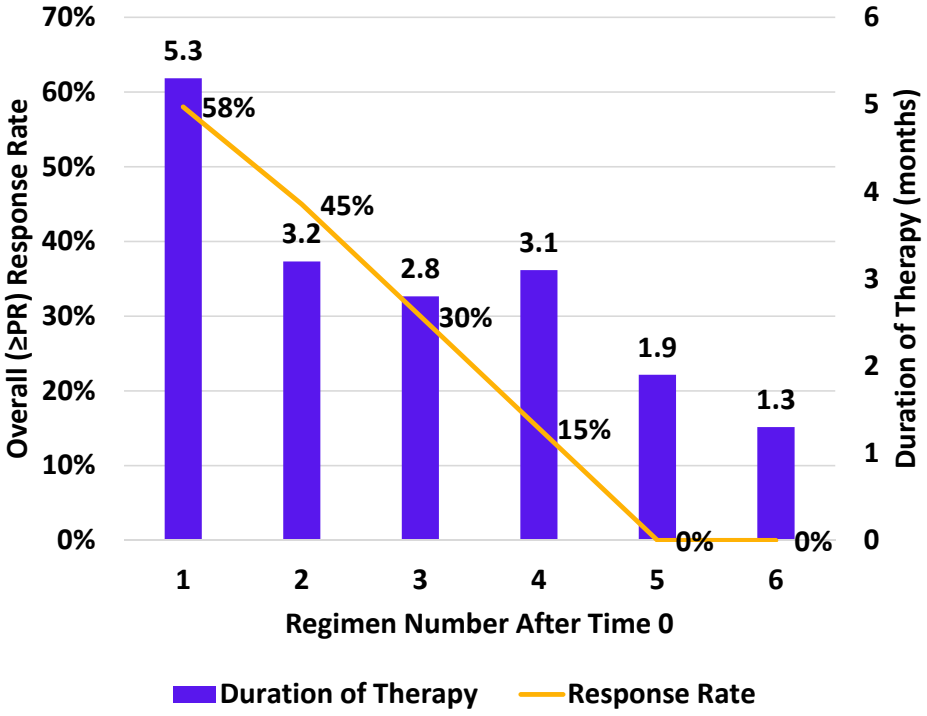


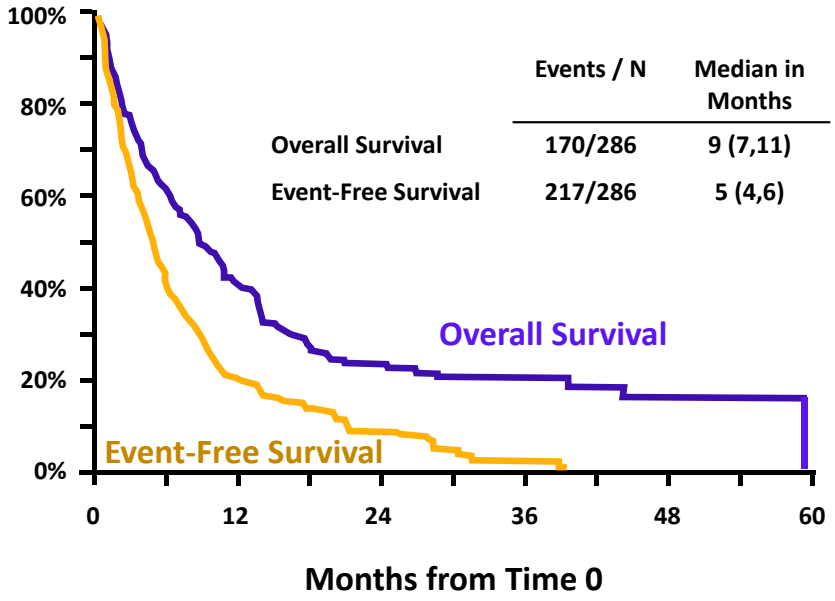
CT=continuous therapy; FDT=fixed duration of therapy

Palumbo A, et al. *JCO.* 2015;33(30):3459-3466.

CT significantly improved PFS1, PFS2, and OS. The improvement in PFS2 suggests that the benefit reported during first remission is not cancelled by a shorter second remission

Natural History of MM at Relapse





This study shows the natural history of MM after it is non-responsive to novel therapies. These results serve as a reference for comparison of ongoing trials of new drugs for MM

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

Treatment Options for Relapsed/Refractory MM (RRMM)

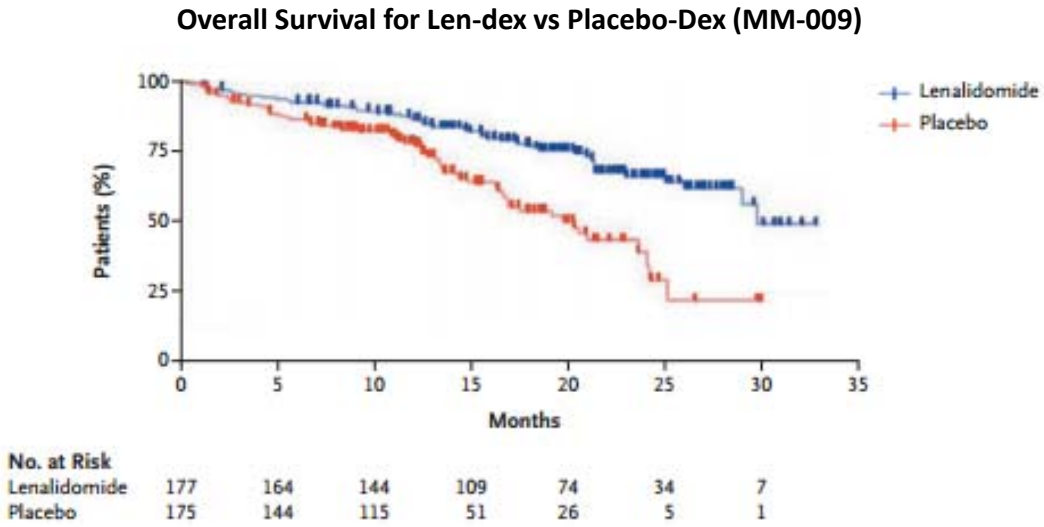
- Newer classes of drugs
  - Immunomodulators, proteasome inhibitors, monoclonal antibodies, histone deacetylase (HDAC) inhibitors
- Conventional chemotherapy
  - Dexamethasone/prednisone, cyclophosphamide, melphalan, anthracyclines, DCEP, VDT-PACE
- Combinations of new and older drugs
- Promising drugs in clinical trials

DCEP=Dexamethasone/cyclophosphamide/etoposide/cisplatin
VDT-PACE=Bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etopside

IMiDs: Lenalidomide-Dex Superior to Dex in RRMM

Two studies demonstrate that lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory MM (MM-009 and MM-010)

Best Response	MM-009		MM-010	
	Len/Dex	Dex	Len/Dex	Dex
Overall response	61%	20%	60%	24%
CR + nCR	24%	2%	25%	5%
PR	37%	18%	35%	19%
Duration of response (months)	16	5	17	8



Weber DM, et al. *N Engl J Med.* 2007;357(21):2133-2142. (MM-009)
Dimopoulos MA, et al. *N Engl J Med.* 2007;357(21):2123-2132. (MM-010)

IMiDs: Pomalidomide-Dex Active in RRMM

	IFM (21 of 28 days)	IFM (28 of 28 days)	Mayo (2 mg)	Mayo (4 mg)	MM02 (4 mg)
N	43	41	35	35	120
CR	2%	0%	0%	3%	1%
>VGPR	9%	5%	14%	11%	1%
>PR	**42%**	**39%**	**26%**	**26%**	**33%**
>MR	41%	39%	49%	40%	45%
DOR	4 mos	4 mos	12 mos	NA	11 mos

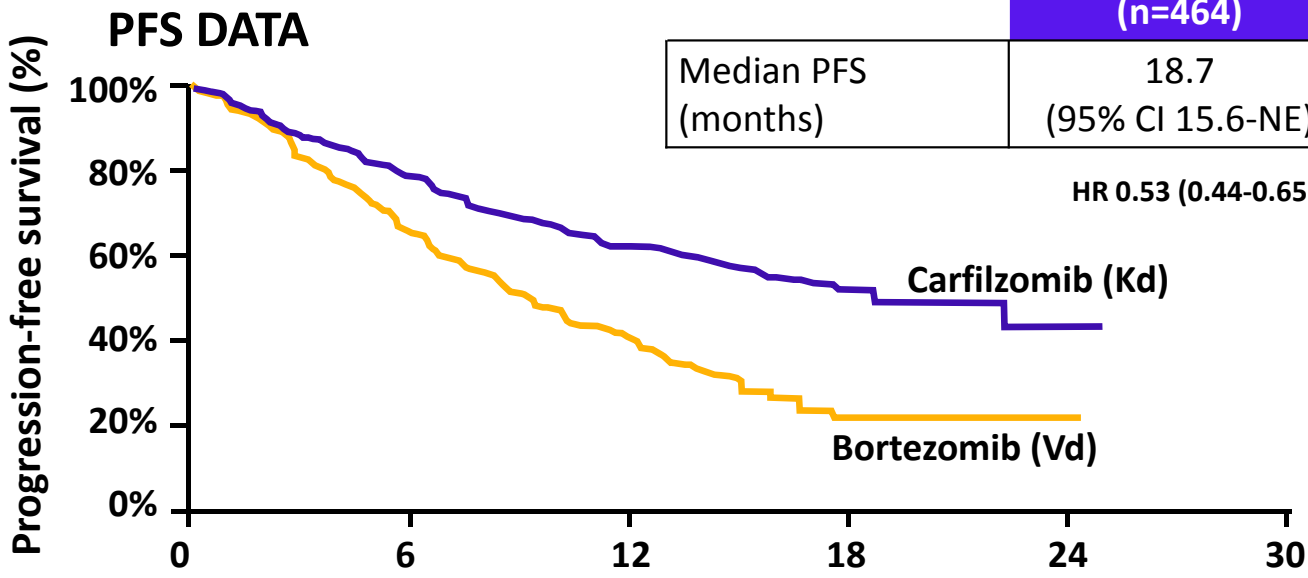
Leleu X, et al. *Proc ASH* 2010; Abstract 859. (IFM)
Lacy MQ, et al. *Proc ASH* 2010; Abstract 863. (Mayo)
Richardson PG, et al. *Blood.* 2014;123(12):1826-1832. (MM02)

CR=complete response; DOR=duration of response; IMiDs=immunomodulatory drugs; MR=median response; PR=partial response; VGPR=very good partial response.

Proteasome Inhibitors: Kd vs Vd in RRMM (ENDEAVOR)

	Carfilzomib (Kd) (n=464)	Bortezomib (Vd) (n=465)
Median PFS (months)	18.7 (95% CI 15.6-NE)	9.4 (95% CI 8.4-10.4)

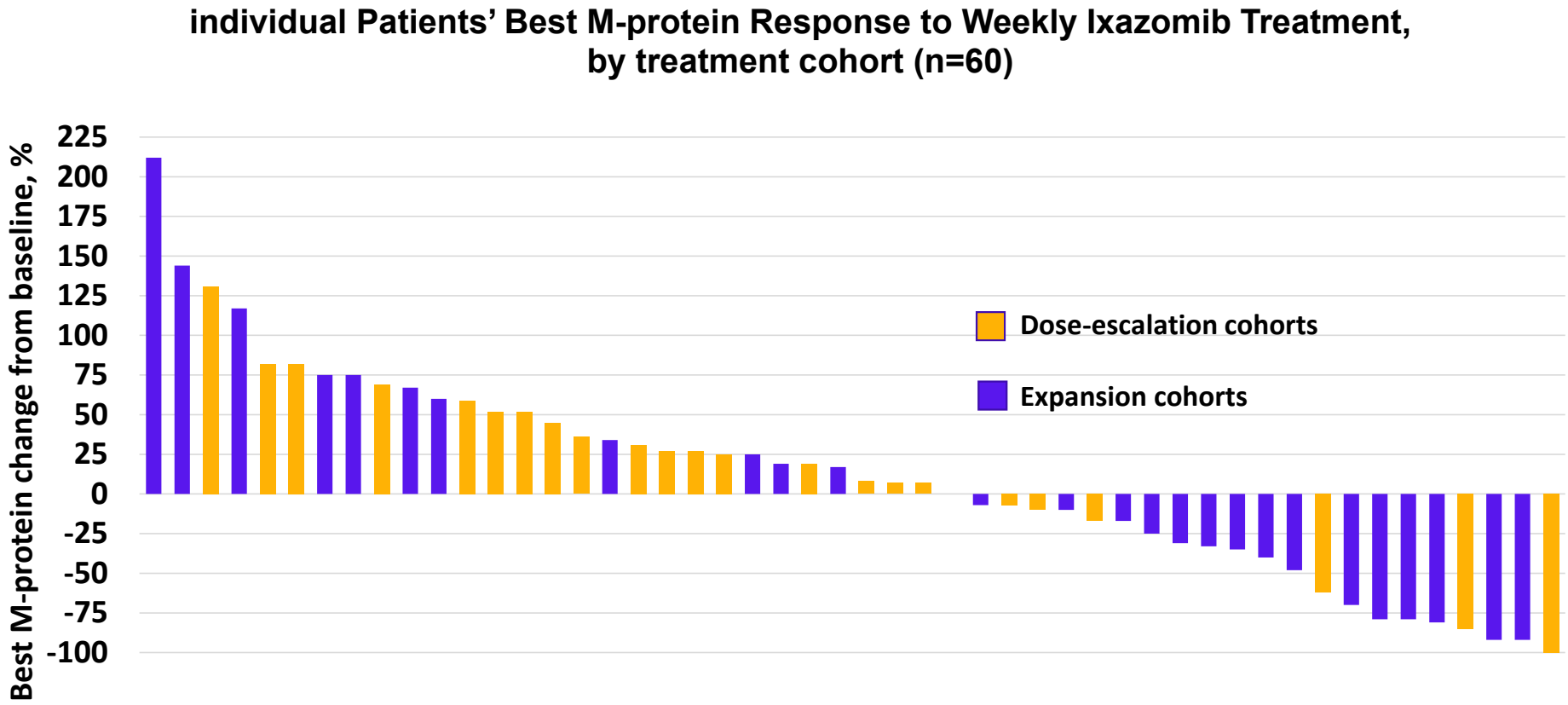
HR 0.53 (0.44-0.65); P < 0.0001



Number at risk						
Carfilzomib	464	331	144	41	4	0
Bortezomib	465	252	81	12	1	0

Dimopoulos MA, et al. *Lancet.* 2016;17(1):27-38.

Proteasome Inhibitors: Once-Weekly Ixazomib in RRMM

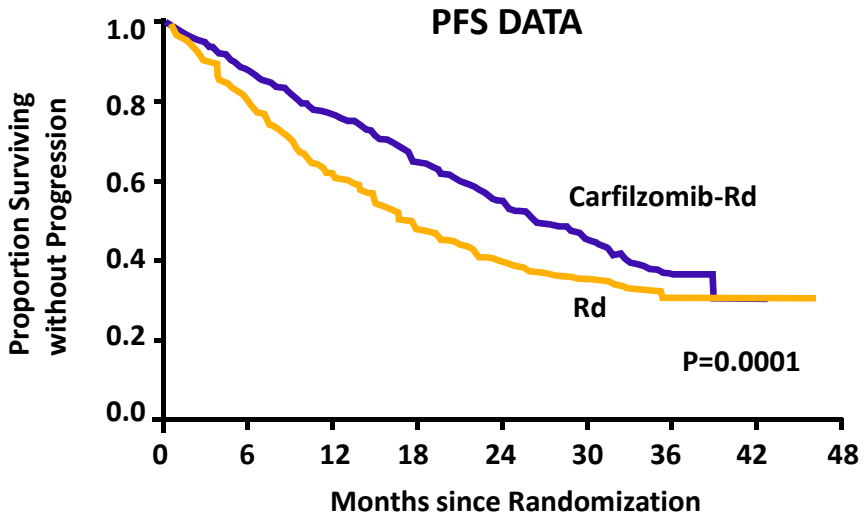


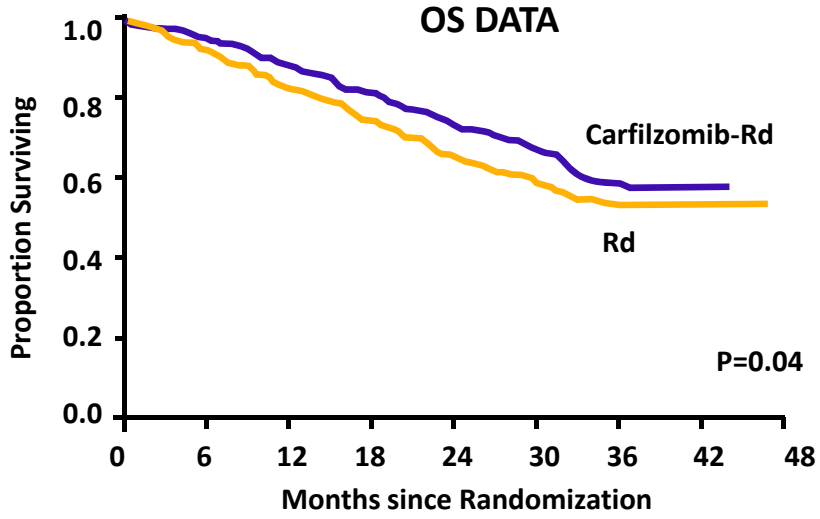
Kumar SK, et al. *Blood*. 2014;124(7):1047-1055.

PI-IMiD Combinations: Carfilzomib-Rd vs Rd in RRMM

Progression-free Survival	Carfilzomib-Rd (N=396)	Rd (N=396)
Median PFS – months	26.3	17.6
Hazard ratio for CRd vs Rd (95% CI)	0.69 (0.57-0.83)	

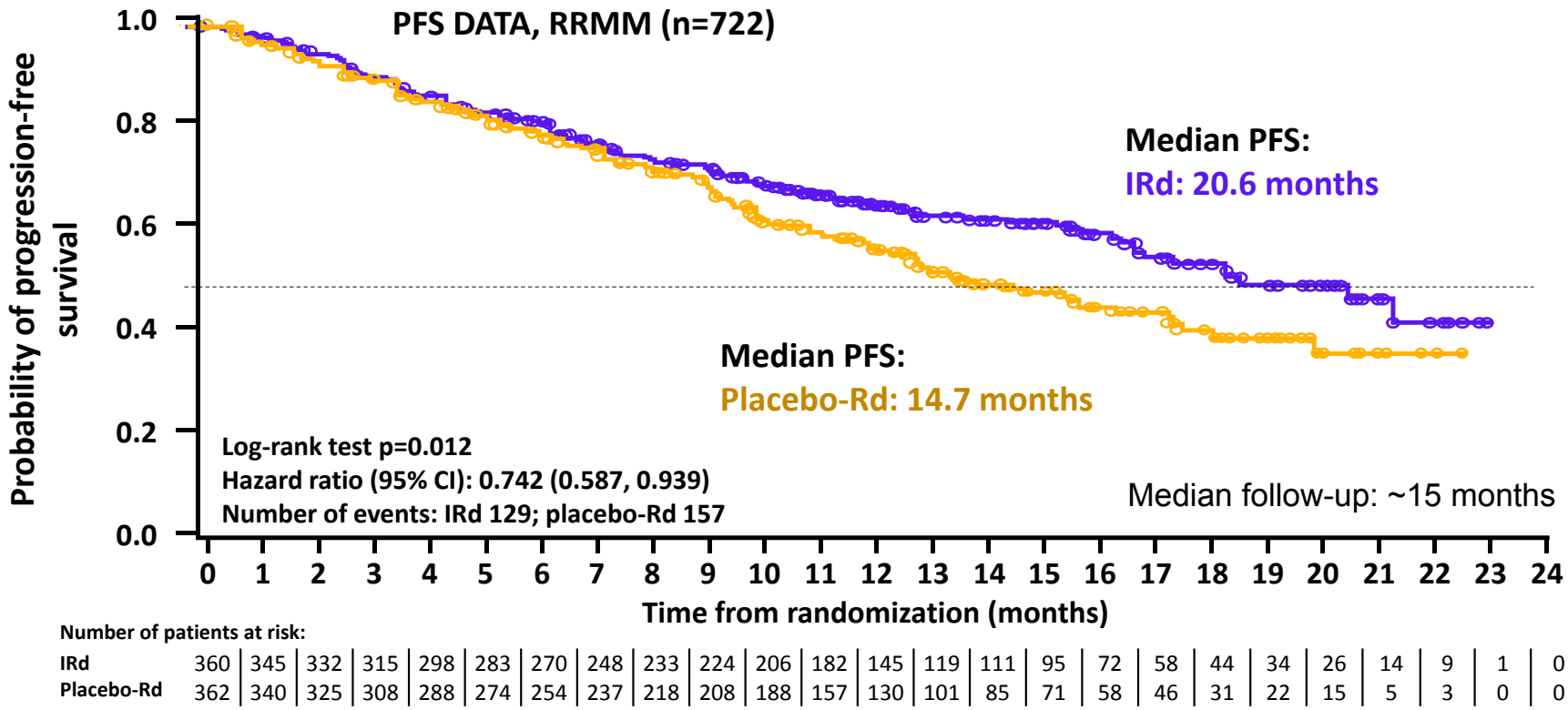
Overall Survival	Carfilzomib-Rd (N=396)	Rd (N=396)
24-month OS – % patients	73.3	65.0
Hazard ratio for CRd vs Rd (95% CI)	0.79 (0.63-0.99)	





Stewart AK, et al. *N Engl J Med*. 2015;372:142-152.

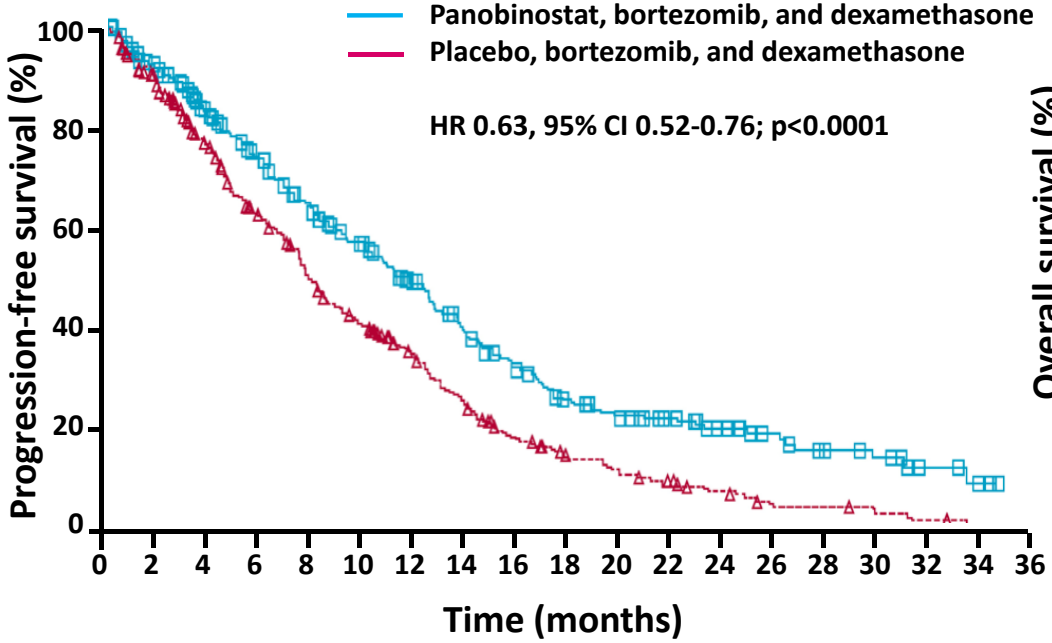
PI-IMiD Combinations: IRd vs Rd (TOURMALINE-MM01)

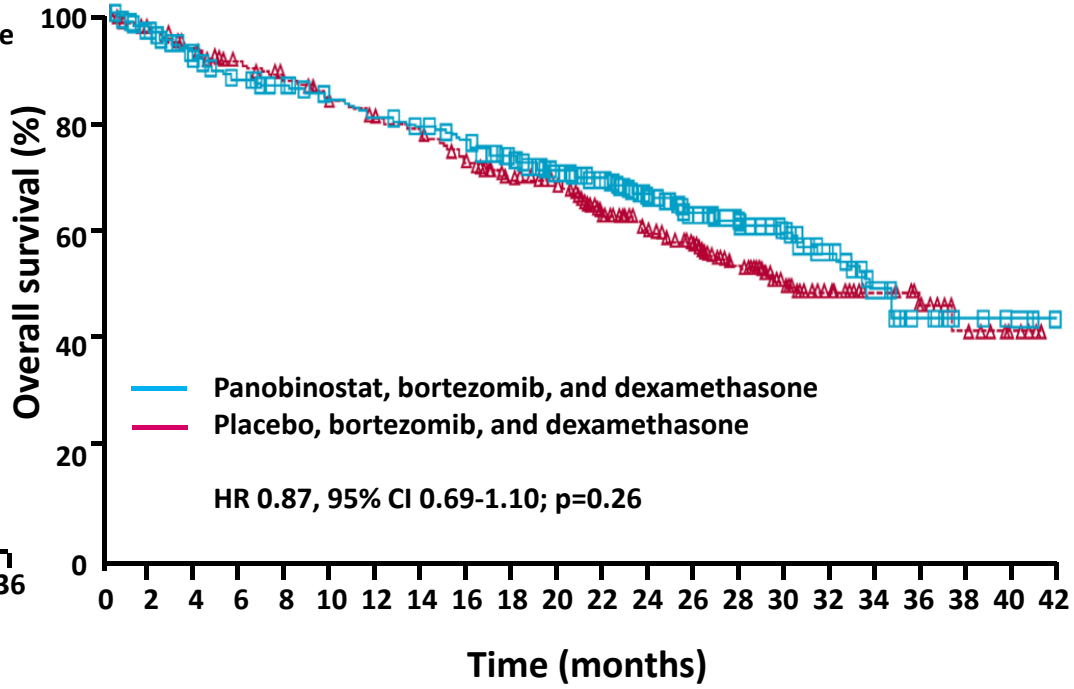


Moreau P, et al. ASH 2015: Abstract 727.

IRd = ixazomib weekly plus lenalidomide and dexamethasone (Rd)

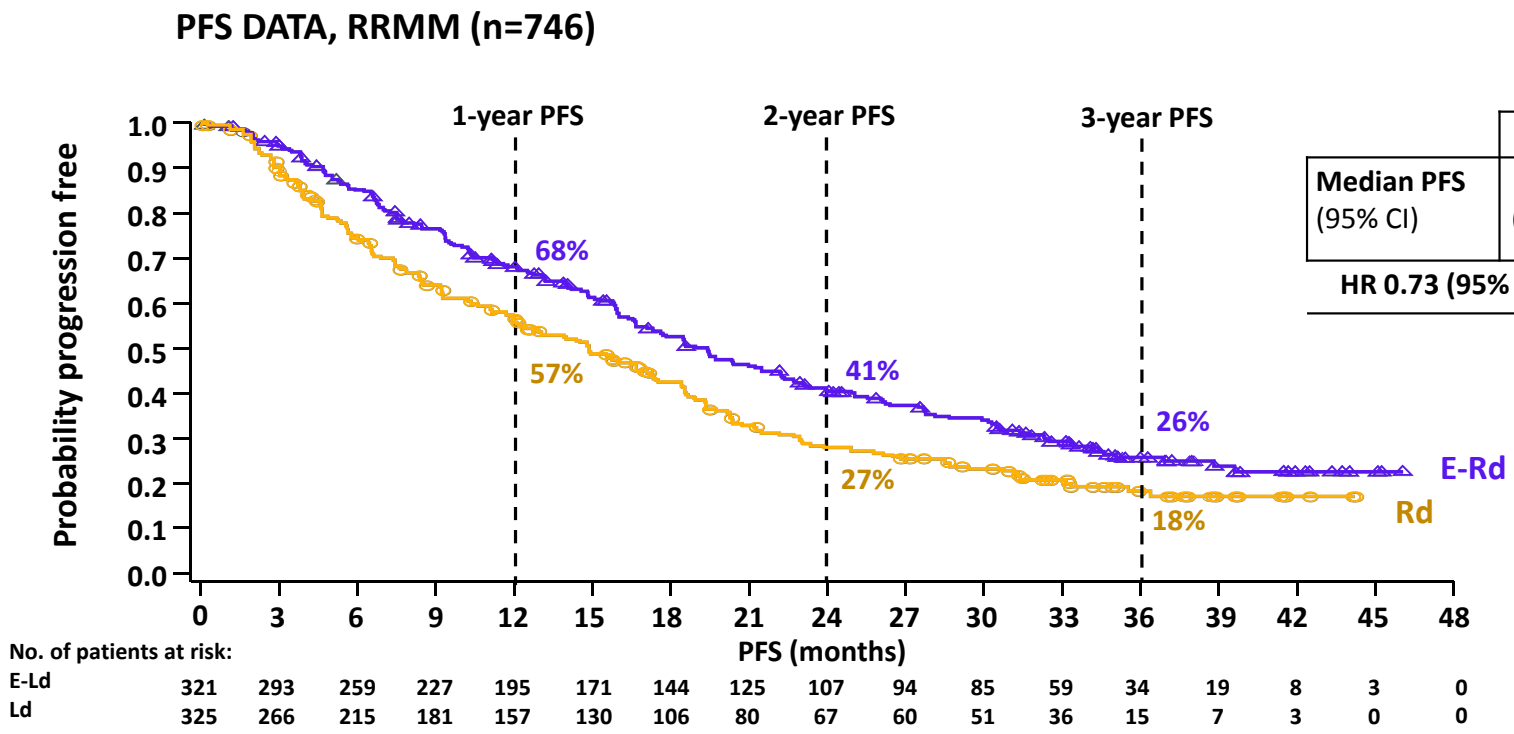
Panobinostat +/- Bortezomib-Dex





San Miguel et al, Lancet Oncology, 2014, 5(11), 1195–1206

Monoclonal Antibodies: Elotuzumab + Rd (ELOQUENT-2)



	E-Rd	Rd
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

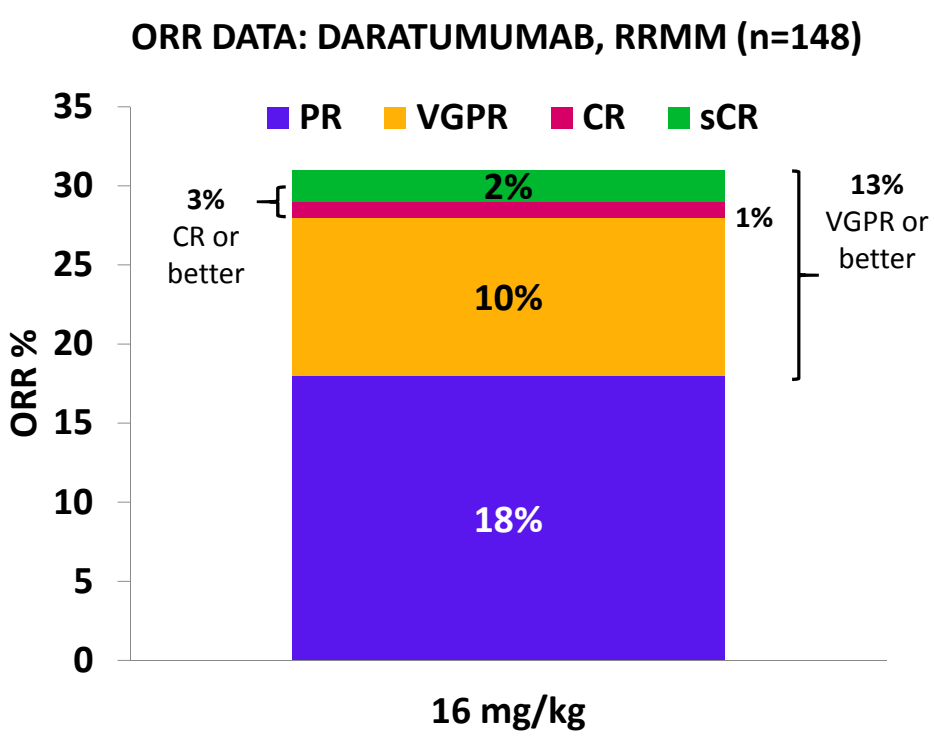
HR 0.73 (95% CI 0.60, 0.89); p=0.0014

ORR: 79% (ERd) vs 66% (Rd)

Addition of elotuzumab to Rd leads to effective and durable benefit

Dimopoulos MA, et al. ASH 2015: Abstract 28.

Monoclonal Antibodies: Daratumumab (SIRIUS and GEN501)



	DARA 16 mg/kg (N = 148)	
	%	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**31%**	**24% to 39%**
Best response		
sCR	2%	0.4% to 6%
CR	1%	0.2% to 5%
VGPR	10%	5% to 15%
PR	18%	12% to 25%
MR	6%	3% to 11%
SD	46%	38% to 54%
PD	12%	7% to 19%
VGPR or better (sCR+CR+VGPR)	13%	8% to 19%
CR or better (sCR+CR)	3%	1% to 8%

Daratumumab (DARA) induced rapid, deep, and durable responses in heavily pretreated, highly refractory MM. Among 46 responders, 40 were alive after median follow-up of 14.8 months (87%). Median DOR was 7.6 months

Usmani S, et al. ASH 2015: Abstract 29.

Summary of General Approaches for Treating MM

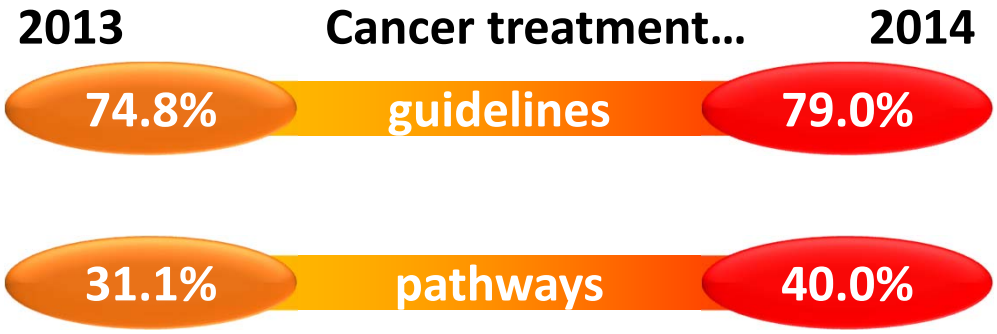
- Regimens and approaches that have worked in the past should be tried again, presuming the patient is not refractory
- Because no therapy is curative, all options need to be tried sequentially
- No good data exist regarding optimal regimens or sequencing
- Patients with MM should be encouraged to participate in ongoing clinical trials

Current Practice Guidelines Review and Application of Clinical Pathways

John Fox, MD, MHA
Senior Medical Director
Associate Vice President, Medical Affairs
Priority Health

Guideline- and Pathways-Based Programs are Among the Key Payer-led Management Initiatives in Oncology

Percentage of MCOs following cancer treatment guidelines or pathways, 2013 and 2014



The percentage of MCOs following both cancer treatment guidelines and pathways has increased since the 2013 study period.

N=105; Pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Predominant Treatment Guidelines for MM

NCCN Clinical Practice Guidelines in Oncology

- Features an extensive set of treatment algorithms and menus of therapeutic options following disease progression

IMWG Guidelines

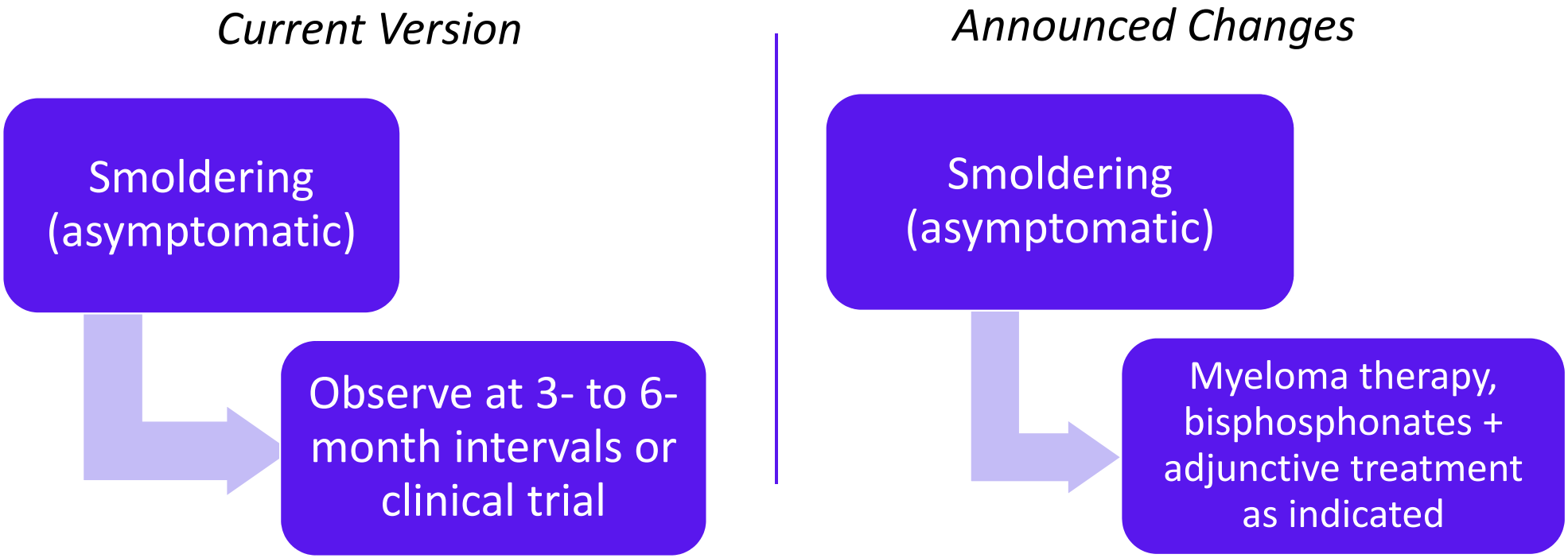
- Details recommended therapies and accompanying dosing schedules for specific clinical demographics of patients

mSMART Treatment Guidelines

- Employs a unique risk-adapted approach that recommends treatment in alignment with disease stratification according to cytogenetics

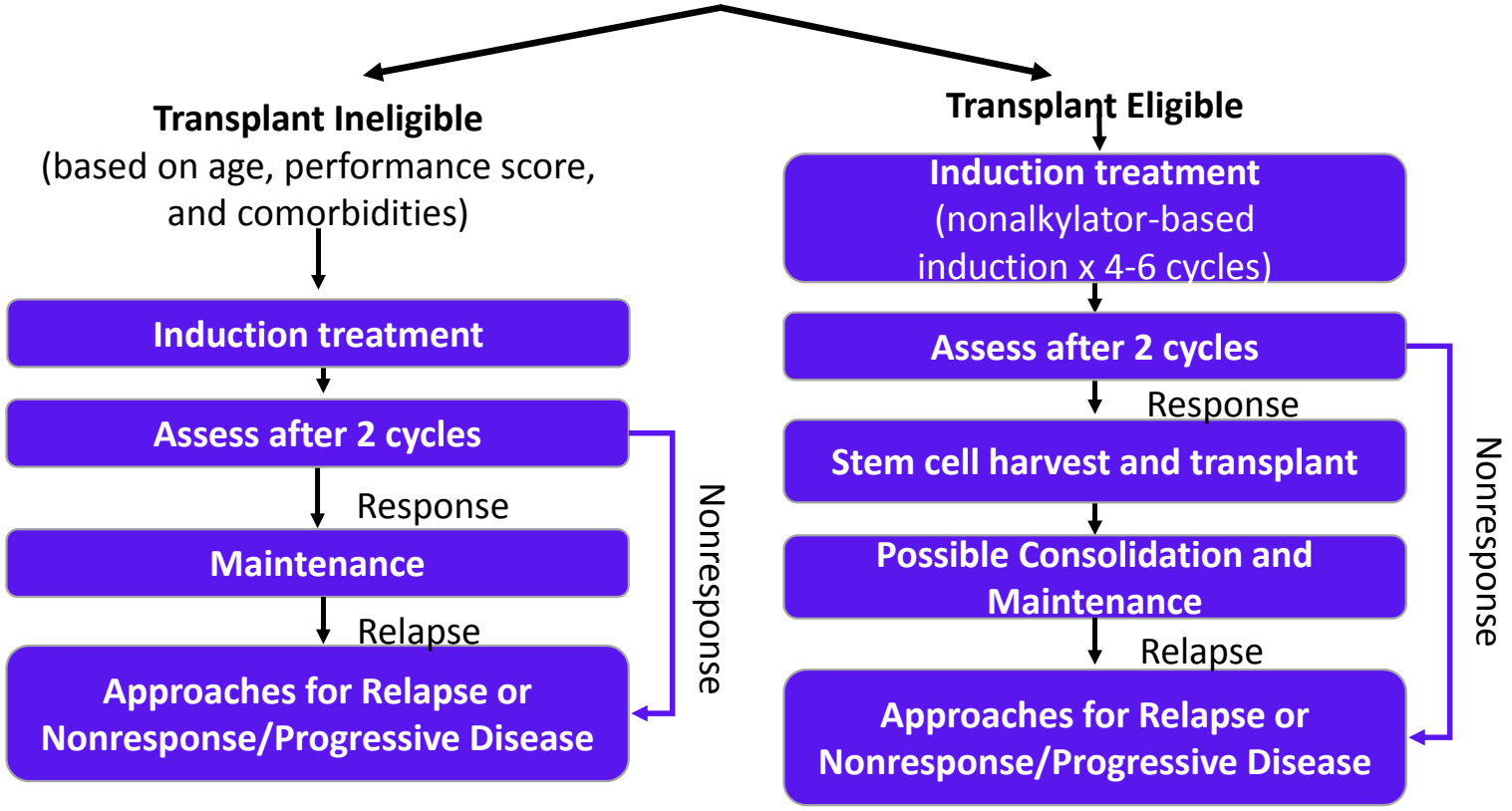
NCCN=National Comprehensive Cancer Network
IMWG=International Myeloma Working Group
mSMART=Mayo Stratification of Myeloma and Risk-adapted Therapy

Announced Changes to the NCCN Practice Guidelines for MM Recommend Treatment Before Development of Active Disease



Anderson KC. Presented at: NCCN Annual Meeting; March 31–April 2, 2016; Hollywood, FL.

The NCCN Clinical Practice Guidelines Provide a Blueprint for Treatment Strategies in MM



NCCN Clinical Practice Guidelines: Multiple Myeloma. v3.2016.

NCCN Clinical Practice Guidelines in Oncology: Primary Therapy for MM

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide/dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide/dexamethasone (category 1)	• Carfilzomib/lenalidomide/dexamethasone • Dexamethasone (category 2B) • Ixazomib/lenalidomide/dexamethasone • Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1) • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category 1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Ixazomib/lenalidomide/dexamethasone • Liposomal doxorubicin/vincristine/ dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

NCCN Clinical Practice Guidelines: Multiple Myeloma. v3.2016.

NCCN Clinical Practice Guidelines in Oncology: Therapeutic Options for Previously Treated MM

Preferred Regimens	Other Regimens
• Repeat primary induction therapy (if relapse at >6 mos) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Ixazomib • Ixazomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 1) • High-dose cyclophosphamide • Lenalidomide/dexamethasone (category 1) • Panobinostat/bortezomib/dexamethasone (category 1) • Pomalidomide/dexamethasone (category 1) • Thalidomide/dexamethasone	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone • Panobinostat/carfilzomib

NCCN Clinical Practice Guidelines: Multiple Myeloma. v3.2016.

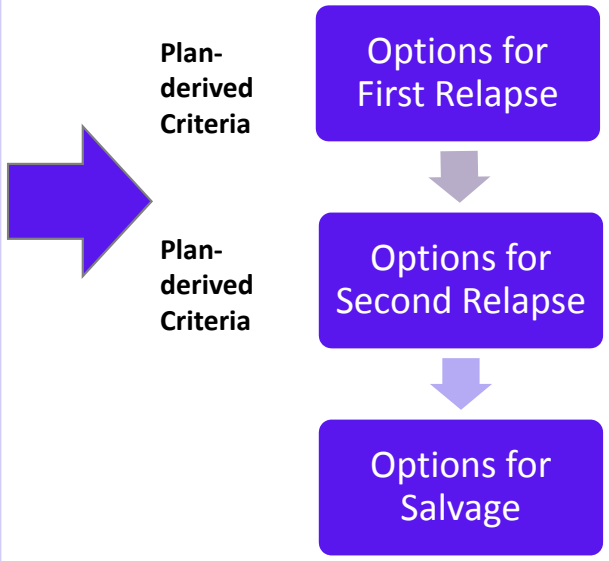
Pathways Initiatives Condense an Expansive Menu of Clinical Options into a More Concise, Stepwise Process as a Pragmatic Decision Support Tool

Example: Previously Treated MM

NCCN Clinical Practice Guideline

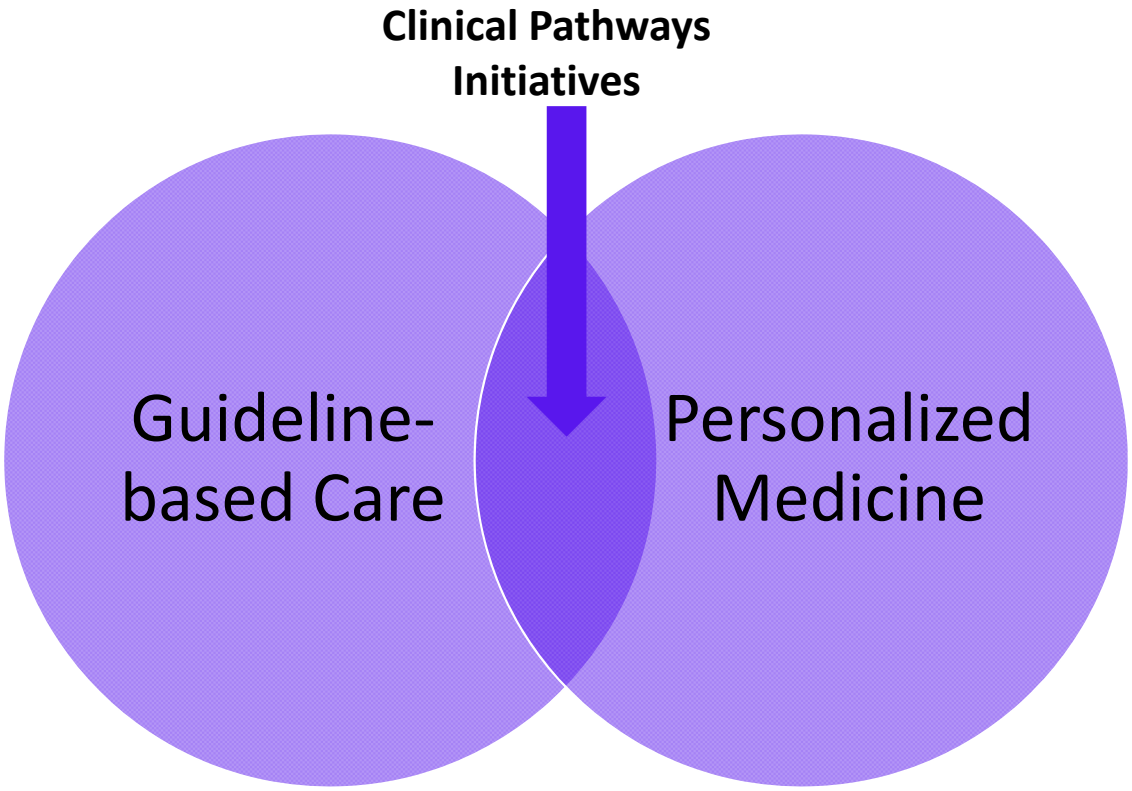
Preferred Regimens	Other Regimens
• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Ixazomib • Ixazomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 1) • High-dose cyclophosphamide • Lenalidomide/dexamethasone (category 1) • Panobinostat/bortezomib/dexamethasone (category 1) • Pomalidomide/dexamethasone (category 1) • Thalidomide/dexamethasone	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/ dexamethasone • Panobinostat/carfilzomib

Clinical Pathways Program



NCCN Clinical Practice Guidelines: Multiple Myeloma. v3.2016.

Clinical Pathways Initiatives Aim to Reduce Treatment Variability While Allowing Individualized Care in Oncology

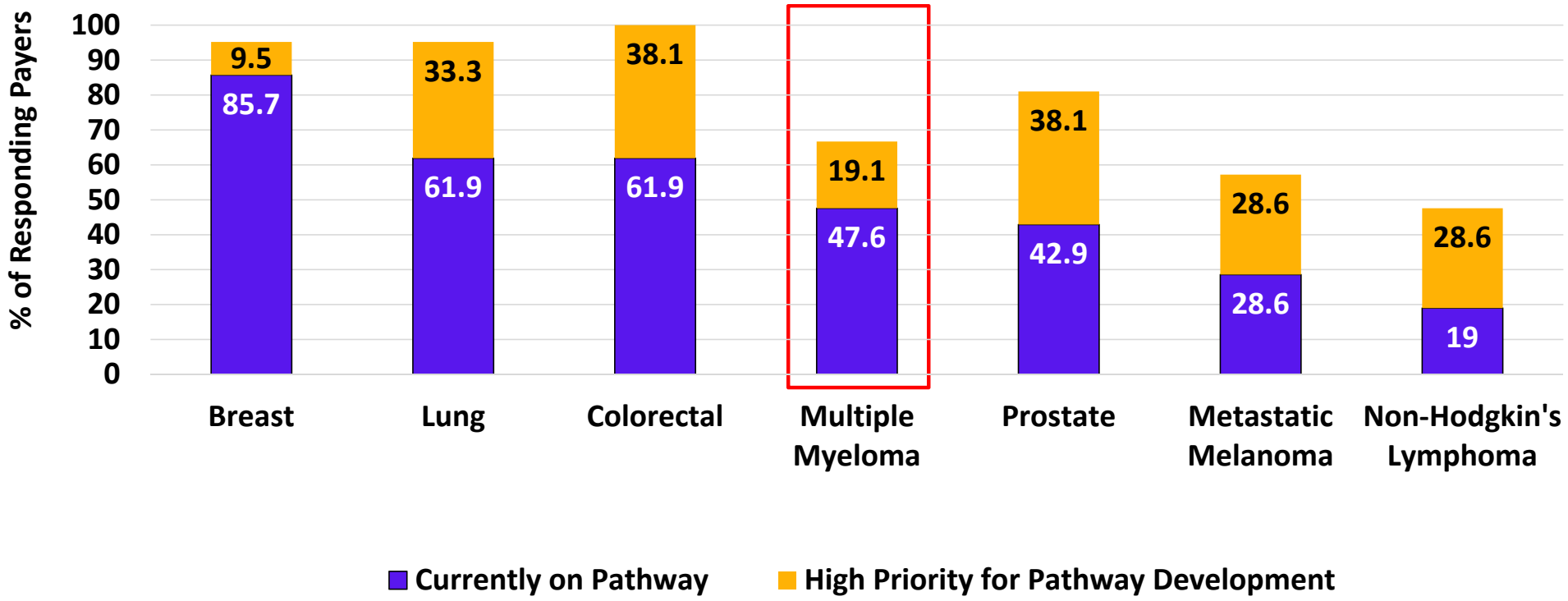


Pathways-based Initiatives Vary in Scope and Implementation But Share Several Key Characteristics

Clinical pathways initiatives…

- …use clinical trial and other evidence-based data to guide rational therapeutic decisions
- …offer formal structural elements to guide decisions
- …are often primarily derived from NCCN guidelines
- …allow for coordination with appropriate clinical trials (prospective) and real-world prospective clinical trials
- …can improve quality of care and coordination within a health care system as well as decrease overutilization

Pathways Programs are Gaining Popularity for High-incidence Solid Tumors and Selected Costly Hematologic Malignancies



Greenapple R. *J Oncol Pract*. 2013;9:81-83.

Pathways Programs May Guide Diagnosis, Surveillance, and Supportive Care in Addition to Active Treatment in MM

BISPHOSPHONATES

Have demonstrated increased survival and decreased bone complications

Medicare costs for bone disease is $25,000

- May significantly save cost by preventing complications

Increased risk of osteonecrosis of the jaw

- Zolendronic acid vs pamidronate?
- Limit use to 18-24 months?
- Could you decrease interval if disease controlled?
- Mandate dental exam BEFORE starting therapy

Schulman KL, et al. *Cancer.* 2007;109:2334-2342.
Kyle RA, et al. *J Clin Oncol*. 2007;25:2464-2472.
Terpos E, et al. *Blood*. 2013;121:3325-3328.

Pathways Programs May Guide Diagnosis, Surveillance, and Supportive Care in Addition to Active Treatment in MM

- Preventing Thrombotic Complications
  - Rates of deep vein thrombosis (DVT) as high as 25% reported with immunomodulatory drugs (IMiDs) and dexamethasone
  - Costs of Treating DVT > $13,000

	Aspirin (n=220)	Warfarin (n=220)	Enoxaparin (n=219)
First 6 months	6.4%	8.2%	5.0%
Entire follow-up	8.6%	10.0%	7.8%

Hull RD, *Thromb Haemost*. 1995;74:189-196.
Palumbo A, et al. *J Clin Oncol.* 2011;29(8):986-993.

Characterizing the Value of Pathways-based Initiatives

In addition to being frequently developed via a collaboration between payers and network oncologists, pathways initiatives offer distinct value to both groups of stakeholders:

Payers

- Reduce treatment variability and eliminate inappropriate care, specifically at end of life
- Streamline payer staff effort associated with prior authorizations

Providers

- Pathways are integrated into provider-practice interface, web-based access
- Pathways updated on a regular basis (ie, quarterly, upon new product approval)

Both

- Provide direction in selecting appropriate therapy based on efficacy, safety, and cost
- Incentives specific to each program, with ability to tailor how providers are rewarded for adherence

Clinicians and Administrators are Largely Supportive of Guideline-based Decision-support Tools

In a survey of community cancer center stakeholders, the following ranked highest among effective practices that improve care in MM:

- Multidisciplinary approach with a strong dedicated team
- Physician knowledge about MM (ie, experienced, motivated, significant clinical expertise)
- ***Offering personalized care***
- ***Reviewing and following established guidelines (NCCN, ASCO)***
- Use of current therapies
- Established referral networks
- Provision of supportive care
- Provision of clinical trials in MM

These components were identified also as necessary for good patient care:

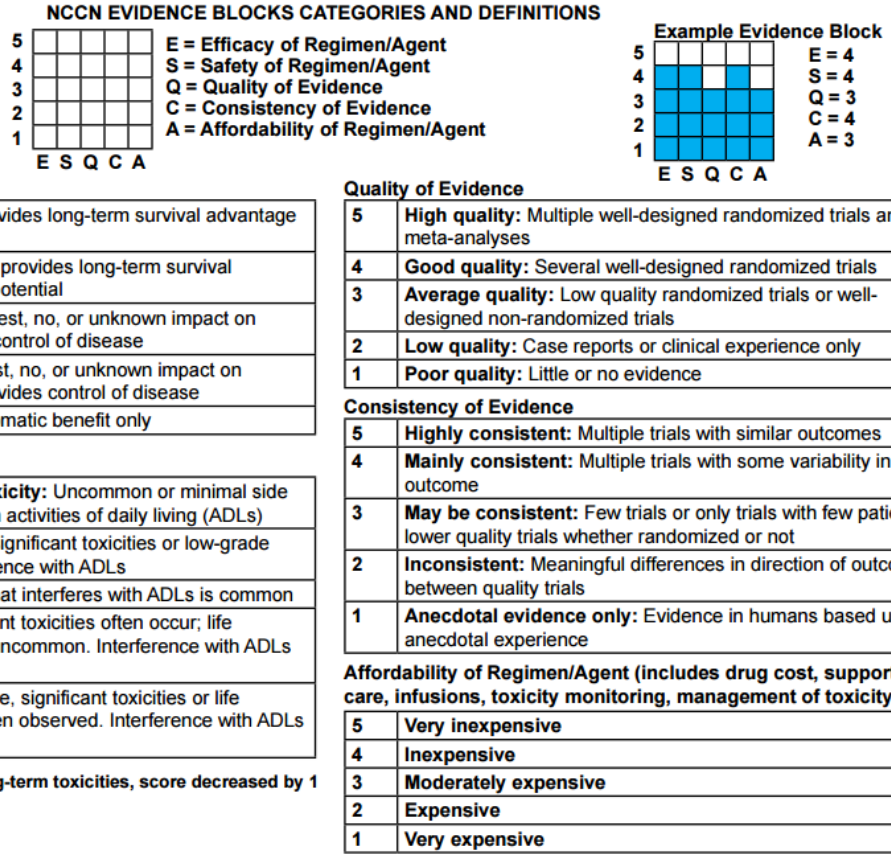
- Social work services, support groups
- ***Staff education (in-service programs)***
- Patient assistance for financial coordination and transportation
- ***Clear clinical pathways***

Multiple Myeloma Resources & Tools for the Multidisciplinary Team. Available at: http://www.accc-cancer.org/resources/MultipleMyeloma-Improving-Care-Project.asp. Accessed April 11, 2016.

Implications of Pathways-based Programming in the New Accountable Care Ecosystem

- The emergence of accountable care organizations (ACOs), bundled payments, and at-risk models will likely make the cost of cancer therapies a higher priority in decision-making processes
  - Discussions will consider the total cost of care, including supportive care, imaging, and procedures
  - Some pathways programs are currently addressing these
- Utilization of pathways-based initiatives in an accountable care environment may require more intensive pharmacoeconomic analyses
  - These cumulative factors reiterate the importance of cost-effectiveness analyses and comparative effectiveness analyses
- Vendors are collaborating with ACOs and building their own patient-centered medical home (PCMH) models and incorporating pathways
  - Pathway participants may be at an advantage since they are already familiar with the system when pathways are incorporated into these business models

NCCN Evidence Blocks and Similar Assessment Tools Provide Further Guidance in Assigning a Hierarchy of Treatment Regimens in Clinical Pathways Programs



NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

5 4 3 2 1
E S Q C A

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block

5 4 3 2 1
E S Q C A

E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

NCCN Evidence Blocks – Multiple Myeloma. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloma_blocks.pdf. Accessed April 11, 2016.

Sample of the NCCN Evidence Blocks for Preferred Regimens in Previously Treated MM

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[10]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)
- Elotuzumab[11]/lenalidomide/dexamethasone (category 1)
- Ixazomib[12]
- Ixazomib[12]/dexamethasone
- Ixazomib[12]/lenalidomide/dexamethasone (category 1)
- High-dose cyclophosphamide
- Lenalidomide/dexamethasone[13] (category 1)
- Panobinostat/bortezomib/dexamethasone[14] (category 1)
- Pomalidomide[15]/dexamethasone[13] (category 1)
- Thalidomide/dexamethasone[13]

NCCN Evidence Blocks – Multiple Myeloma. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloma_blocks.pdf. Accessed April 11, 2016.

Questions Remain for Payers that Will Continue to Shape Pathways-based Initiatives

- How can stakeholders vary parameters to minimize total cost of care while ensuring optimal outcomes?
- What are the most important outcomes, clinical and economic?
- Can patient-reported outcomes be integrated into the equation?
- How much value should be assigned to patient-reported outcomes?
- How should brand, generic, and biosimilar drugs be positioned in pathways?
- Should providers demand access to pathways (ie, integrated into electronic medical record [EMR]) for real-time for decision support?
- Should participation be mandatory? What are the incentives for participation and adherence? What are the consequences of selecting an “off-pathway” therapy?
- Should providers be allowed to develop their own pathways (as recommended by ASCO)?

Summary

- Clinical pathways-based initiatives condense an expansive menu of treatment options from consensus guidelines into a concise decision-support tool
- Pathways programs have gained traction for solid tumors and selected hematologic malignancies, including MM
- Platforms with web-portal access or other integrated options that offer real-time functionality, including decision support and real-time claims adjudication, benefit both payers and providers
- With increased focus on value and accountable care, pathways-based initiatives provide an evidence-based tool for managing appropriate utilization in a high-cost therapeutic space

Analyzing the Available Data to Assess the Value of MM Treatment Options

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University of Utah College of Pharmacy
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Director of Outcomes, Program in Personalized Health Care
University of Utah Health Sciences Center

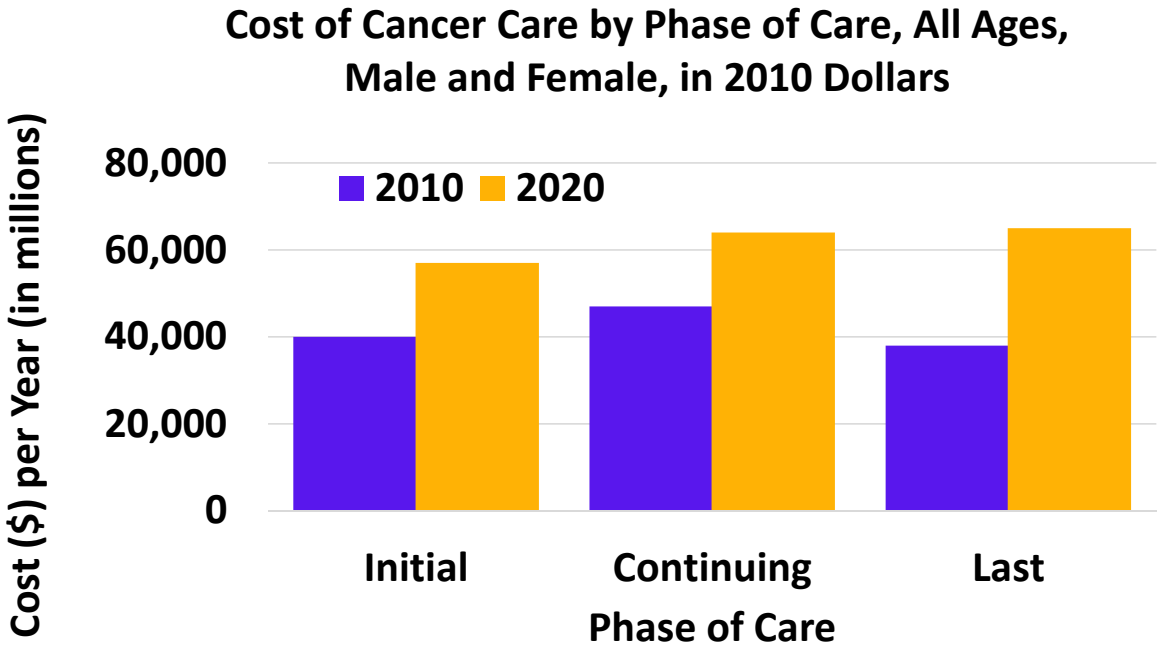
The Economic Burden of Cancer Care

- Assuming a 2% annual increase in medical costs in the initial and final phases of care, the projected direct cost of cancer care is expected to reach $173 billion by 2020
- Drug costs represent a significant component of the economic burden, with selected regimens and targeted therapies already topping $100,000 per patient per year
- Overall, the current trend is attributable to several factors:
  - Rising drug acquisition costs
  - A more diverse armamentarium of targeted oncolytics/supply-induced demand
  - Increasing survivorship due to advances in available therapies, resulting in prolonged treatment duration

Mariotto AB, et al. *JNCI*. 2011;103.

Cancer is Characterized by Progressively High Costs Across the Continuum of Care

MM and Other Hematologic Malignancies Contribute Greatly to Costs in the "Continuing" Phase of Care with Ongoing, Chronic Treatment



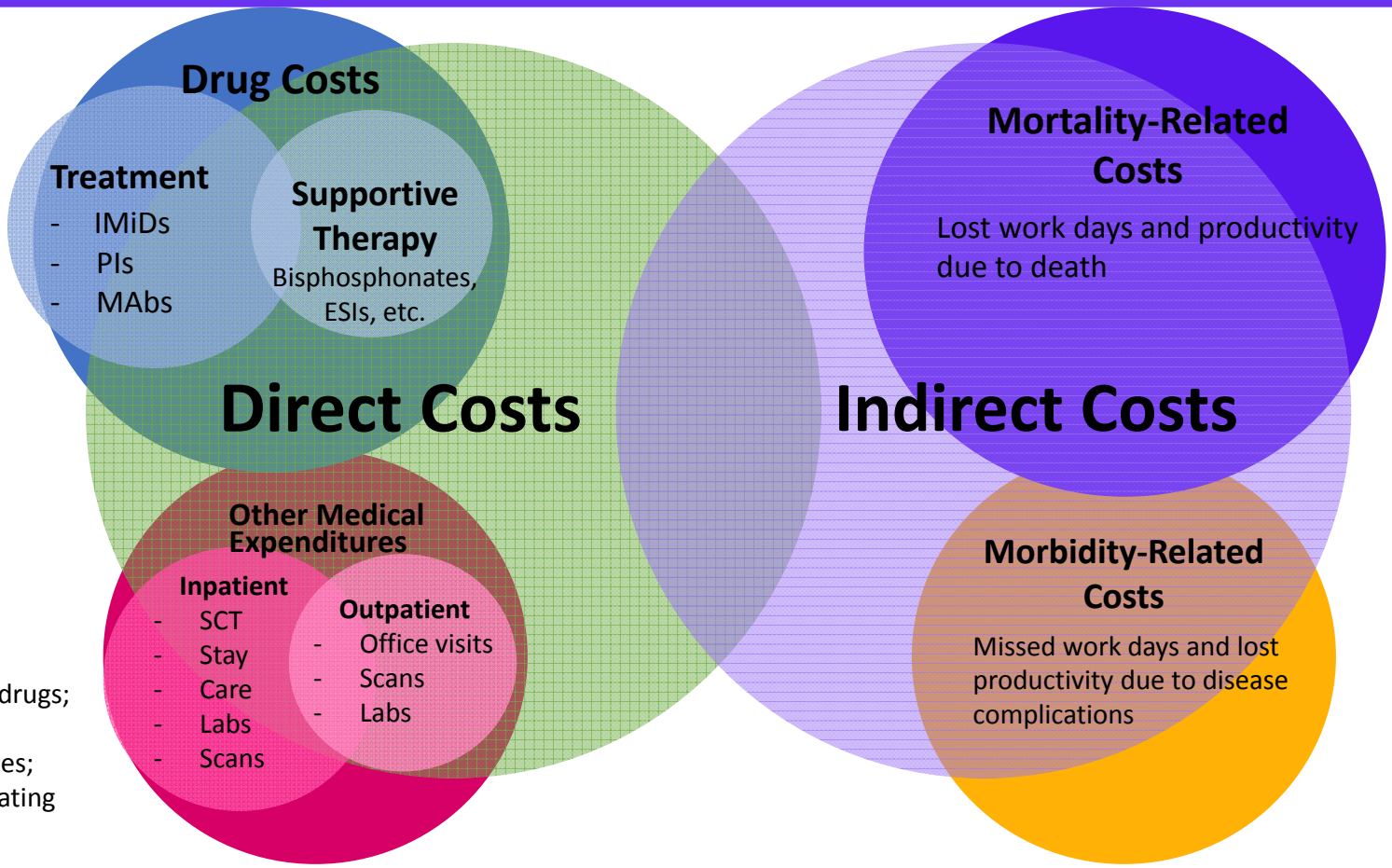
Assumptions:

- Incidence – Trend (follows 1996 – 2005 trend)
- Survival – Trend (follows 1996 – 2005 trend)
- Cost Increase – 3% per year

http://costprojections.cancer.gov

Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the Cost of Cancer Care in the U.S.: 2010-2020. *J Natl Cancer Inst*. 2011.

Interrelated Cost Components of MM



IMiDs=immunomodulating drugs;
PIs=proteasome inhibitors;
MAbs=monoclonal antibodies;
ESAs=erythropoietin-stimulating agents;
SCT=stem cell transplant.

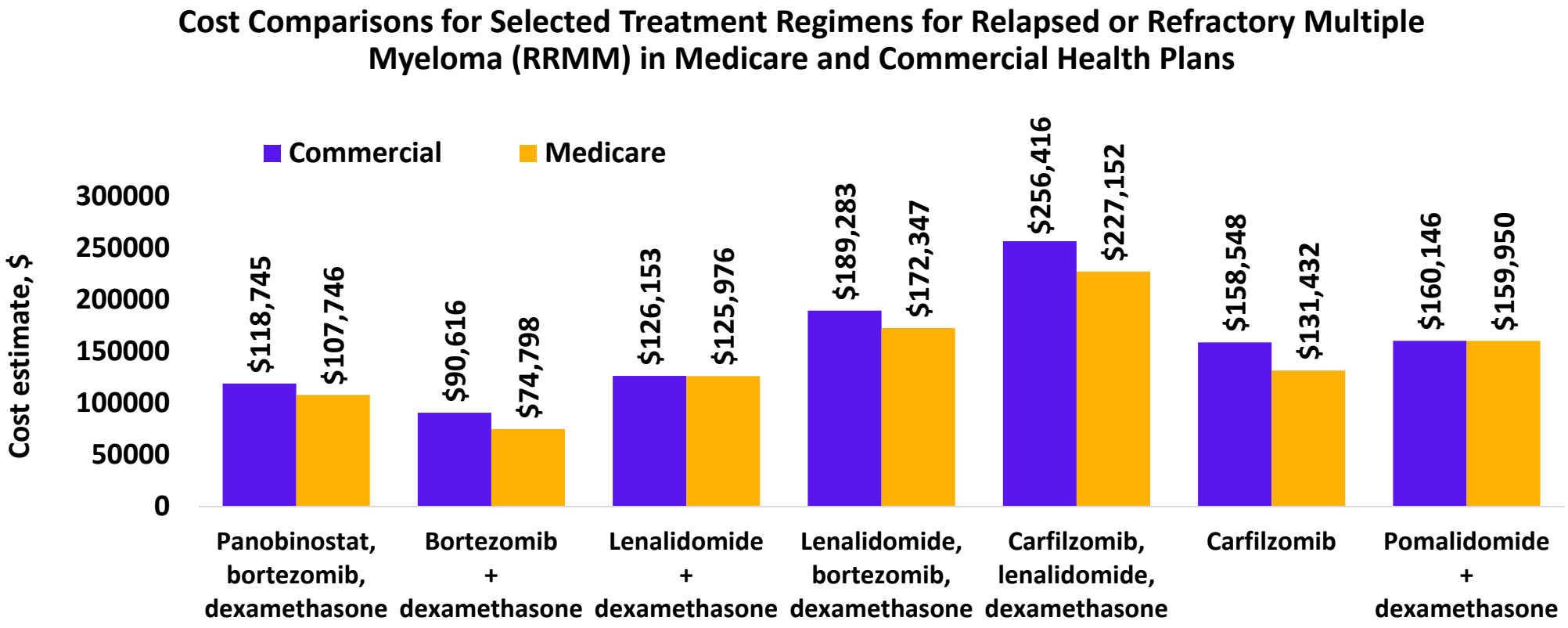
Pharmacoeconomic Evaluations of MM Therapies Seek to Answer Basic Questions

1. What is the most effective way to accurately assess the cost-utility of available therapies?
2. What is the optimal sequence of agents to use based on assessment of patient risk and response?
3. What is the role of emerging agents?
4. What is the economic impact of adverse events and their subsequent effect on adherence?

Key Considerations for MM-related Economic Assessments

Attempt to look at the history of therapy over the lifetime of a particular patient, rather than a single regimen at an isolated point in time	• It may be inadequate to look at frontline alone, considering the patient is likely to receive a different agent in the next course of therapy; analyses should strive to look at lifetime costs instead of upfront costs
Costs related to adverse events (AEs) and the management of AEs is an area for considerable analysis	• Assessments of MM therapies must account for the cost-effectiveness of treatment regimens as well as the costs related to their associated AEs and the cost-effectiveness of supportive care agents used in AE management

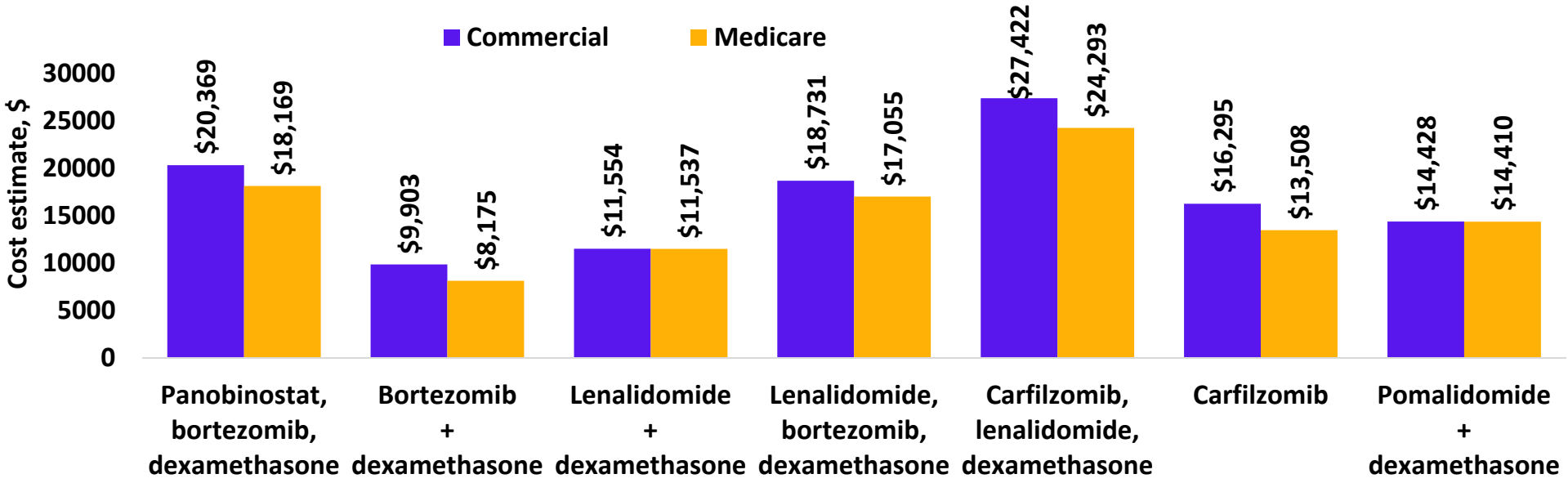
Estimating Expenditures for RRMM Regimens, Administration, Prophylaxis and Adverse Event (AE) Monitoring, and for the Treatment of Grade 3 or 4 AEs



Roy A, et al. *Am Health Drug Benefits*.2015;8(4):204-215.

Estimating Expenditures for RRMM Regimens, Administration, Prophylaxis and AE Monitoring, and for the Treatment of Grade 3 or 4 AEs

Total Costs per Patient per Month with Selected Treatment Regimens for Relapsed or Refractory Multiple Myeloma (RRMM) in Medicare and Commercial Health Plans*



*Monthly cost per patient receiving therapy is the total cost divided by the median duration of therapy needed to obtain 12 months of progression-free survival.

Roy A, et al. *Am Health Drug Benefits*.2015;8(4):204-215.

Several Issues Confound Economic Analyses of Oncolytic Agents

- Paucity of comparative trials in general and particularly with recently-approved agents
- Few randomized trials look at specific sequencing of agents over the course of treatment
- Apparent difficulties associated with the logistics of pulling data from different studies to perform comparative effectiveness research (CER)
- Further issues exist in the utilization of cohort studies

The ASCO Conceptual Framework to Assess the Value of Cancer Treatment Options

In 2013, the American Society of Clinical Oncology's Value in Cancer Care Task Force began developing a framework for comparing the relative clinical benefit, toxicity, and cost of treatment in the medical oncology setting.

At the clinical level, the goal of the ASCO framework is to provide a standardized approach to assist physicians and patients in assessing the value of a new drug treatment for cancer as compared with one or several prevailing standards of care.

Schnipper LE, et al. *J Clin Oncol*.2015;33:2563-2577.

Based on the IOM's Elements of Quality Health Care Delivery, Three Elements Define Value According to the ASCO Framework

The Institute of Medicine's elements of quality health care delivery:

- **Safety**
- **Effectiveness**
- **Patient centeredness**
- **Timeliness**
- **Efficiency**
- **Equity**

- **Clinical Benefit (Efficacy)**
- **Toxicity (Safety)**
- **Cost (Efficiency)**

Schnipper LE, et al. *J Clin Oncol*.2015;33:2563-2577.

The ASCO Framework: Advanced Disease

1. Determine Clinical Benefit
   a. Overall survival (OS), Progression-free survival (PFS), Response rate (RR)
2. Determine Toxicity
   a. Number of grade 3 to 5 toxicities
3. Determine Bonus Points
   a. Palliation of symptoms
   b. Treatment-free interval
4. Determine Net Health Benefit
   a. Add scores from steps 1-3 above
5. Determine Cost
   a. Drug acquisition cost (DAC) and patient copay per month
6. Summary Assessment
   a. Evaluate scores against total possible points for steps 1-4 and weigh with cost

Schnipper LE, et al. *J Clin Oncol*.2015; 33:2563-2577

Cost-Effectiveness Analyses (CEAs)

- The overarching goal of CEAs is to maximize the total amount of health benefits for a budget constraint
- Incremental cost-effectiveness ratios (ICER) or incremental cost-utility ratios (ICUR) are calculated to compare each treatment strategy with the next
- The strategy with the lowest ICER is not necessarily the most cost-effective strategy, as decision-making authorities may be willing to spend more health benefit dollars
  - Instead, the ratios are compared to a country-specific ceiling threshold to determine the most cost-effective strategy (ie, strategy with the ICER that is closest to the ceiling threshold without going over is considered cost-effective)
  - A threshold value represents the willingness to pay for an additional unit of health gain

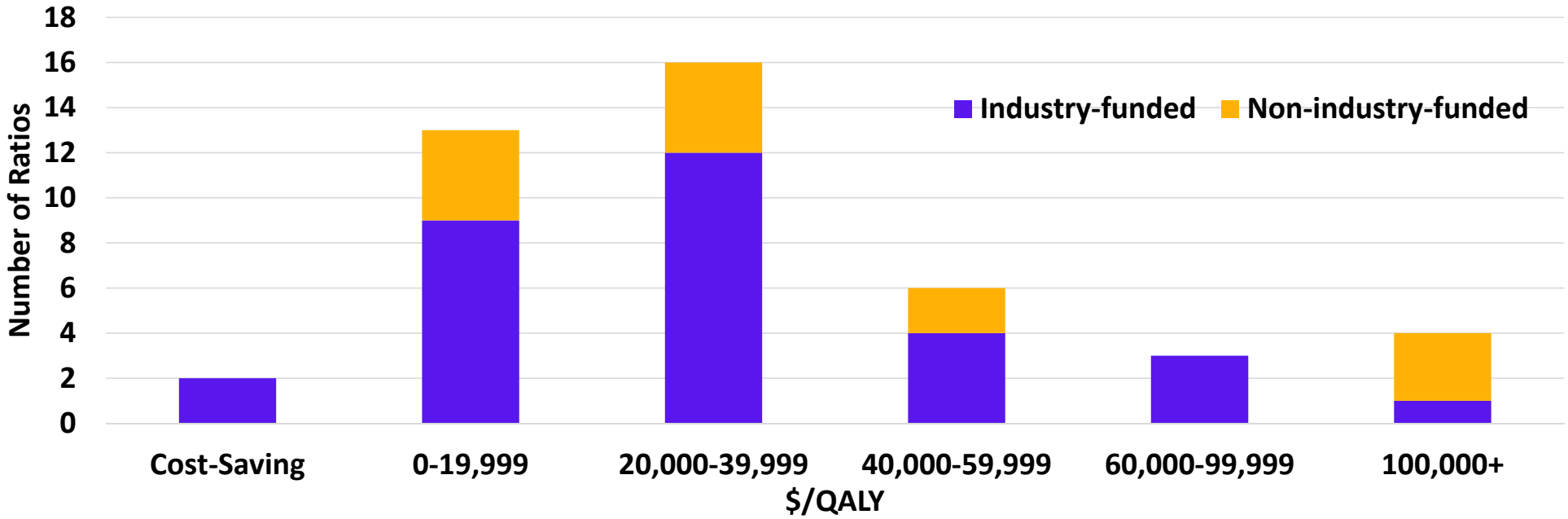
Rochau U, et al. *Clin Rev Onc Hem*.2015;94:164-178.

Overall Cost Effectiveness Analysis of Innovative Therapies for MM and Other Hematologic Malignancies

- Analyzed cost-effectiveness studies related to hematologic malignancies from the Tufts Medical Center Cost-Effectiveness Analysis Registry, focusing on studies of innovative therapies
- Studies that met inclusion criteria were categorized by 4 cancer types (CML, CLL, NHL, MM) and 9 treatments (interferon-α, alemtuzumab, bendamustine, bortezomib, dasatinib, imatinib, lenalidomide, rituximab alone or in combination, and thalidomide)
- Examined study characteristics and stratified cost-effectiveness ratios by type of cancer, treatment, funder, and year of study publication
- 29 studies published in the years 1996-2012 (including 44 cost-effectiveness ratios) met inclusion criteria, 22 (76%) of which were industry funded

Saret CJ, et al. *Blood*. 2015;125:1866-1869.

Innovative Therapies for MM and Other Hematologic Malignancies Provide Reasonable Value for Their Cost



- Most ratios fell below $50,000 per QALY (73%) and $100,000 per QALY (86%)
- Industry-funded studies (n=22) reported a lower median ratio ($26,000 per QALY) than others (n=7) ($33,000 per QALY), but the difference was not statistically significant

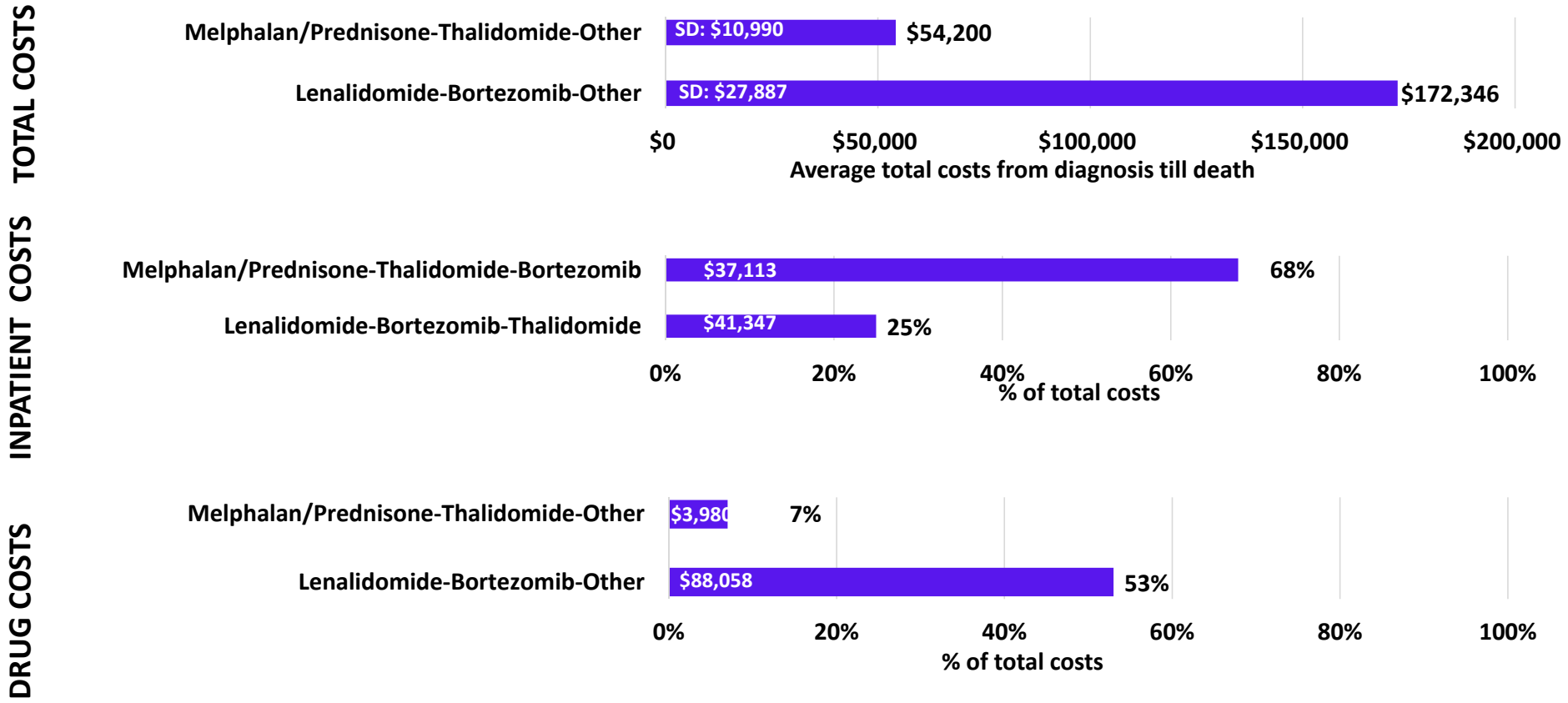
Saret CJ, et al. *Blood*. 2015;125:1866-1869.

Real-World Cost-effectiveness of 19 Different Multiple Myeloma Treatment Regimens Using a Full Disease Model

- Researchers developed a patient-level simulation (PLS) model for elderly (>65) patients with MM diagnosed since 2004
  - Real-world data (N=621) including patient and disease characteristics, treatment information, outcomes, and resource use were obtained from the Population-based HAematological Registry for Observational Studies (PHAROS)
  - Parametric survival models including patient characteristics (age, performance status, comorbidities, laboratory values) and treatment were used to predict OS of commonly-used treatment pathways
- 5 treatment categories were distinguished: melphalan/prednisone, thalidomide-based regimens, bortezomib-based regimens, lenalidomide-based regimens, other regimens not including a novel agent
  - These comprised 19 individual treatment pathways (ie, regimens)
- Monthly costs per treatment per line were calculated based on real-world data
- Compared to real-world prescription, survival could be improved at a cost of $48,543 per QALY and $31,902 per life-year gained (lenalidomide-thalidomide-bortezomib)

Blommestein HG, et al. *Blood.* 2013;122:2930.

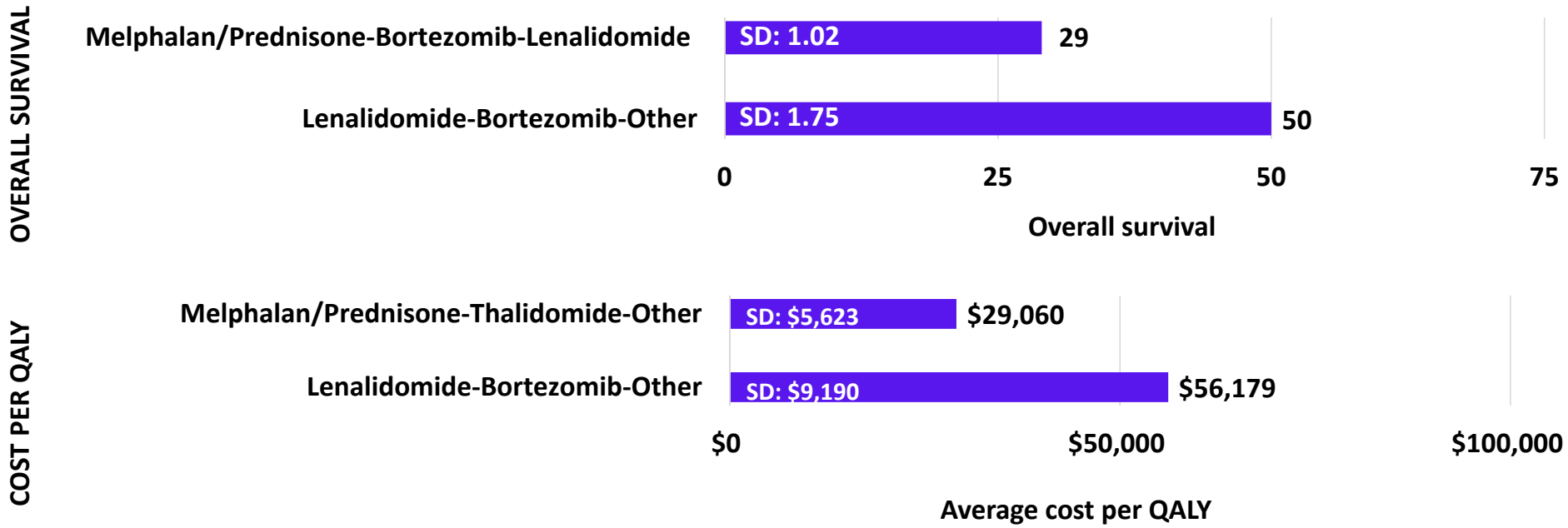
Range of Total Costs from Diagnosis Until Death and Drug and Inpatient Share of Total Costs



Blommestein HG, et al. *Blood.* 2013;122:2930.

SD=standard deviation

Range of Overall Survival and Cost Per QALY



Blommestein HG, et al. *Blood.* 2013;122:2930.

SD=standard deviation

Summary

- Novel therapies in MM have proven cost-effective in terms of ICER according to selected modeling studies
  - The extended survival and complex disease progression inherent to MM implies that several different agents
    have a place in therapy
- Still, considering the high cost associated with these agents, their use and anticipated outcomes must be carefully weighed against economic factors to maximize patient benefit
- Further studies are necessary to establish a hierarchy of therapeutic agents and/or treatment algorithms
- As new data emerges, strategies such as CER, the ASCO framework, and the GRADE approach should be employed to assess the value of emerging agents and establish the appropriate sequence of treatment options
- Payer intervention via specialty pharmacy management will likely play a crucial role by ensuring appropriate, evidence-based utilization, and minimizing treatment-related adverse events

Faculty Disclosure

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

Jeffrey Dunn, PharmD, MBA

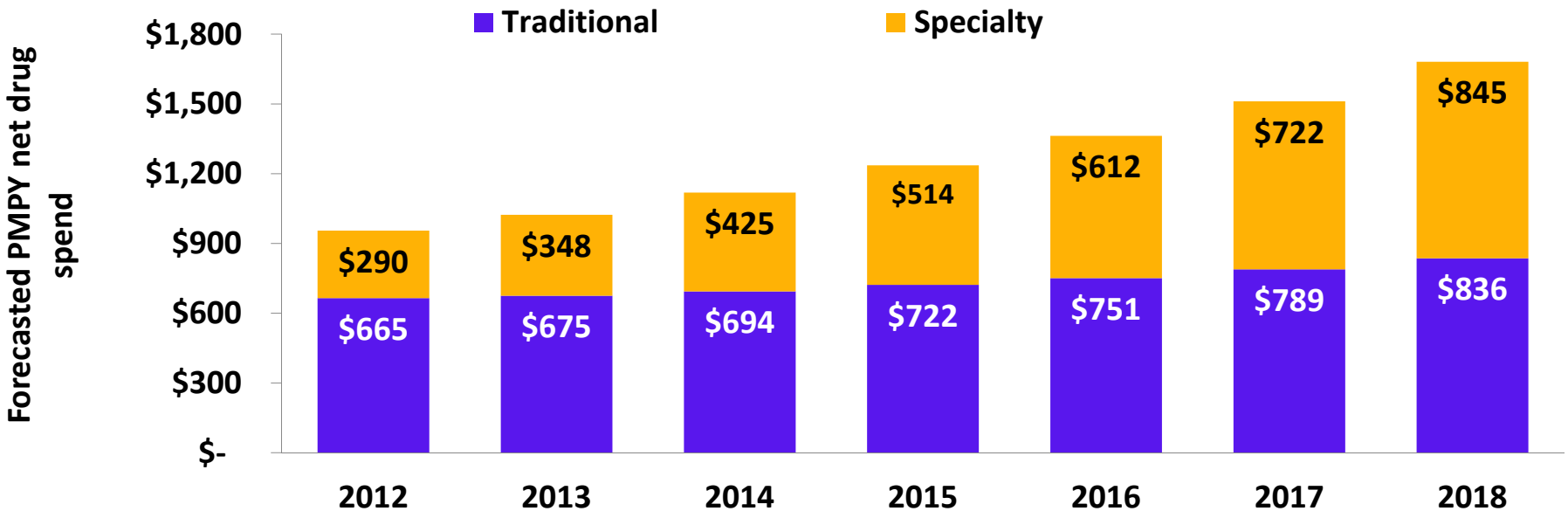
No financial interest/relationships relating to the topic of this activity

Plan Benefit Designs and Specialty Pharmacy Considerations in MM

Jeffrey Dunn, PharmD, MBA
Chief Clinical Officer
Senior Vice President
VRx Pharmacy Services, LLC

The Specialty Drug Trend is Growing at an Unprecedented Rate

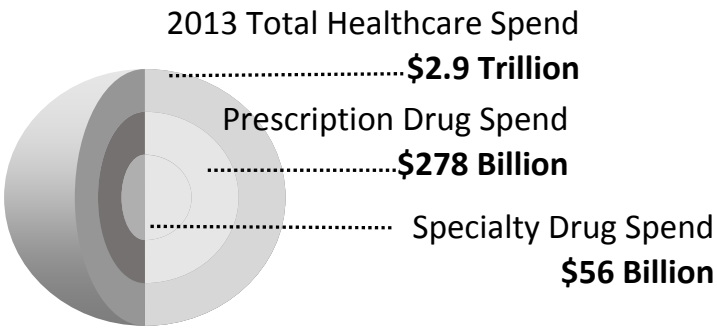
Spending on specialty drugs is projected to surpass sales of traditional medications by 2018



PMPY=per member per year.

This Boom in Specialty Drug Growth Underscores the Crucial Role of Specialty Products in Modern Health Care

- Importance of pharmacy in the Integrated Care Model is growing
- Pharmacy can contribute to both overall patient care and help decrease overall health care costs



- Non-specialty trend flat to modest increase
- Specialty trend increasing and forecasted to continue

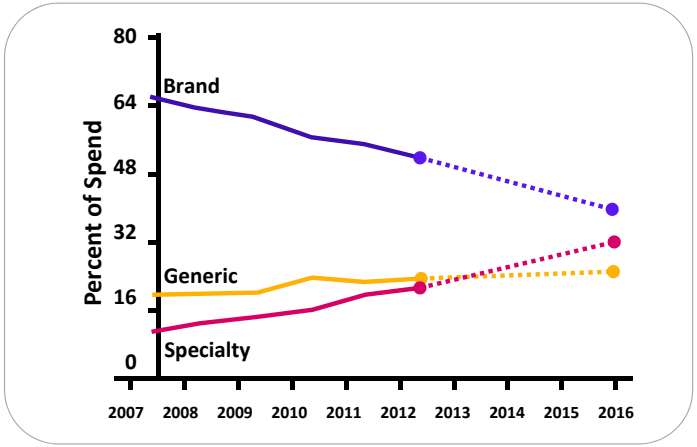


Chart and spend statistics adapted from Pembroke Consulting 2013-2014 Economic Report on Retail, Mail, and Specialty Pharmacies, and data from the U.S. Centers for Medicare and Medicaid Services Office of the Actuary.

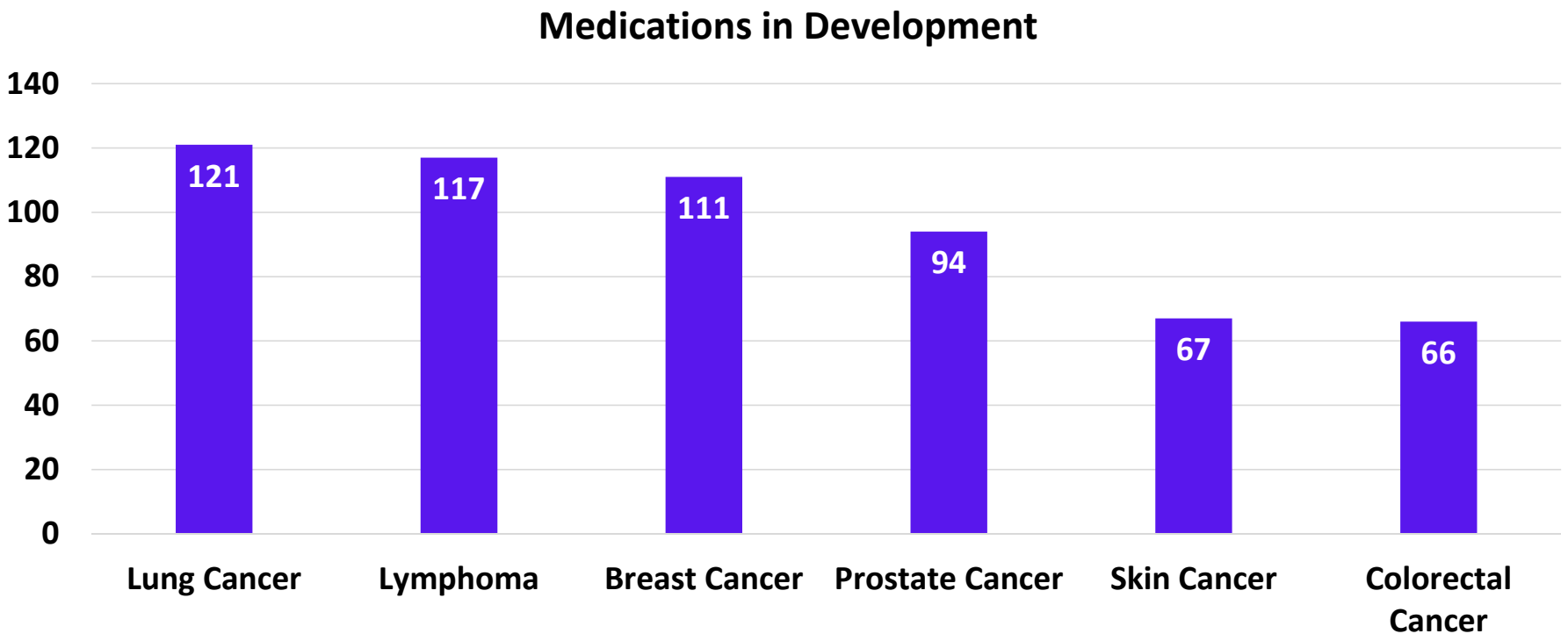
Oncology Remains a Key Driver of the Specialty Drug Trend

			TREND		
RANK	**THERAPY CLASS**	**PMPY SPEND**	**UTILIZATION**	**UNIT COST**	**TOTAL**
1	Inflammatory conditions	$89.10	10.3%	14.7%	25.0%
2	Multiple sclerosis	$53.31	3.5%	6.2%	9.7%
3	Oncology	$49.62	9.3%	14.4%	23.7%
4	Hepatitis C	$38.44	-2.2%	9.2%	7.0%
5	HIV	$31.53	4.6%	12.0%	16.6%
6	Growth deficiency	$7.12	2.8%	2.8%	5.6%
7	Cystic fibrosis	$6.64	12.5%	40.9%	53.4%
8	Pulmonary hypertension	$5.85	13.4%	4.8%	18.1%
9	Hemophilia	$5.79	4.9%	15.4%	20.4%
10	Sleep disorders	$4.57	5.5%	18.5%	24.1%
	TOTAL SPECIALTY	**$341.21**	**6.8%**	**11.0%**	**17.8%**

PMPY=per member per year.

Express Scripts. Drug Trend Report 2015. Available at: http://lab.express-scripts.com/lab/drug-trend-report. Accessed April 11, 2016.

This Trend Will Continue into the Foreseeable Future with an Impressive Oncology Pipeline and Four New Therapeutics Approved for MM in 2015 Alone



EMD Serono Specialty Digest™, 9th Edition, Managed Care Strategies for Specialty Pharmaceuticals. Available at: http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed April 11, 2016.

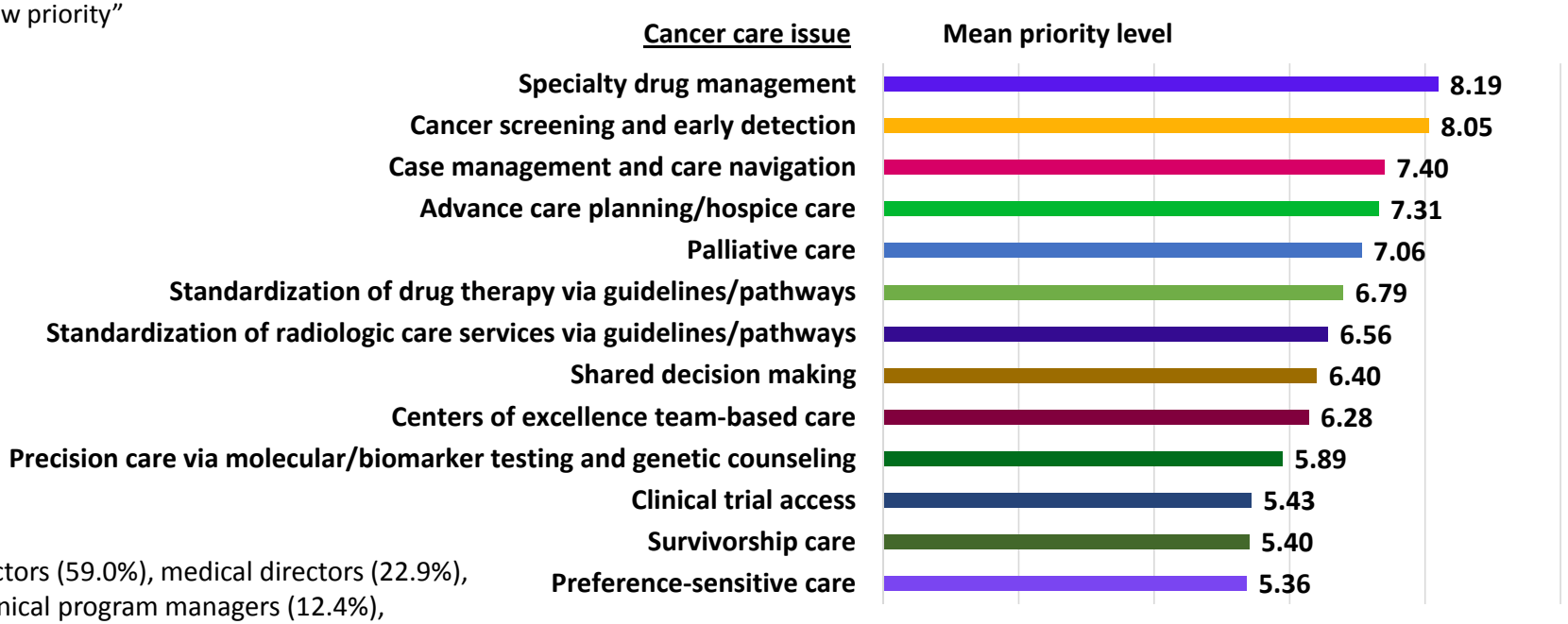
As a Result, Attitudes Toward the Management of Oncology Therapies Have Changed: Cancer is No Longer "Untouchable"

*Clinical, pharmacoeconomic, humanistic, societal, etc

Many Familiar Cancer Care Issues Continue to Top the List of Priorities Among Managed Care Stakeholders

Level of Priority MCOs Place on Cancer Care Issues

- Respondents rated issues on a 10-point scale:
  - 10 = "very high priority"
  - 1 = "very low priority"



N=105; pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

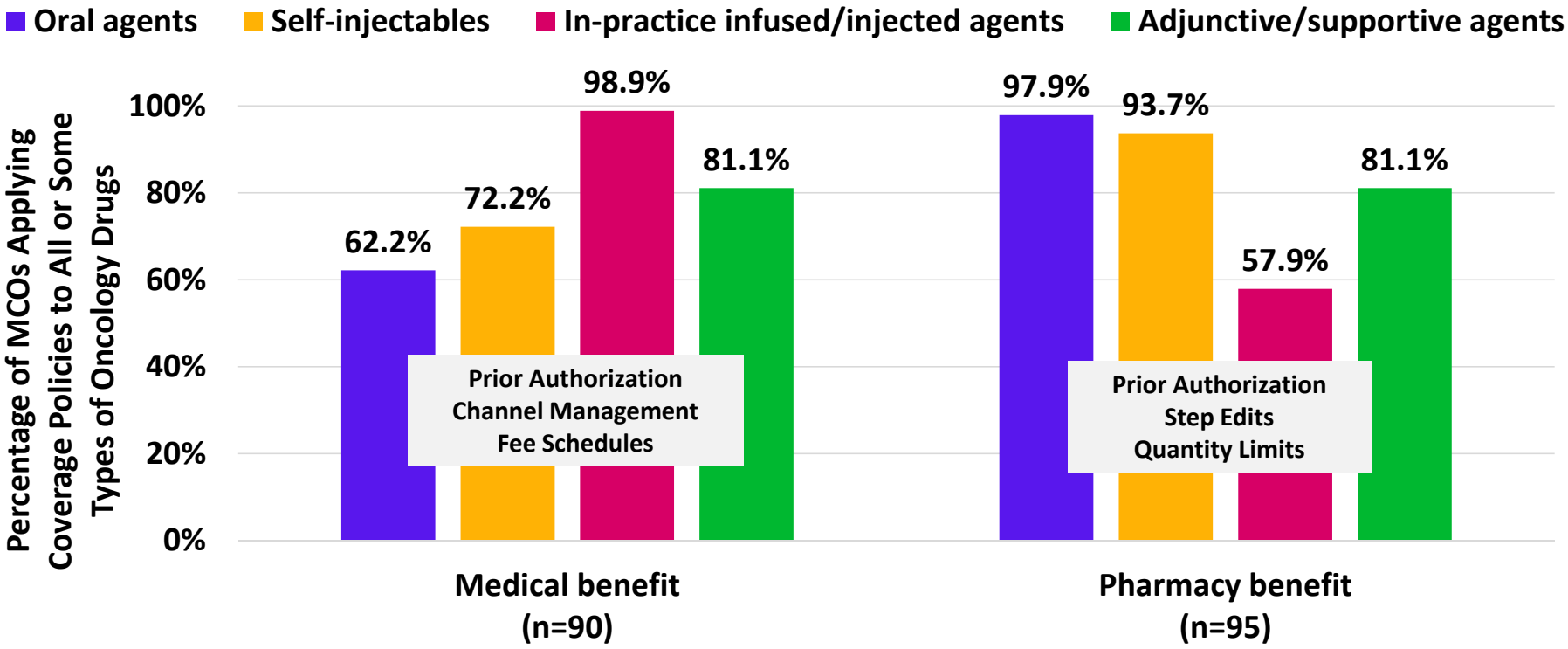
2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Payer-led Initiatives in Oncology Require Traditional Approaches Based on Benefit and Formulary Considerations in Addition to Specialty Drug Management

Benefit Design (Cost Share) & Formulary

+

MCOs Most Actively Manage Provider-infused Agents Under the Medical Benefit and Oral Agents Under the Pharmacy Benefit



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2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Utilization Management via Traditional Prior Authorization Remains the Most Common Intervention

Management strategies	Percentage of MCOs	Effectiveness rating*
Prior authorization protocols	91.4%	3.31
Drug quantity/days' supply limitations	86.7%	3.05
Member cost sharing via dollar copays and percent coinsurance	68.6%	2.64
Formulary tiering	68.6%	2.96
Step therapy	63.8%	3.09
Preferred drug therapy	61.0%	3.00
Closed specialty pharmacy network	56.2%	3.10
Recommendations regarding specialty drug benefit design	52.4%	2.82
Fee schedule management to lower drug expenditures	43.8%	3.11
Split-fill (ie, short fill) for oral oncology drugs	33.3%	2.91
Transparency around oncology care costs and quality of care	26.7%	2.68
Narrowed oncology provider network	18.1%	2.89

*5-point scale, 1 = not at all effective, 5 = extremely effective

N=105; pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

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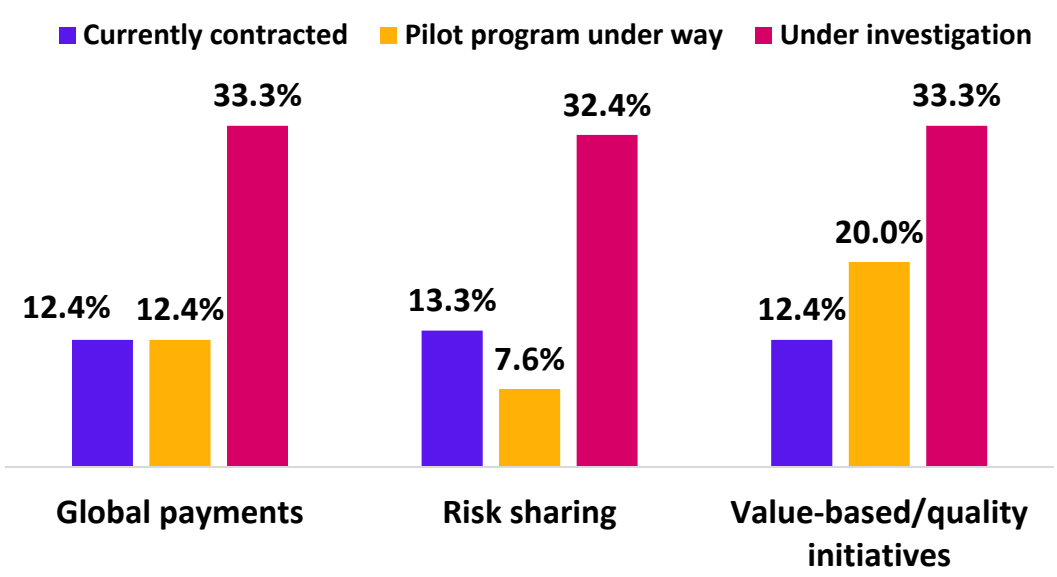
These Utilization Management Interventions and Other Strategies are Often Tempered to Minimize Pushback

- Formularies are relatively all-inclusive of FDA-approved oncology therapies
- Prior authorization criteria for oncology therapies are generally limited to indication/diagnosis
- Claims denials are subject to appeals with liberal evidentiary requirements
- Oncology networks are often involved in decision-making surrounding clinical pathways and similar initiatives

At the Same Time, Initiatives Aimed at Network Oncologists are Generating Further Interest from MCOs

Payment models implemented or piloted with network oncologists



Quality/performance measures most frequently included in value-based/quality initiatives	Percentage of MCOs (N=34)
Adherence to clinical pathways and/or guidelines	76.5%
Generic drug use	76.5%
Preferred drug use	52.9%
Hospitalizations and emergency room visits	41.2%
Patient satisfaction	38.2%
Overall cancer costs per patient	32.4%
Cancer screening and preventive measures	32.4%
Palliative care/pain management	26.5%
Advance care planning	26.5%

N=105; pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

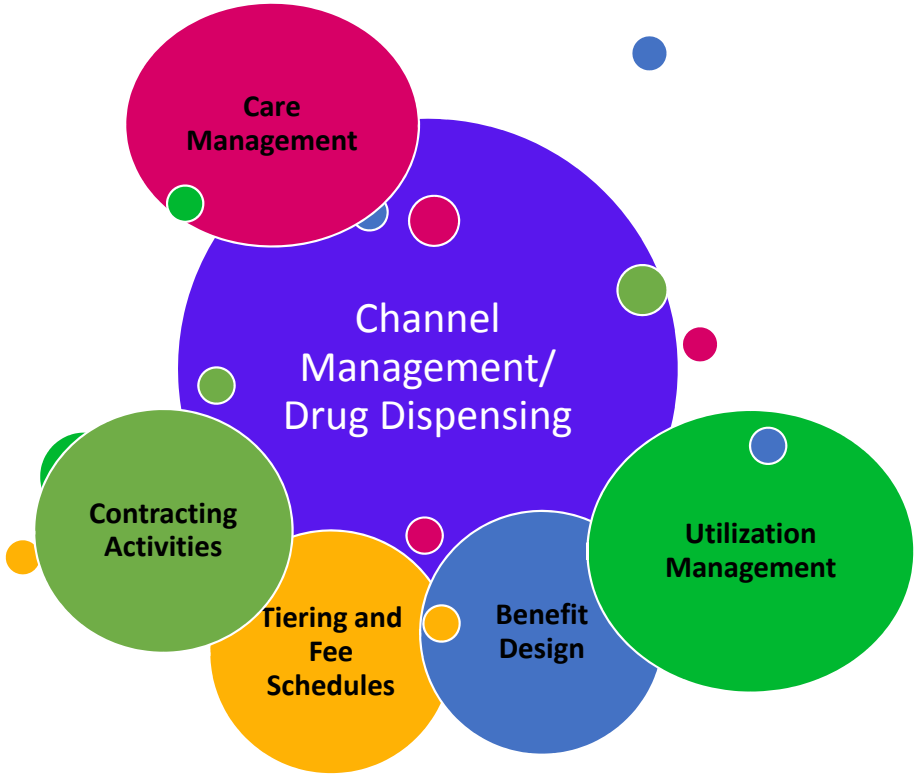
2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Health Care Reform is Further Reshaping the Dynamic of Oncology Practice

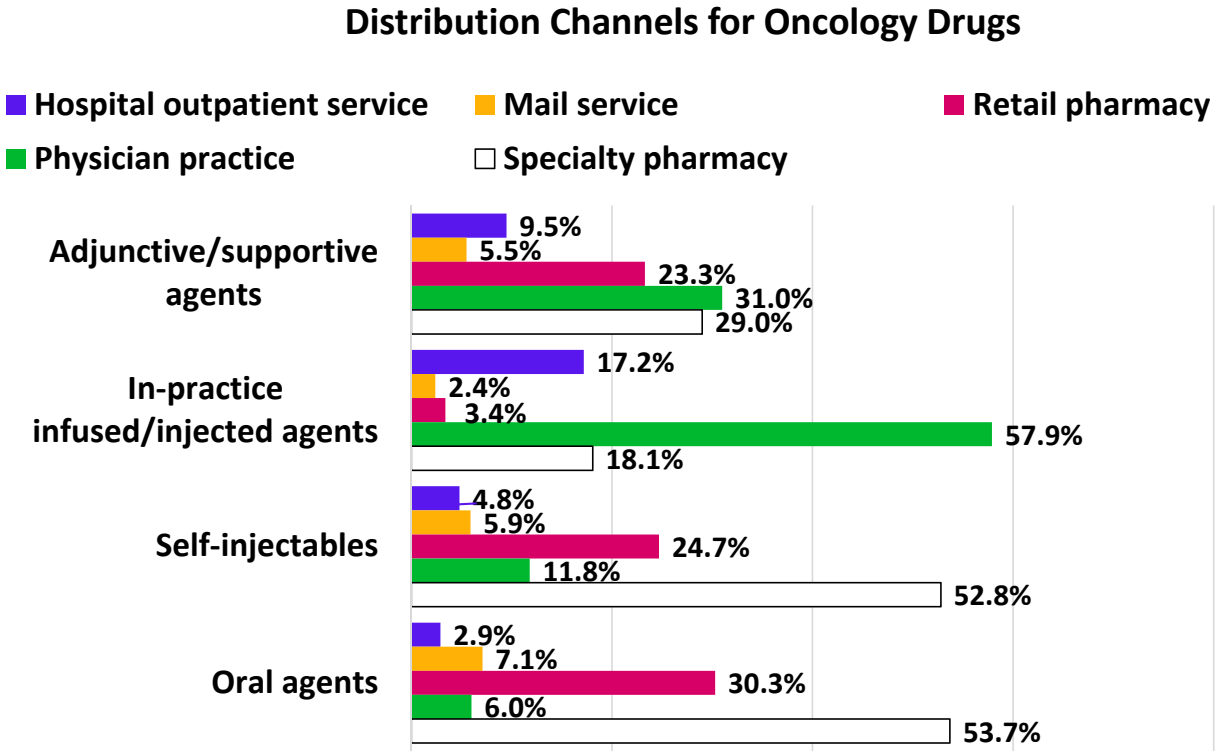
- The average oncology practice size has increased.
  - Practices are being acquired by health systems and smaller practices are aggregating as a means of mitigating financial risk.
- The number of oncologists in nearly every subspecialty has increased over the past decade, but practices are struggling; since 2013:
  - 82% increase in clinics closed
  - 22% increase in practices struggling financially
  - 5% increase in practices sending patients elsewhere
  - 143% increase in practices acquired (or with a hospital agreement)
  - 46% increase in practices merged (or acquired)
- These changes are generally viewed as unfavorable by payers, as the health system/hospital is generally the most costly setting for the delivery of oncology services for all stakeholders.

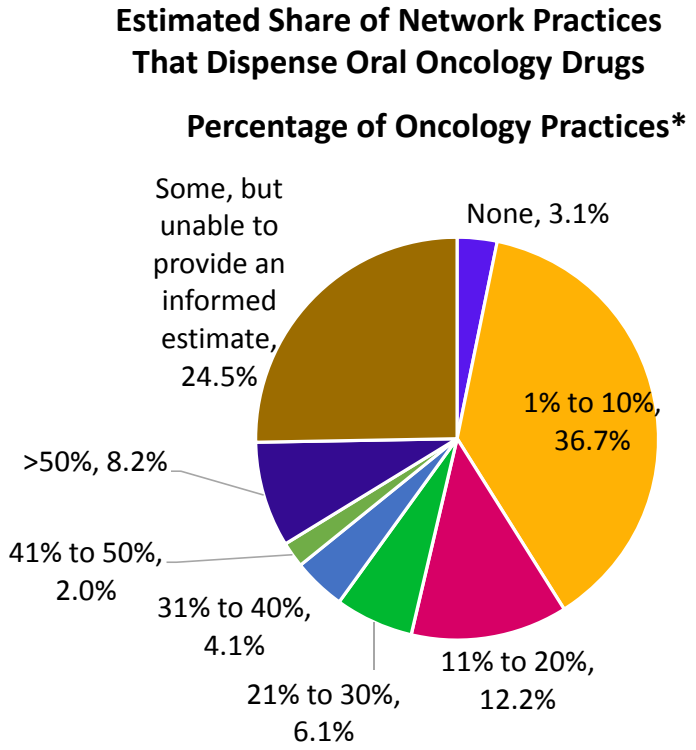
Community Oncology Alliance. Practice Impact Report, 2014. Available at: http://www.communityoncology.org/UserFiles/Community_Oncology_Practice_Impact_Report_10-21-14F.pdf. Accessed April 11, 2016.

These New Challenges Emphasize a Multifaceted Approach to Specialty Drug Management



A Shift Towards Facility Distribution Has Resulted In Further Increased Attention to Channel Management





*Refers to private community-based practices within the MCO network.

N=105; pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Drug Dispensing

- Drug Management Strategies
  - Medical Claim Site of Care Optimization
  - Pharmacy Channel Management

Site of Care Example

Place of Service	Cost per Unit	Units	Cost Per Claim	Claims per Year	Annual Cost
MD office or home infusion	$70	50	$3,500	7	$24,500
HOPD (average)	$111	50	$5,500	7	$38,850
HOPD (highest cost hospital)	$360	50	$18,000	7	$126,000

Internal Utilization and Pricing Data.

HOPD=hospital outpatient department.

Fee Schedules: ASP Reimbursement Benchmarks

ASP+ Rate	MD: non-oncology		MD: oncologist		Home Infusion		Stand-Alone Infusion	
	Comm.	MA-PD	Comm.	MA-PD	Comm.	MA-PD	Comm.	MA-PD
Low	6.0%	5.0%	6.0%	5.0%	5.0%	5.0%	5.0%	20.0%
Mean	**10.1%**	7.1%	**11.6%**	8.1%	8.8%	8.1%	9.6%	8.1%
High	20.0%	15.0%	25.0%	20.0%	15.0%	20.0%	20.0%	20.0%

- While the Medicare Part B program currently reimburses providers ASP+6%, a CMS initiative has proposed an ASP+2.5% model with a flat fee of $16.80 per drug per day, regardless of the drug's price
- A second phase of the proposed model would implement value-based purchasing tools similar to those employed by commercial payers and PBMs

EMD Serono Specialty Digest™, 9th Edition, Managed Care Strategies for Specialty Pharmaceuticals. Available at: http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed April 11, 2016.
CMS. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2016-Press-releases-items/2016-03-08.html. Accessed April 11, 2016.

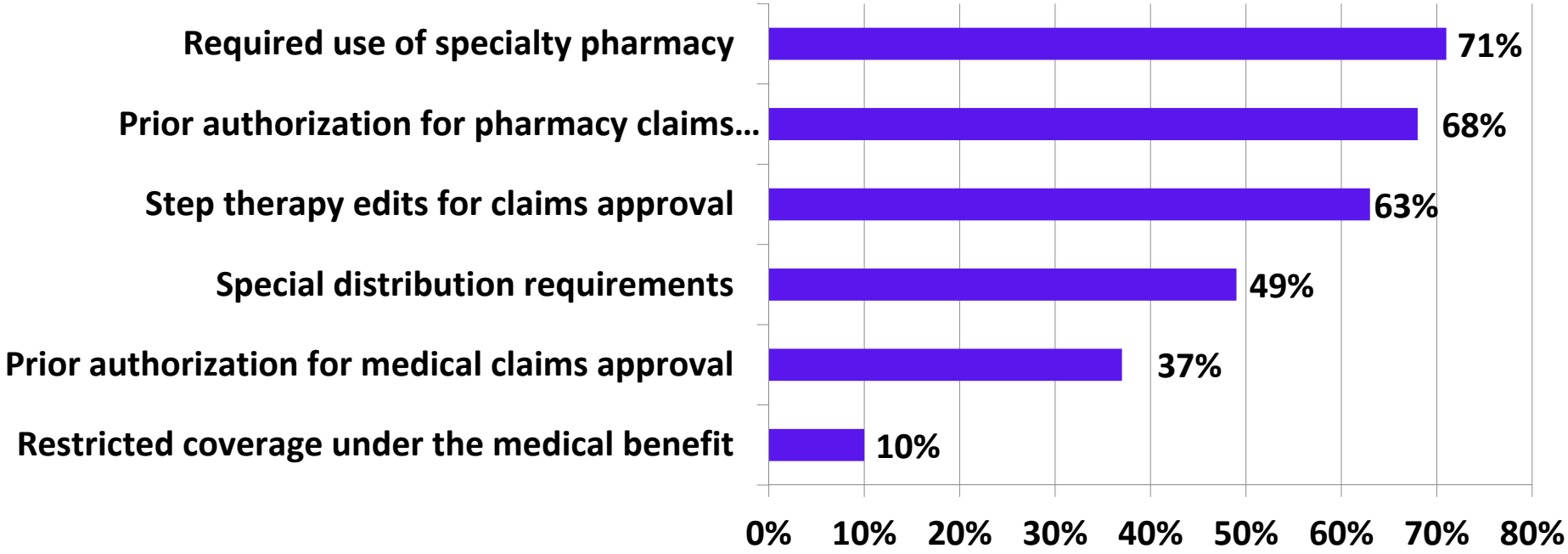
Fee Schedule Considerations

- Oncology Reimbursement
  - Therapeutic vs adjunctive
- Other specialty categories
  - Rheumatology
  - Neurology
- Generic/biosimilar vs brand medications
- Professional services

Benefit Design Strategies

- Multi-specialty Tier Benefit
  - Increasing number of generic products
  - Biosimilars
  - Preferred products
  - Differentiation based on clinical efficacy and cost effectiveness

Key Components in Current Benefit Design Strategies



Midwest Business Group on Health, 2014.

Plans Need to Find a Balance Between Outcomes, Cost Shifting to Patients, and Compliance to Therapy

- Member decision factors
  - Cost share
  - Compliance
  - Efficacy/tolerability

- Benefit design factors
  - Medical vs pharmacy
  - Copay vs coinsurance
  - Specialty tiers

Specialty Care Management

Program

- Specialty Pharmacy MTM
  - Integration with care management
  - Coordinate site of care
  - Ensure appropriate dosing
  - Adherence
  - Education on use
  - Expectation management

Actions

- Design program workflow and integration with care management
- Analyze utilization to select targeted drugs/disease states
- Train personnel:
  - Specialty diseases
  - Medications
  - Site of care logistics

The Role of Specialty Pharmacy Management is Expected to Increase

Among 30 SPP stakeholders surveyed regarding changes in required patient use of an SP to acquire oncology therapies…

Change over the past 12 months			Type of oncology drug/administration	Change forecast for the next 12 months		
Decrease	No change	Increase		Decrease	No change	Increase
0.0%	23.3%	76.6%	Oral	0.0%	16.7%	83.3%
0.0%	30.0%	70.0%	Patient self-injectable	0.0%	23.3%	76.7%
13.3%	53.3%	33.4%	In-practice injectable/infused	23.3%	43.3%	33.3%
0.0%	16.7%	83.3%	Adjunctive/supportive	3.3%	36.7%	60.0%

N=105; pharmacy directors (59.0%), medical directors (22.9%), clinical pharmacists/clinical program managers (12.4%), executives (4.7%), utilization managers (1.0%)

2015 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed April 11, 2016.

Tools Such as the ASCO Value Framework Lend Insight to Payer-led Management Interventions

THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT

1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY

Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	

Step 3: Determine Bonus Points

3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." **Proceed to Step 3.B.**						**Palliation Bonus Points**
	NO. No bonus points are awarded. **Proceed to Step 3.B.**						
3. B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. **Proceed to 3.C.**						**Treatment-Free Interval Bonus**
	Bonus Points	0	5	10	15	20	
	% Change	> 0%-19%	20%-35%	36%-49%	50%-74%	≥ 75%	
	NO. No bonus points are awarded. **Proceed to Step 3.C.**						
3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. **Proceed to Step 4.**						**Total Bonus Points**

Step 4: Determine the regimen's NET HEALTH BENEFIT

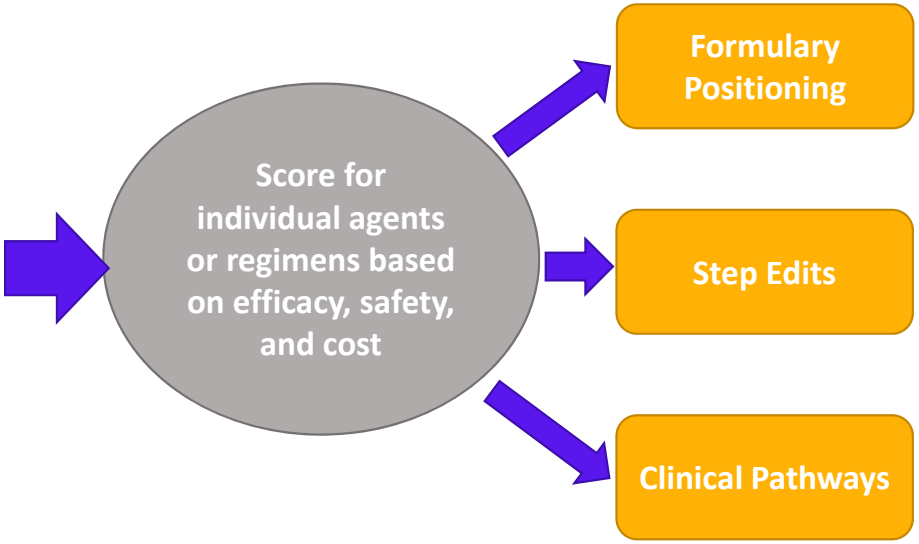
Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130 (100 + 30 bonus points). Proceed to **Step 5.**	Net Health Benefit

Step 5: Determine the regimen's COST

Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month.	**Cost Per Month:** DAC: _____ **Patient Co-Pay:** _____

Step 6: Summary Assessment – Advanced Disease Framework

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
/80	/20	/30	/130	DAC: _____ Patient Payment: _____

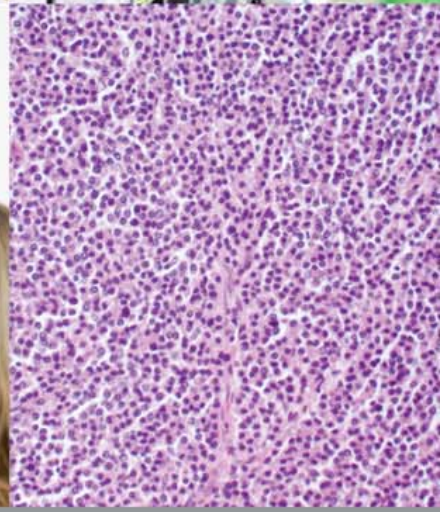


Schnipper LE, et al. *J Clin Oncol*.2015;33:2563-2577.

Summary

- A dramatic rise in the specialty trend is characterized by increased cost and utilization in oncology, which includes a wealth of agents managed under both the medical and pharmacy benefits in MM and other cancer types
- Increasingly limited financial resources and an evolving accountable care ecosystem have dramatically shaped the management of oncology care
- Payers are charged with the task of judiciously managing utilization, while at the same time maintaining provider relations, and tempering the financial burden on the member
- MM utilization management interventions, benefit design strategies, and other key considerations, such as site of care, will all play an important role in future plan activities

MCRB™



An Analysis of the Latest Treatments, Economic Value, and Benefit Designs for Multiple Myeloma

MANAGED CARE REVIEW BOARD™

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