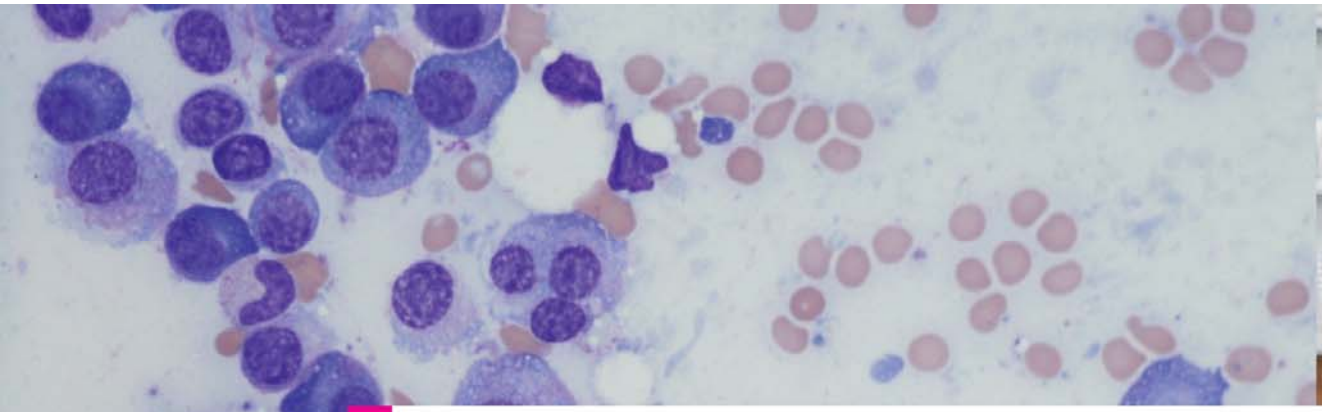
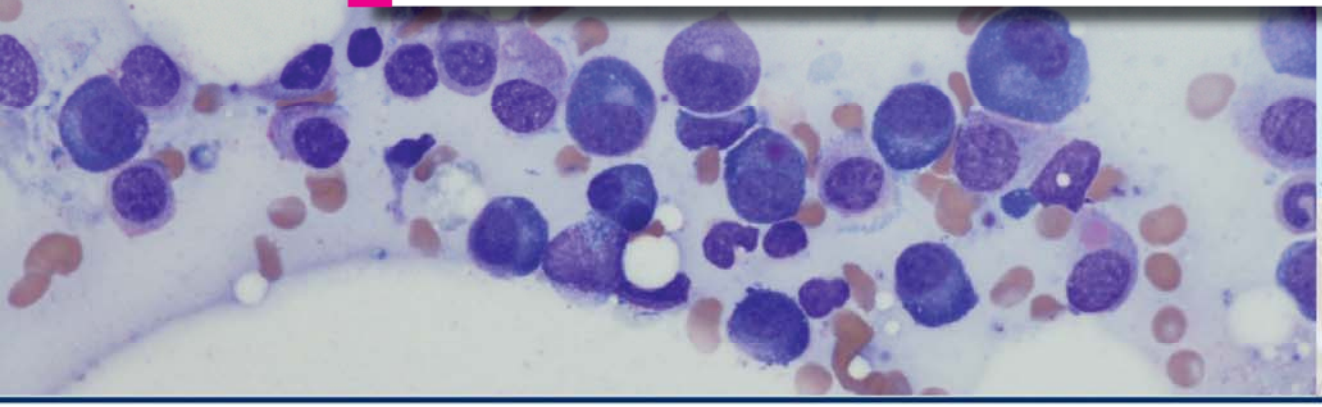


Treatment Options, Clinical Pathways, and Collaborative Care: A Multiple Myeloma Update for Managed Care and Specialty Pharmacy



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

AMCP Academy of Managed Care Pharmacy®

Held in conjunction with AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017.

Educational Objectives

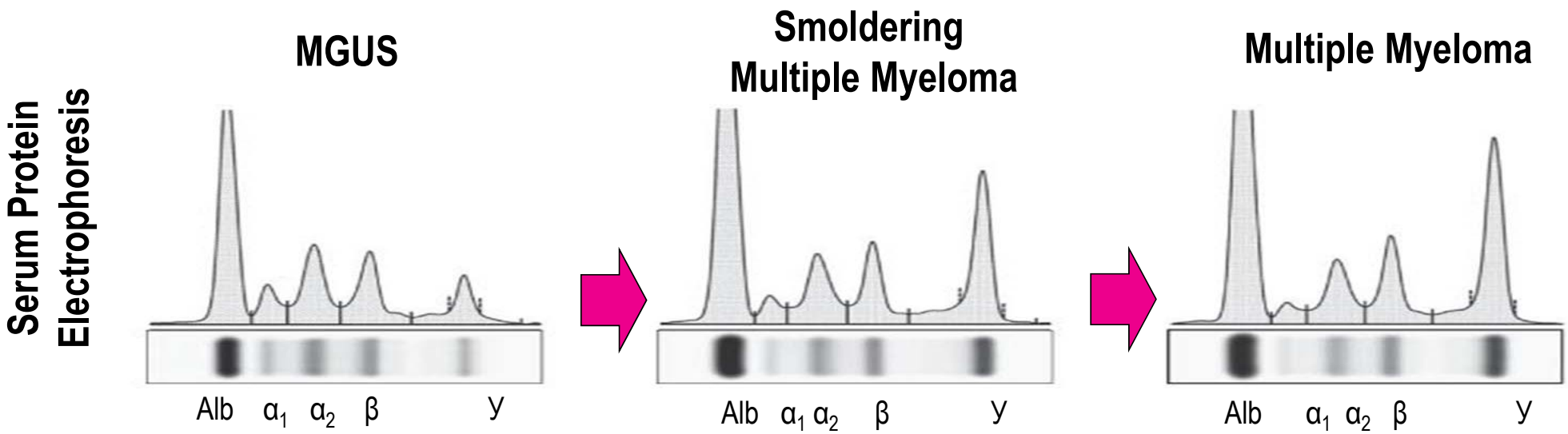
- Evaluate recent clinical data affecting evidence-based treatment guidelines for MM
- Demonstrate the value of clinical pathways initiatives as a means of reducing treatment variability and improving clinical and economic outcomes in the management of MM
- Implement comprehensive care strategies involving effective communication methods
- Integrate innovative oncology pharmacy benefit models with specialty pharmacy management services

The Expanding Treatment Armamentarium and Evolving Clinical and Supportive Care Guidelines

Carol Ann Huff, MD

Associate Professor of Oncology and Medicine,
Johns Hopkins University School of Medicine;
Medical Director, Johns Hopkins Kimmel Cancer Center

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.

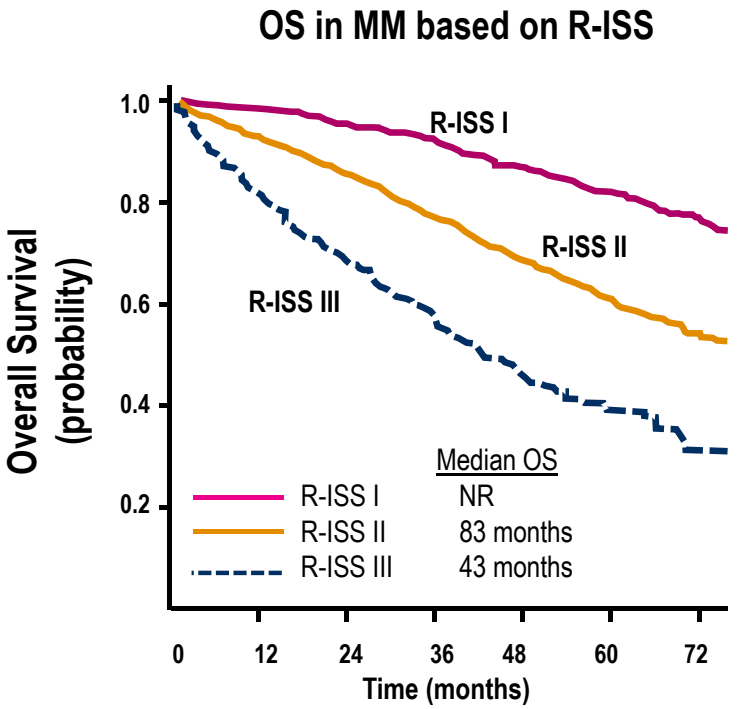
A Stepwise Approach to Treatment of MM

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

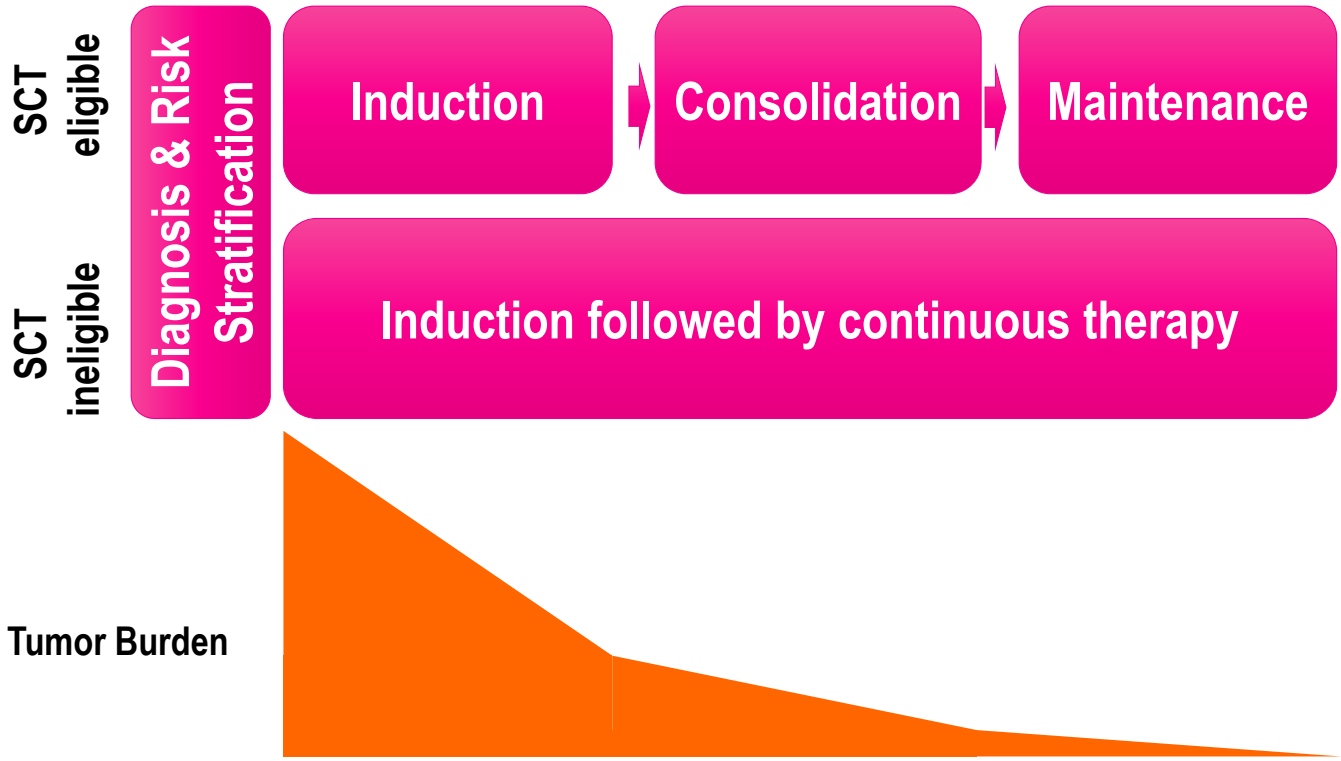
Revised International Staging System for MM

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

Summary of General Treatment Approaches

	Treatment Phase		
	Initial	**Maintenance**	**Relapsed/Refractory**
Goals	Rapidly and effectively control disease; Reverse disease-related complications; Decrease the risk of early death	Sustain treatment effect and prolong PFS; Achieve durable remission	Achieve response; Minimize disease-related complications; Prolong survival; Discontinue active treatment and initiate palliative care during the last months of life
Options	IMiDs and PIs in combination with dexamethasone	Bortezomib and lenalidomide	IMiDs, PIs, monoclonal antibodies, HDAC inhibitors, conventional chemotherapy (DCEP, VDT-PACE), combinations of newer and older drugs
Considerations	Therapy should be easily tolerated with minimal/ manageable toxicity; For transplant-eligible patients, therapy must not interfere with the ability to collect stem cells for transplantation	Effect on OS is inconsistent; Increased toxicity with maintenance therapy, especially over long term; Quality-of-life impact; Cost-of-care implications	Heterogeneity of disease at relapse; Absence of clear biological-based recommendations regarding choice of salvage therapies at various time points of disease progression; Clinical trial enrollment Supportive/palliative care

IMiDs=immunomodulatory drugs; PIs=proteasome inhibitors; PFS=progression-free survival; OS=overall survival; HDAC=histone deacetylase; DCEP=Dexamethasone/cyclophosphamide/etoposide/cisplatin; VDT-PACE=Bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide.

IRd vs Rd in RRMM: Phase 3 TOURMALINE-MM1

*Lenalidomide 25 mg PO Days 1-21; dexamethasone 40 mg PO Days 1, 8, 15, 22

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, OS and PFS in high-risk pts, response (ORR, PR, VGPR, CR, DoR), safety, pain response, global health outcomes, PK analysis, association between response or resistance to ixazomib and cytogenetics

IRd=Ixazomib/lenalidomide/dexamethasone; Rd=lenalidomide/dexamethasone; RRMM=relapsed or refractory multiple myeloma; ECOG PS=Eastern Cooperative Oncology Group performance status PFS=progression-free survival; ORR=overall response rate; CR=complete response; VGPR=very good partial response; PR=partial response; DoR=duration of response; PK=pharmacokinetic.

Moreau P, et al. *NEJM.* 2016:374:1621-1634.

Ixazomib Efficacy: Phase 3 TOURMALINE-MM1

Characteristic	Ixazomib + Rd (n=360)	Placebo + Rd (n=362)	*P* Value
Median PFS, mos	20.6	14.7	0.012*
ORR, %	78.3	71.5	0.035
▪ CR	11.7	6.6	0.019
▪ VGPR	36.4	32.3	
▪ PR	66.7	64.9	
Median time to response, mos	1.1	1.9	
Median DoR, mos	20.5	15.0	
Median TTP, mos	21.4	15.7	0.007†

*HR: 0.742. †HR: 0.712.

PR=partial response; TTP=time to progression

PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high-risk and PI- and IMiD-exposed

Moreau P, et al. *NEJM.* 2016:374:1621-1634.

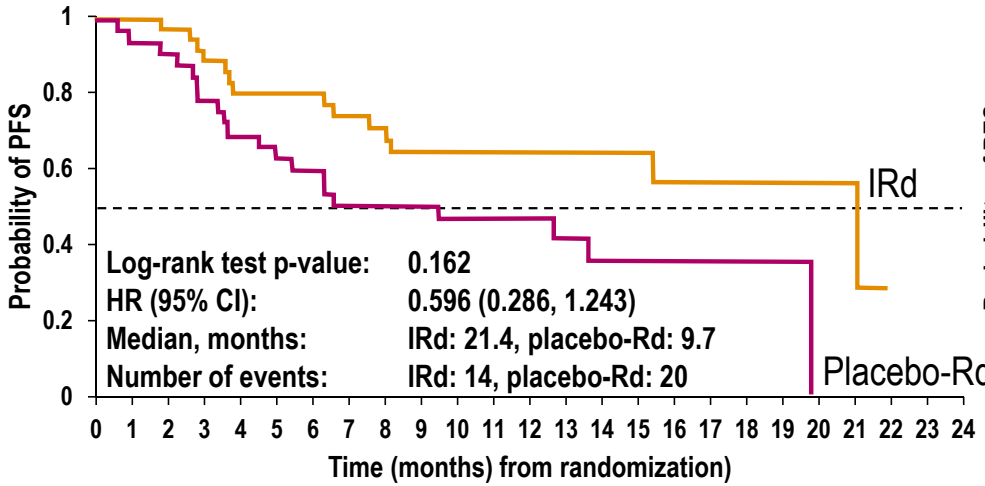
Secondary Analysis of Patients by Cytogenetic Risk: Phase 3 TOURMALINE-MM1

- In an analysis of the efficacy and safety of IRd vs placebo-Rd by cytogenetic status, high-risk cytogenetic abnormalities were assessed at a central laboratory
- Cut-off values were based on false-positive rates of the FISH probes, and were 5%, 3%, and 3% for del(17p), t(4;14), and t(14;16), respectively
- Post-hoc analyses were performed using different cut-offs for del(17p) and t(4;14)
- Of 722 pts enrolled, 552 (76%) had cytogenetic results (97% central laboratory-confirmed), of whom 137 had high-risk abnormalities (75 IRd, 62 placebo-Rd)

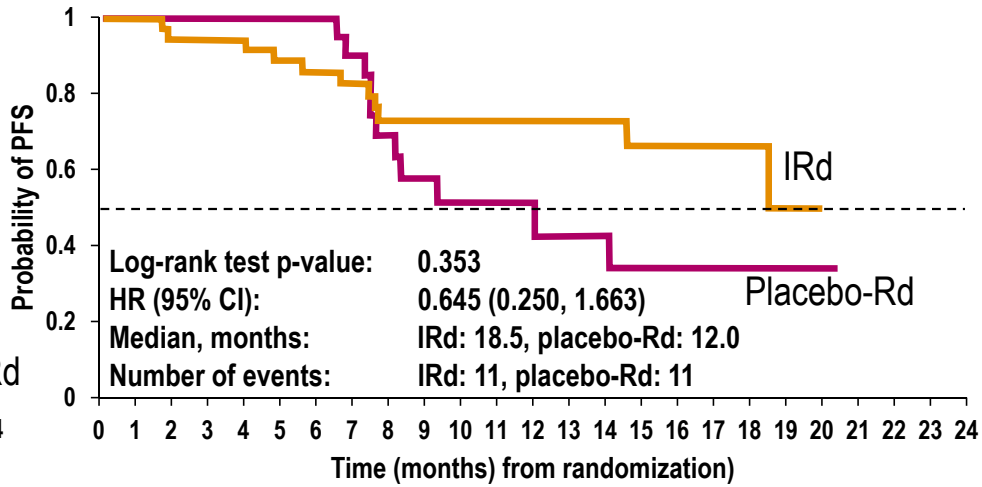
Richardson PG, et al. Poster Presented at the ASCO Annual Meeting; Chicago, IL; June 3-7, 2016.

Secondary Analysis of Patients by Cytogenetic Risk: Phase 3 TOURMALINE-MM1

del(17p) Alone or in Combination with t(4;14) and/or t(14;16)

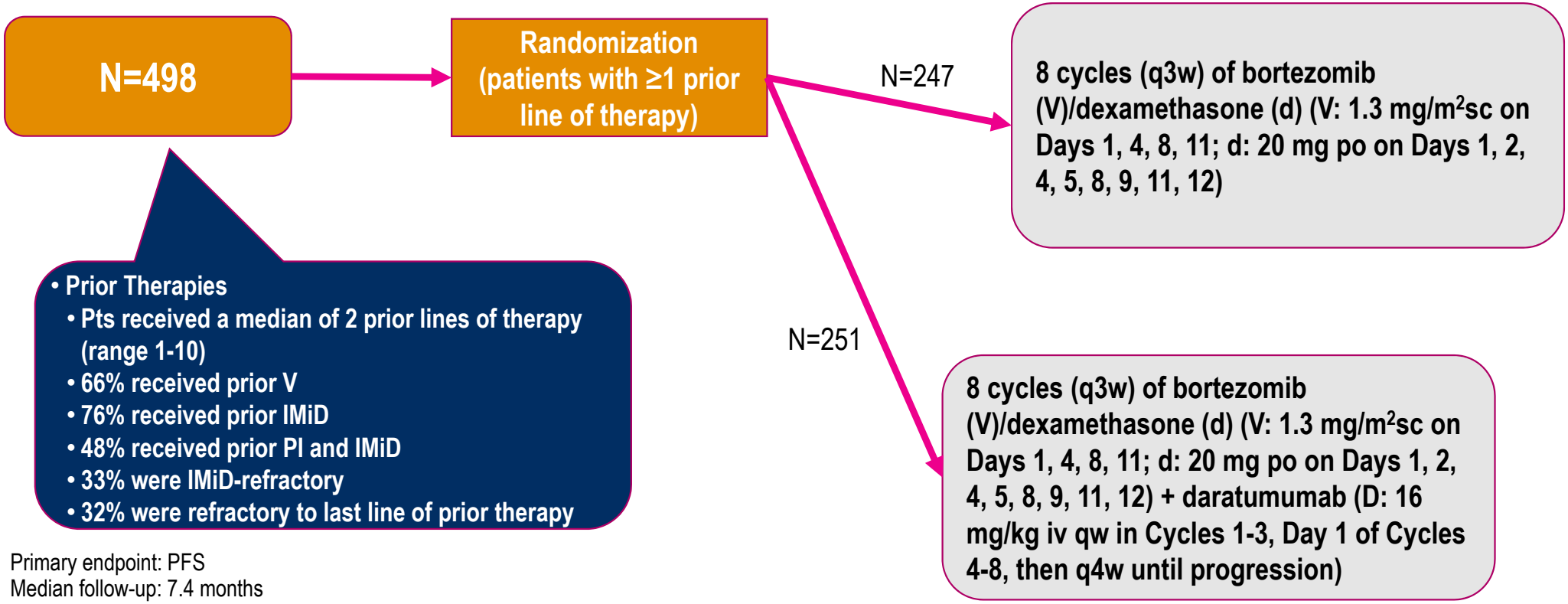


t(4;14) Alone



Richardson PG, et al. Poster Presented at the ASCO Annual Meeting; Chicago, IL; June 3-7, 2016.

DVd vs Vd in RRMM: CASTOR

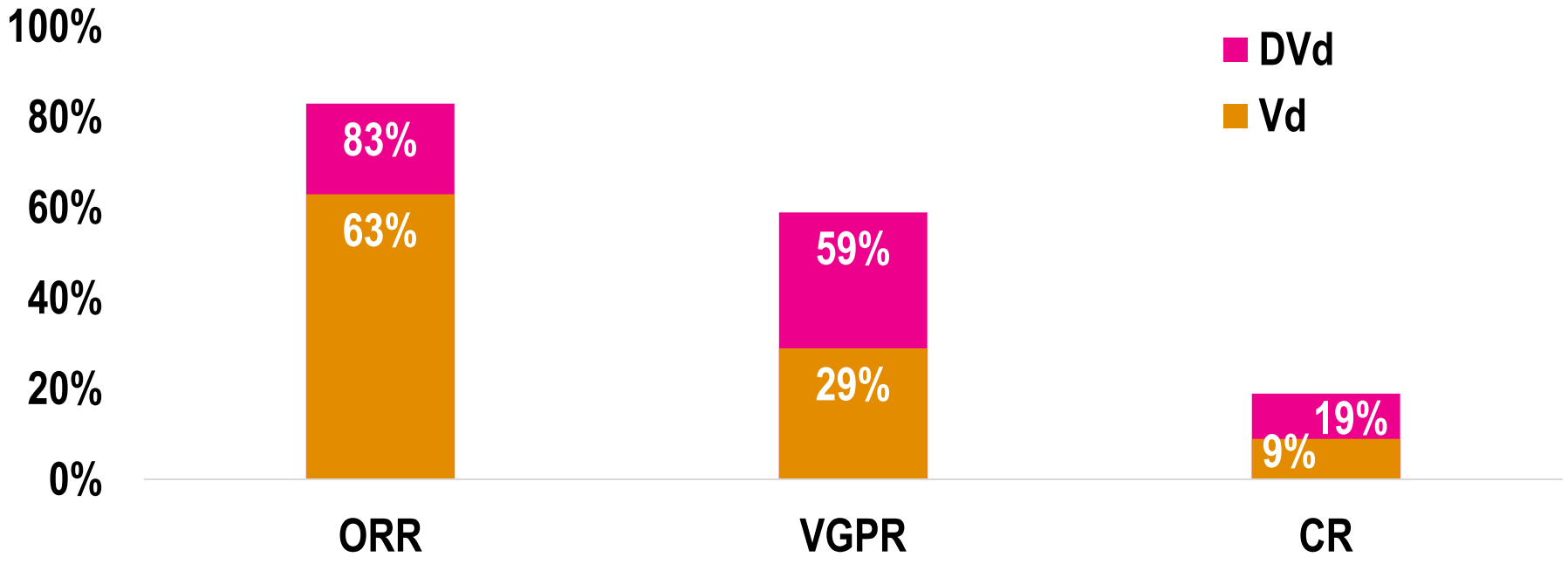


- Primary endpoint: PFS
- Median follow-up: 7.4 months

DVd=daratumumab/bortezomib/dexamethasone; Vd=bortezomib/dexamethasone

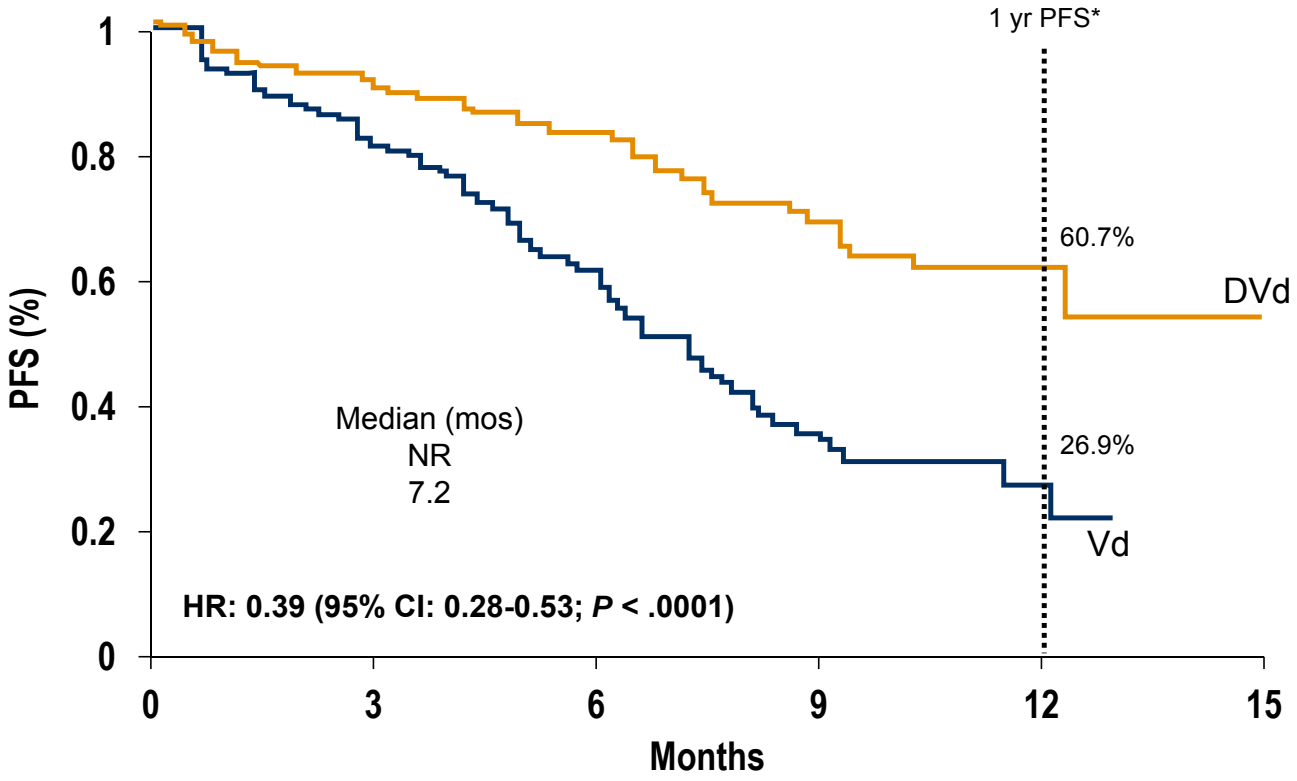
Palumbo A, et al. *NEJM.* 2016;375:754-766.

CASTOR Trial: Response Rates



Palumbo A, et al. *NEJM.* 2016;375:754-766.

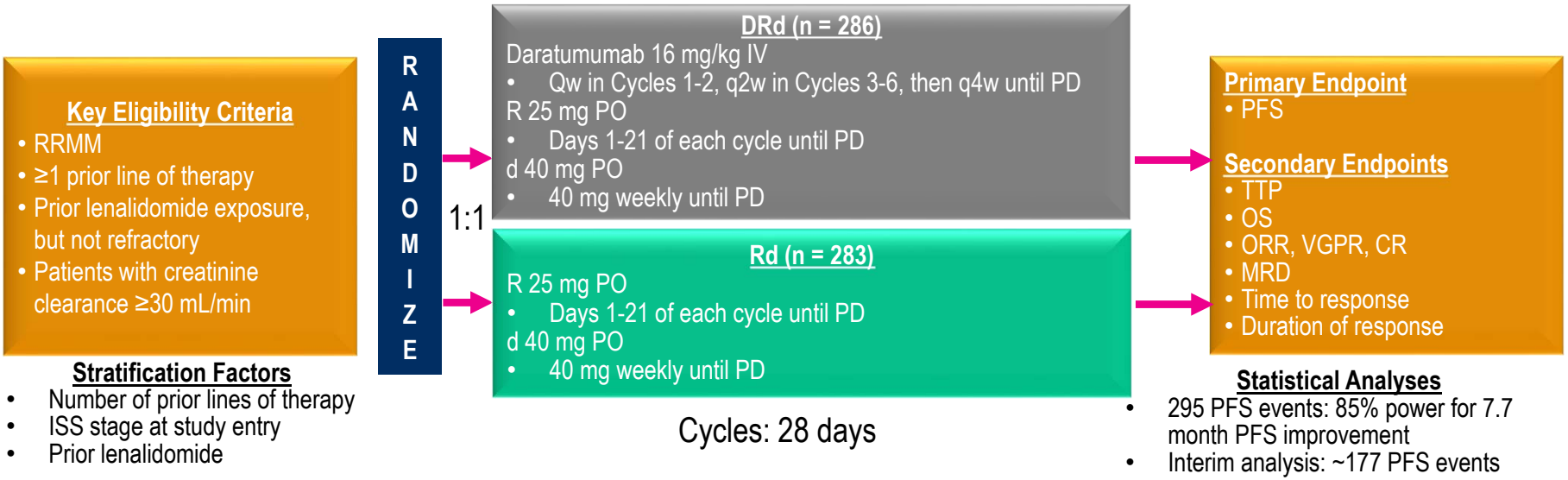
CASTOR: DVd Improves PFS



Palumbo A, et al. *NEJM.* 2016;375:754-766.

DRd vs Rd in RRMM: POLLUX Trial

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

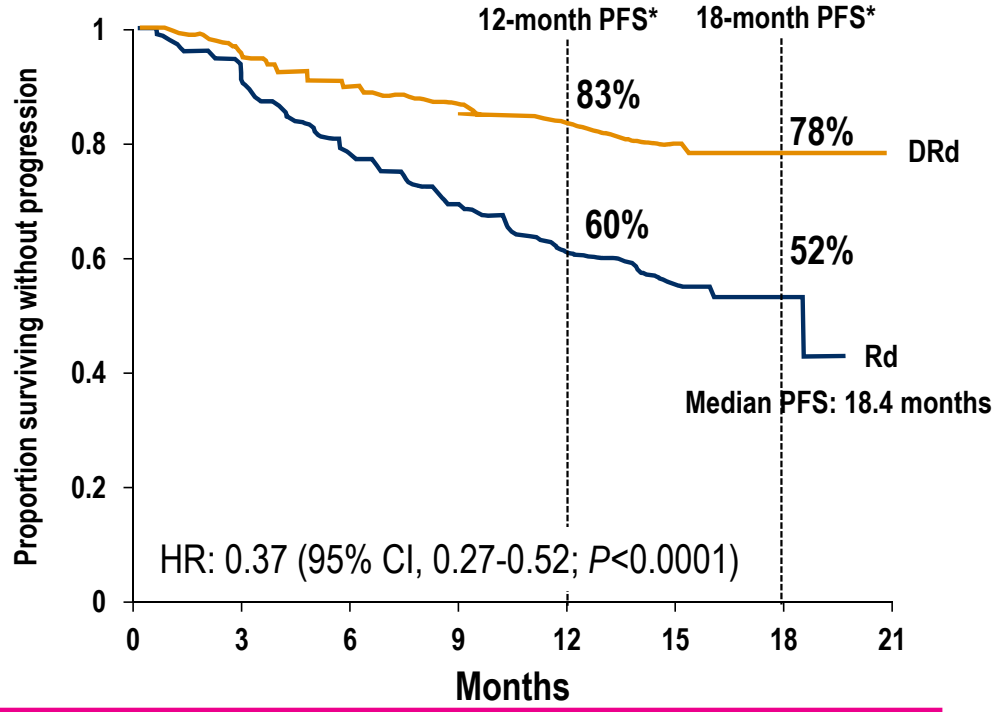


Pre-medication for the DRd treatment group consisted of dexamethasone 20mg[a], paracetamol, and an antihistamine

*On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM=relapsed or refractory multiple myeloma; ISS=international staging system; R=lenalidomide; DRd=daratumumab/lenalidomide/dexamethasone; IV=intravenous; qw=once weekly; q2w=every 2 weeks; q4w=every 4 weeks; PD=progressive disease; PO=oral; d=dexamethasone; Rd=lenalidomide/dexamethasone; TTP=time to progression; MRD=minimal-residual disease

Dimopolous MA, et al. *NEJM*. 2016;375:1319-1331

POLLUX Results: PFS



Number at risk								
Rd	283	249	206	179	139	36	5	0
DRd	286	266	248	232	189	55	8	0

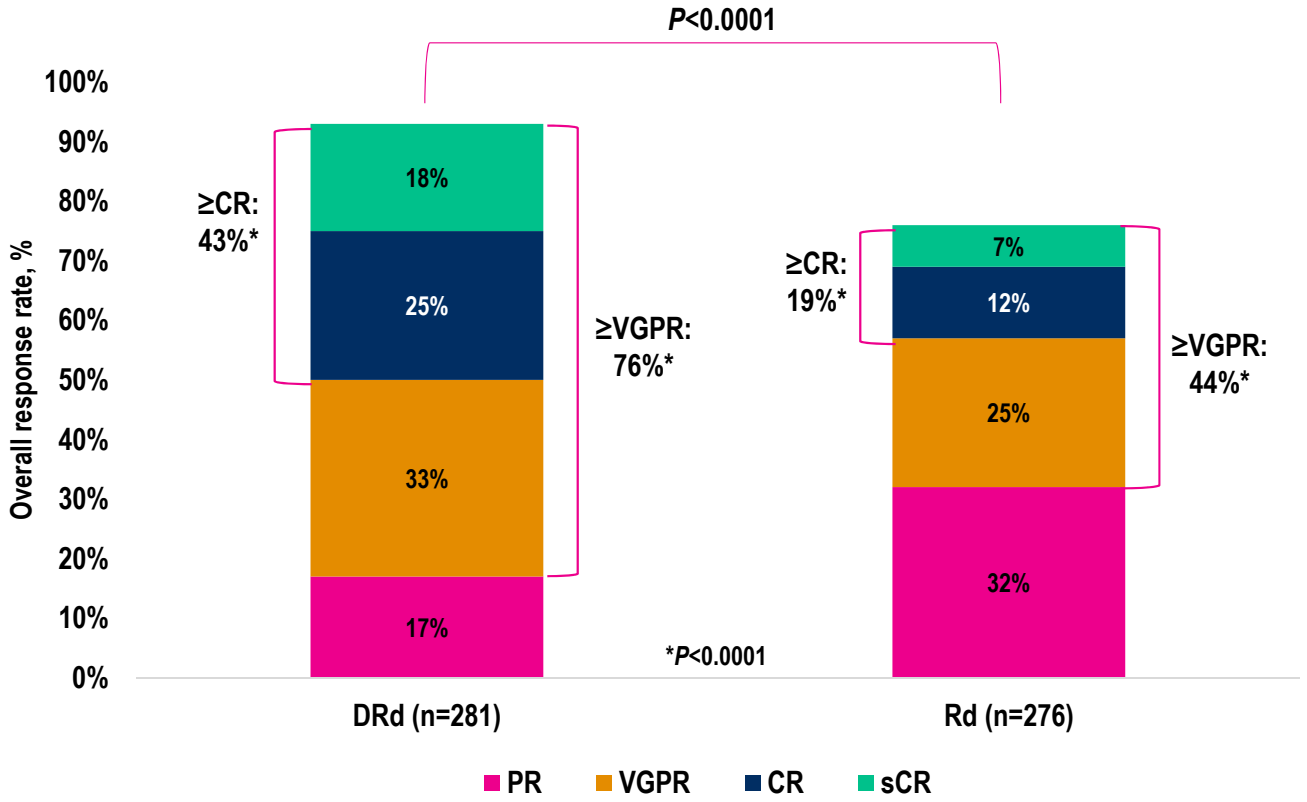
63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio

Dimopolous MA, et al. *NEJM*. 2016;375:1319-1331

POLLUX Results: ORR

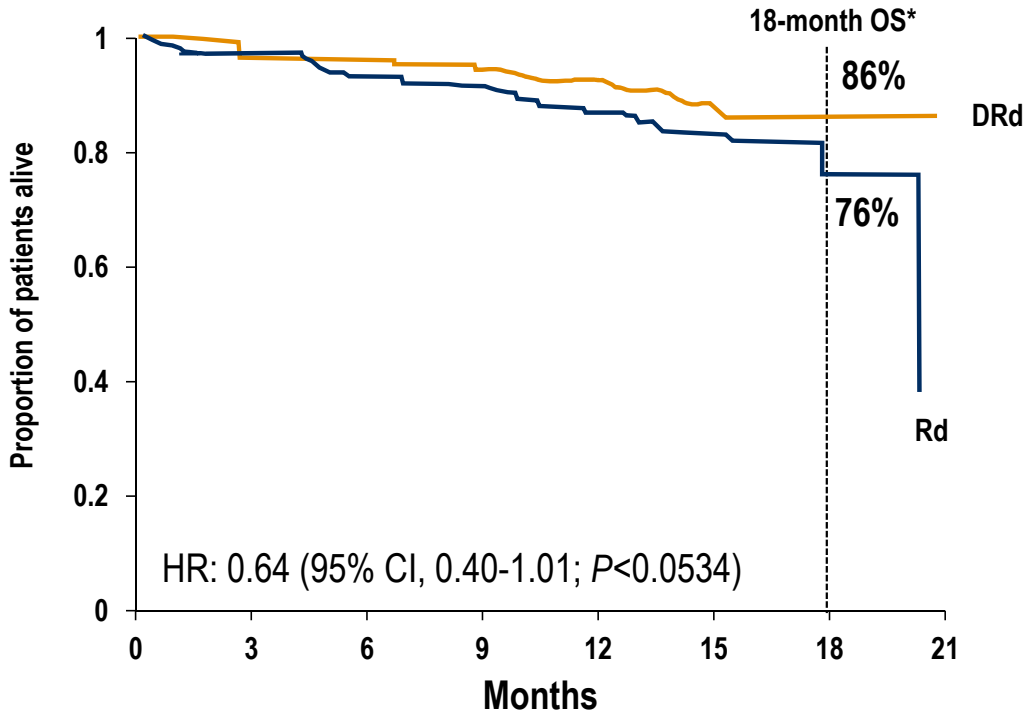
- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd



*When serum interference was suspected, CR was confirmed using the daratumumab interference reflex assay.

Dimopolous MA, et al. *NEJM*. 2016;375:1319-1331

POLLUX Results: OS



Number at risk								
Rd	283	272	255	247	217	74	10	0
DRd	286	277	271	262	224	79	14	0

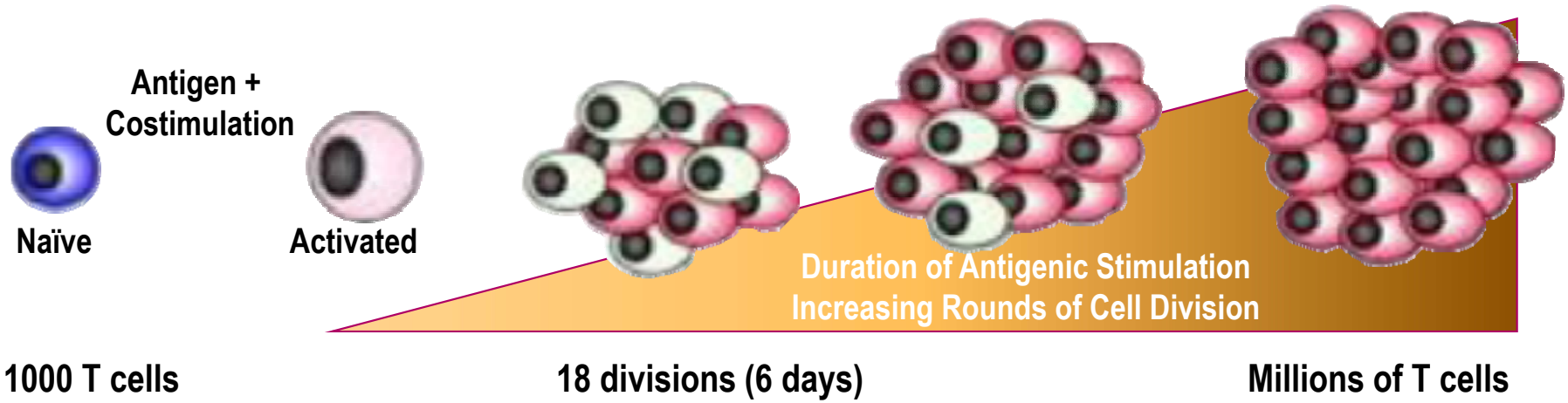
18-month overall survival: 86% in DRd versus 76% in Rd

*KM estimate

Dimopolous MA, et al. *NEJM*. 2016;375:1319-1331

Targeted Agents and Immunotherapies in Development for MM

T cells are Equipped with the Ability to Kill Cancer Cells

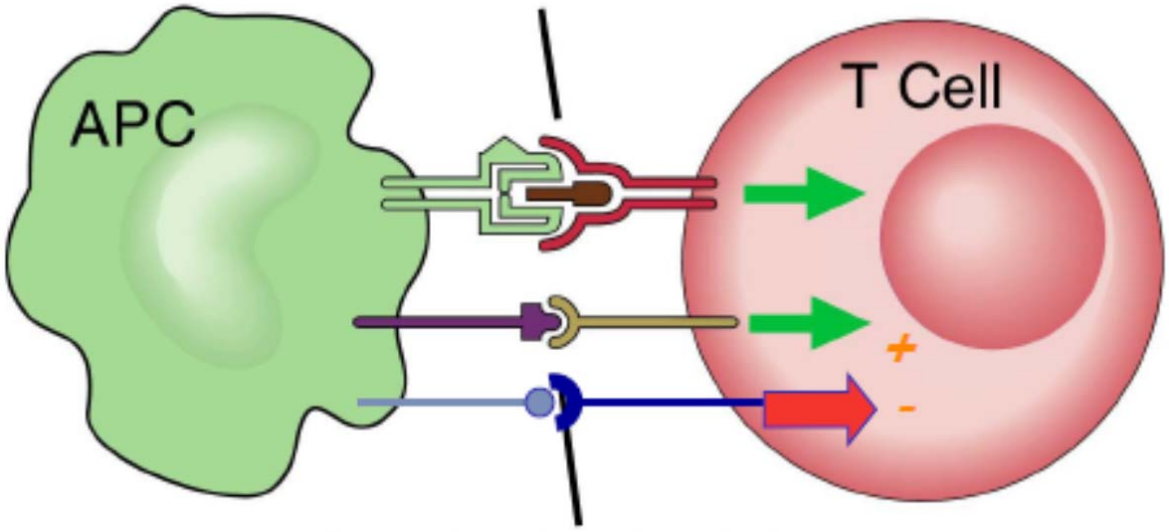


Activation leads to proliferation, thereby increasing anti-oncogenic activity

Freeman GJ, et al. *J Exp Med*. 2000;192:1027-1034.

Dual-signal T Cell Activation

Signal 1: Antigen recognition



Signal 2: Co-stimulation

Signal 2 may be either positive or negative

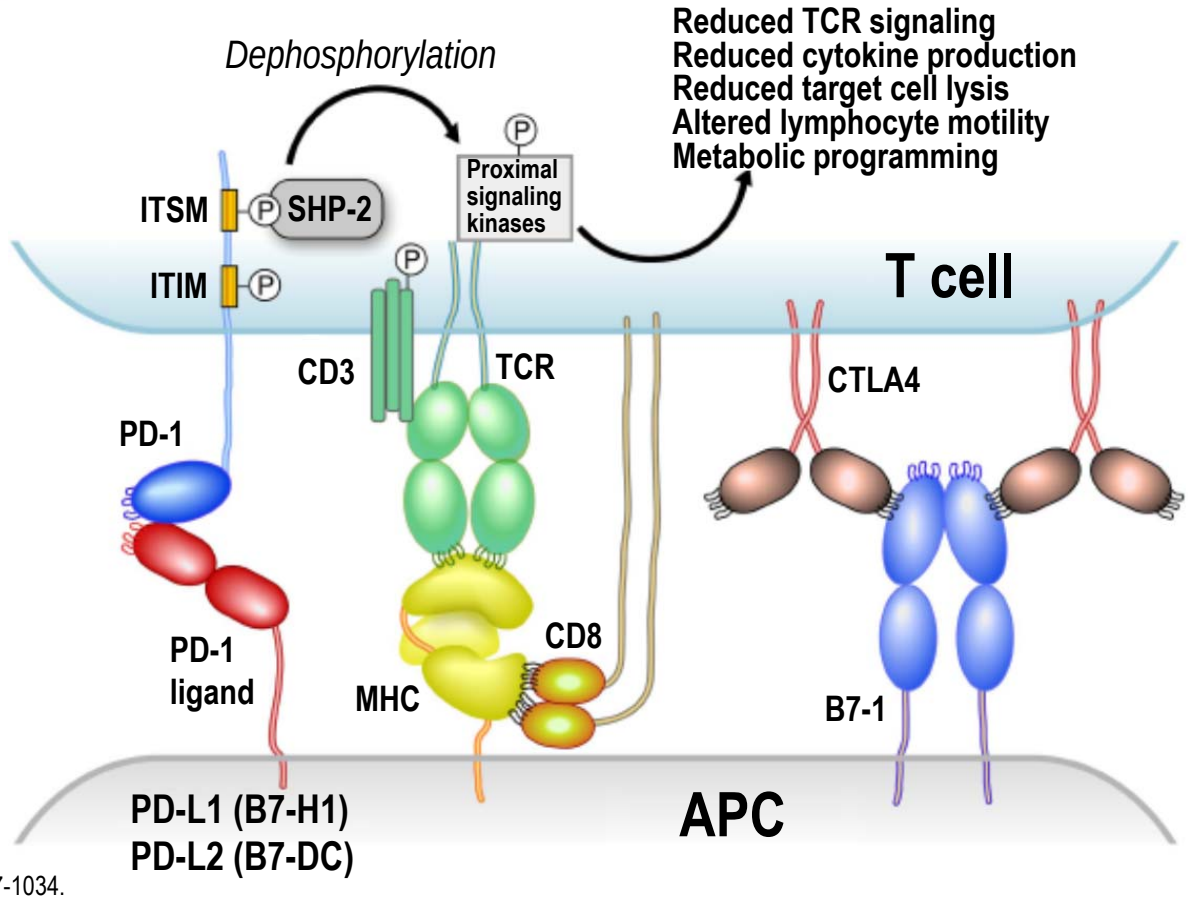
Freeman GJ, et al. *J Exp Med*. 2000;192:1027-1034.

Programmed Death-1 (PD-1)

- Cloned from a CD3-activated T cell
- Hybridomas undergo activation-induced cell death
- Unlike CD95 (Fas) in that it does not directly activate caspases and cause cell death or apoptosis
- Indirect effect on cell death via reduced cytokines, survival factors (↓Bcl-xL, ↑BIM)

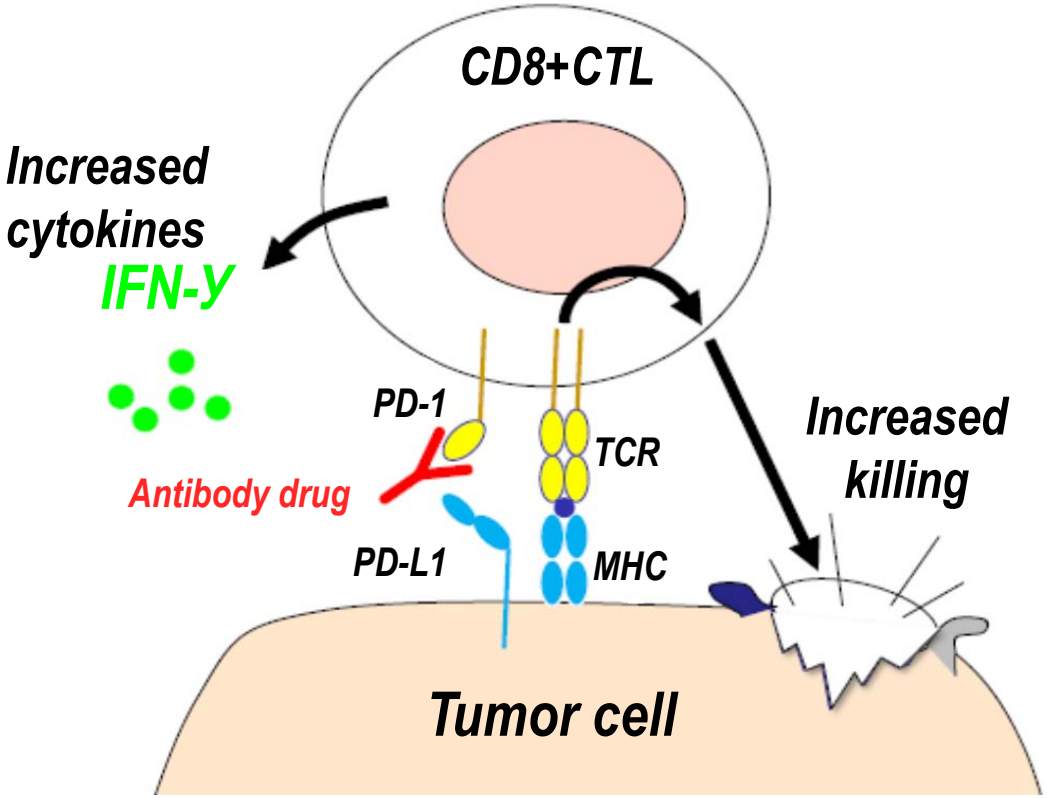
Riley JL. *Immunol Rev*. 2009;229:114-125.

The PD-1 Pathway Inhibits T Cell Activation



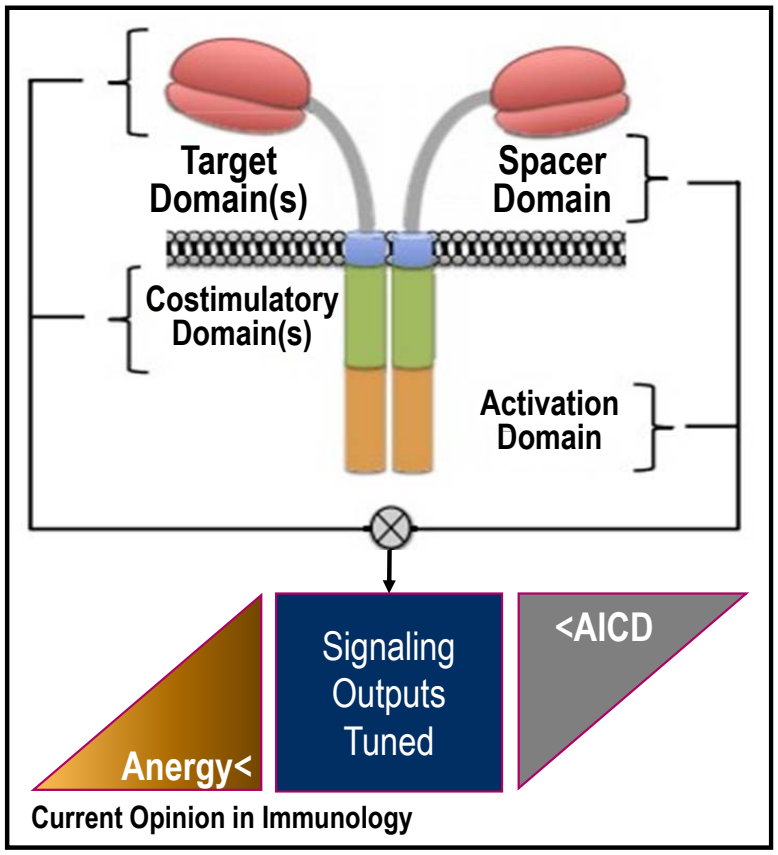
Freeman GJ, et al. *J Exp Med*. 2000;192:1027-1034.

PD-1 or PD-L1 Blockade Stimulates Anti-tumor T Cell Response



Freeman GJ, et al. *J Exp Med*. 2000;192:1027-1034.

Chimeric antigen receptor T-cell therapy (CAR-T)



Jensen MC, et al. *Curr Opin Immunol*. 2015;33:9-15.

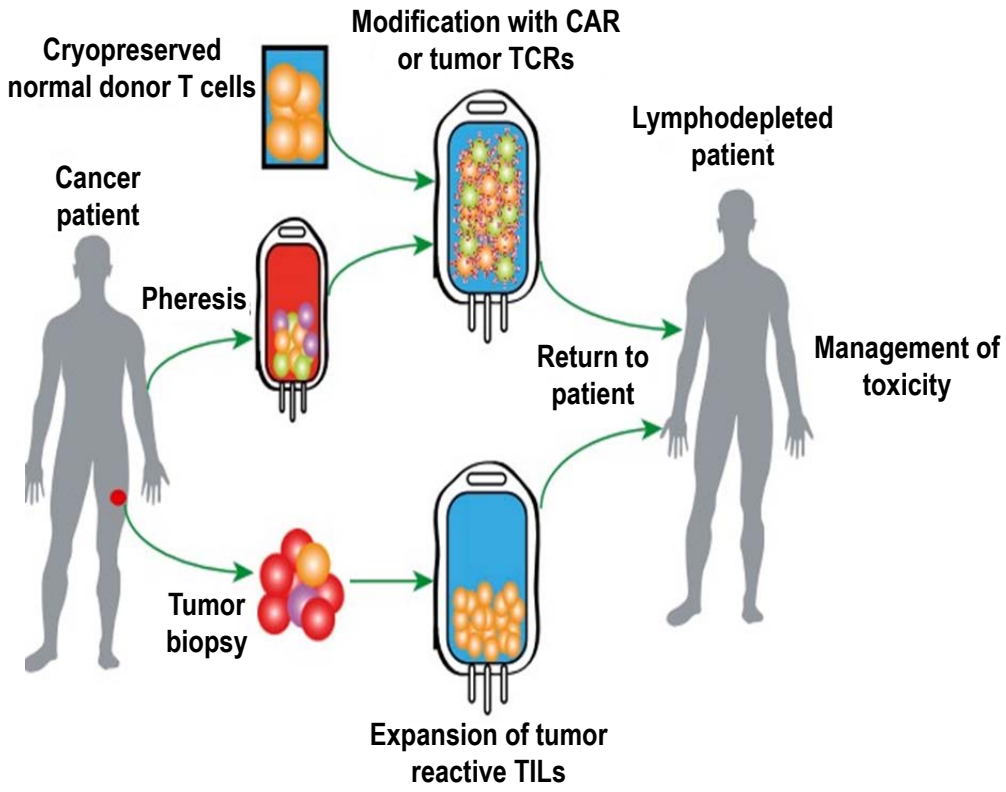
CAR-T cells recognize tumor cells independent of their expression of human leukocyte antigen (HLA) molecules, allowing for the elimination of tumor cells that escape conventional T cells by downregulating HLA and/or mutating components of the antigen processing machinery

Chimeric antigen receptors (CARs) are fusion molecules typically composed of the following:

- An extracellular single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface molecule on the tumor cell
- A spacer domain that provides flexibility and optimizes T cell and target cell engagement
- A transmembrane domain
- Signaling modules that trigger T cell effector functions

CAR-T Therapy: Pathway to the Patient

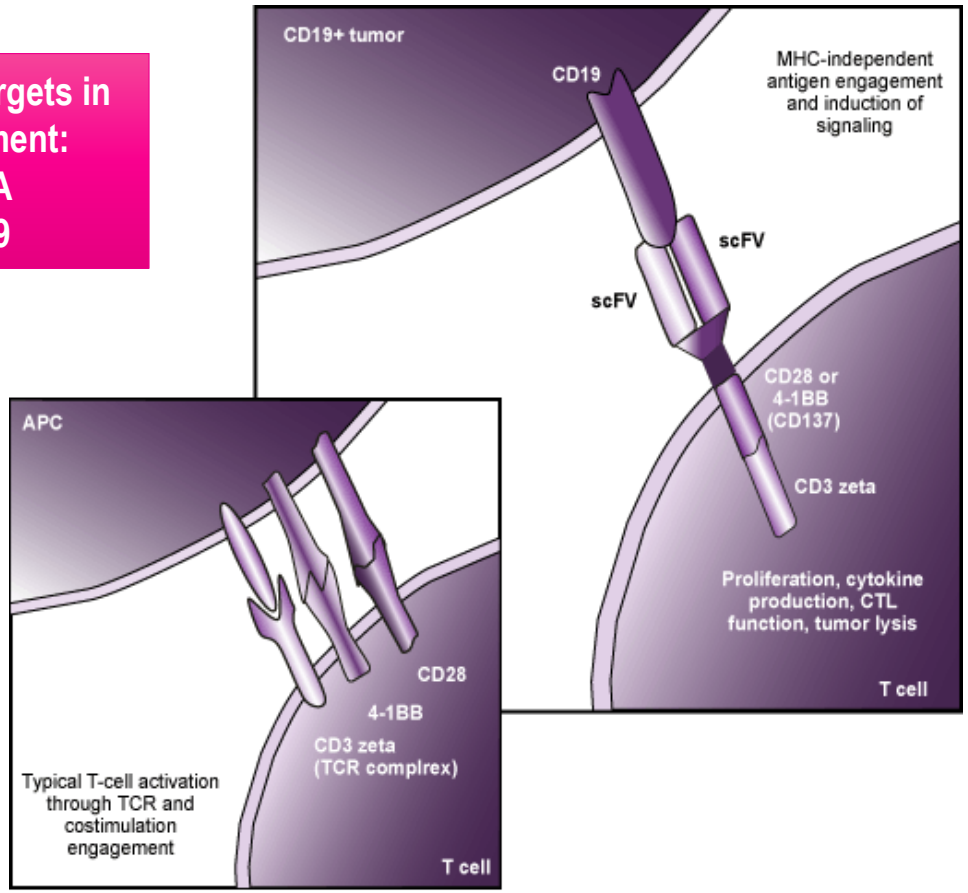
- Normal donor cells can be modified to inactivate their alloreactivity while being armed with antitumor CARs or T cell receptors (TCRs)
- Alternatively, a patient's own cells can be modified with antitumor molecules.
- In solid tumors, biopsy specimens can be used to isolate tumor infiltrating lymphocytes (TILs) for expansion
- In most cases, the patient will require some amount of conditioning before receiving antitumor lymphocyte infusions
- Careful management of toxicities emerging from these therapies is also required



Barrett DM. *J Immunol*. 2015;195:755-761.

CAR-T Cell Therapy in MM

Myeloma targets in development:
BCMA
CD-19



Adapted from Grupp S, et al. ASH 2014. Abstract 380.

Summary

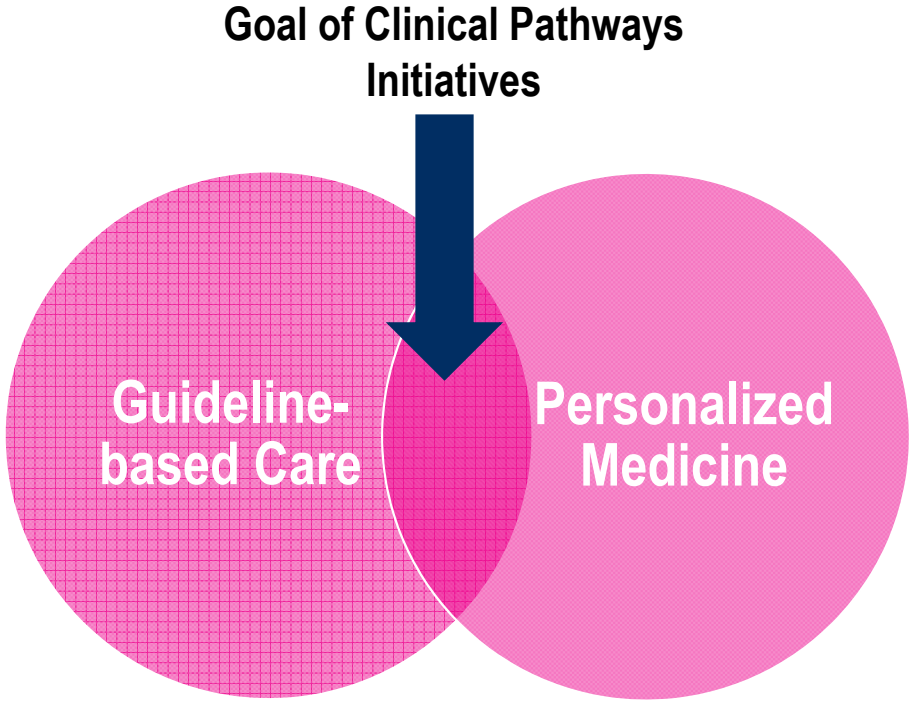
- The management of MM requires a stepwise approach involving the selection of therapy based on initial assessment and risk stratification
- In the event of nonresponse or relapse, a myriad of treatment options are available to the clinician; Because no therapy is curative, options should be tried sequentially
- Emerging data, particularly surrounding targeted therapies and biologics, are regularly reshaping the treatment paradigm and clinical guidelines
- Immunotherapies based on mechanisms affecting T cell activation and regulation demonstrate promise as the next wave of agents to be potentially added to the treatment armamentarium

Practical Strategies for the Implementation of Clinical Pathways

Edmund Pezalla, MD, MPH
Chief Executive Officer
Enlightenment BioConsult, LLC

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

Balancing treatment *standardization* with *personalization* is cited among the top three challenges in cancer care for more than a third of MCOs



2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

Characteristics of Clinical Pathways Programs

- Guide rational therapeutic decisions with evidence-based data
- Offer formal structural elements to guide decisions
- Often based on National Comprehensive Cancer Network (NCCN) Guidelines
- Promote collaboration and integration with clinical trials and registries
- Improve quality of care, efficiency in resource utilization and patient experience

Trends in the Implementation of Pathway Initiatives Among Health Care Payers and Purchasers

According to a recent survey…

- 38% of MCOs have initiated a cancer treatment pathways program
- Adherence to guidelines/pathways are among the most common performance metrics in the value-based quality initiatives (eg, pay-for-performance) underway at more than a third of MCOs
- Measurement of the clinical and cost impact of pathways led the payer/provider initiatives undertaken by 53% of MCOs in 2015
- 21.5% of employers have already developed or plan to implement provider payment strategies tied to compliance with pathways

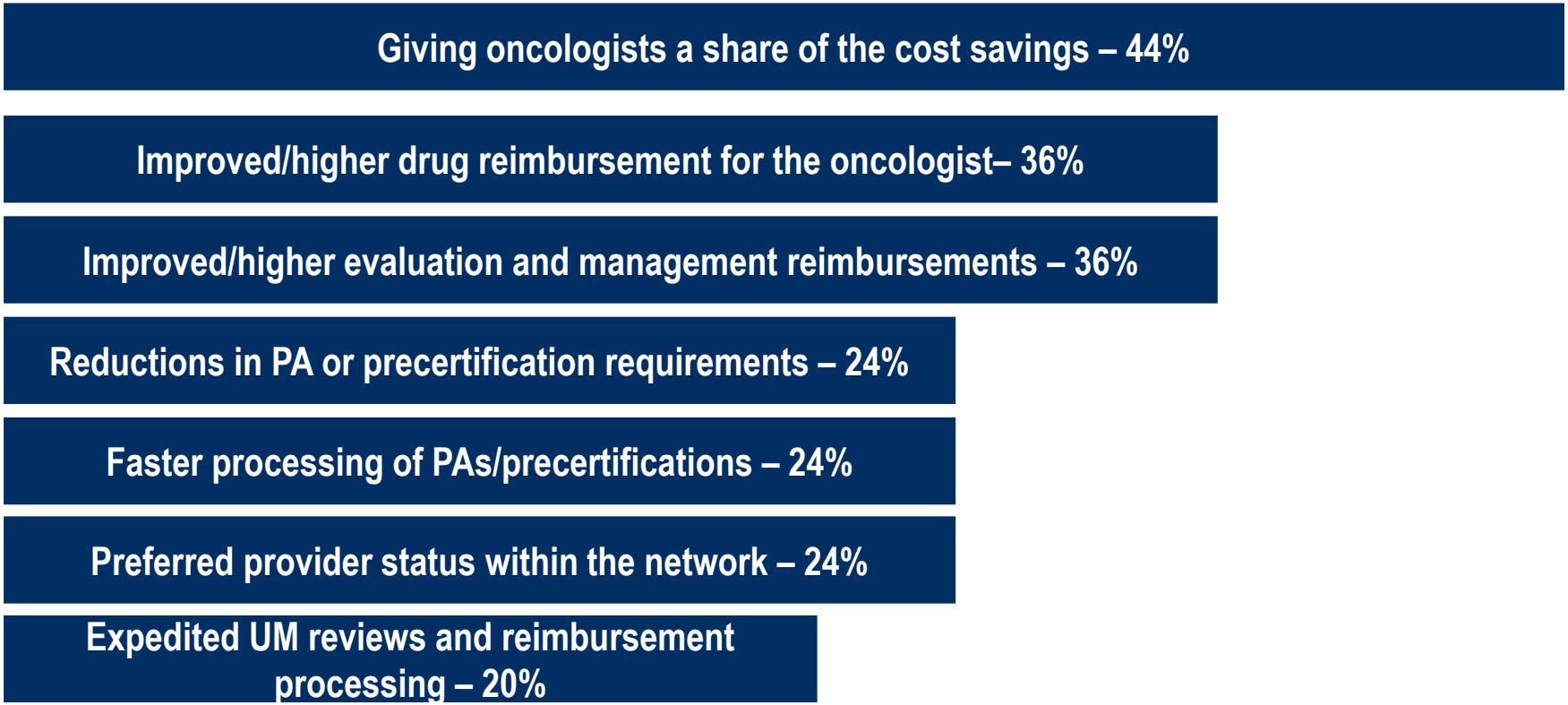
2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

Trends in Oncologist Participation in Pathways Initiatives

- 44.7% of MCOs make voluntary use of pathways the standard
- 42.7% of MCOs incentivize voluntary use
- 7.9% link reimbursement to mandatory use of pathways
- Oncologist participation rates vary, averaging 51.8% for pathways programs, according to MCO estimates
  - Approximately 40% of these oncologists have studies underway to measure the care quality and cost impact of pathways

2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

Common Provider Incentives for Participation in Pathways Programs



2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

Anticipated Increase in Pathway Use by Setting

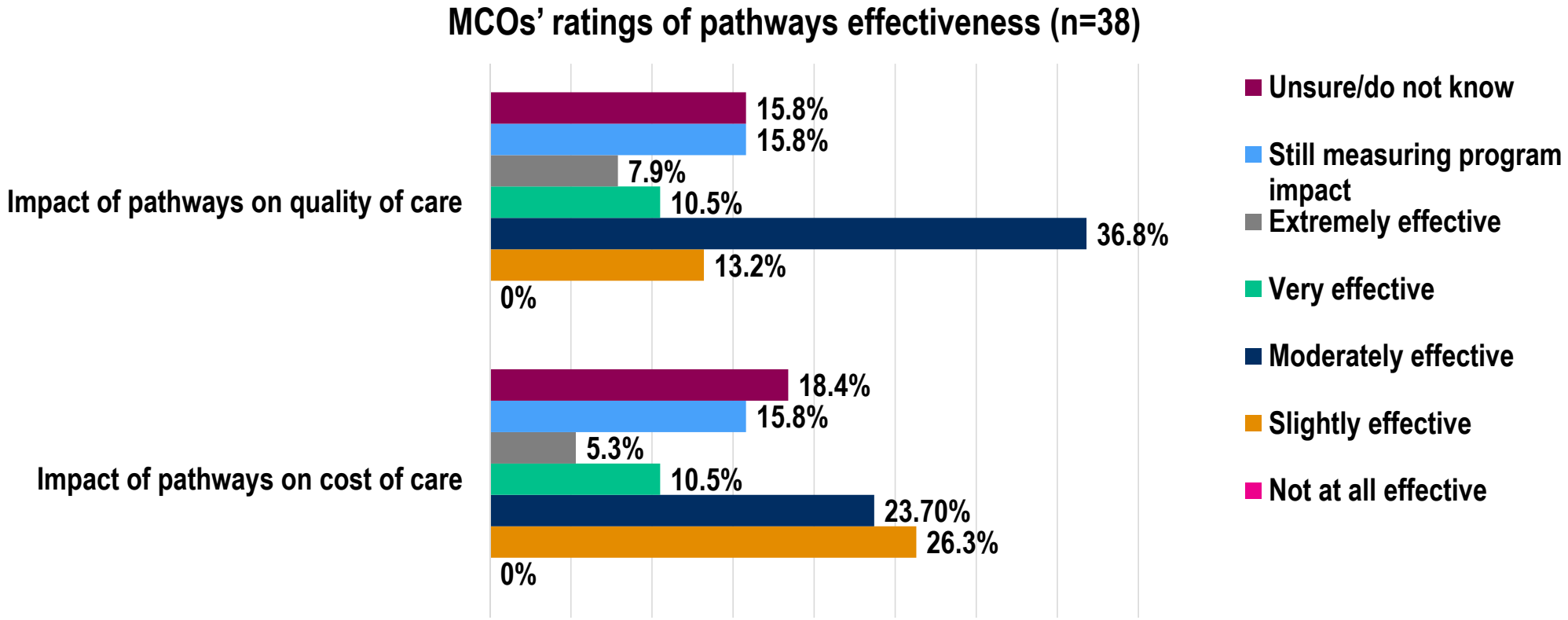
Question:

"Do you expect the use of care pathways (oncology- and/or non–oncology-related) to increase in any of the settings listed below?"

Source: Online survey of 26 payers, providers, vendors

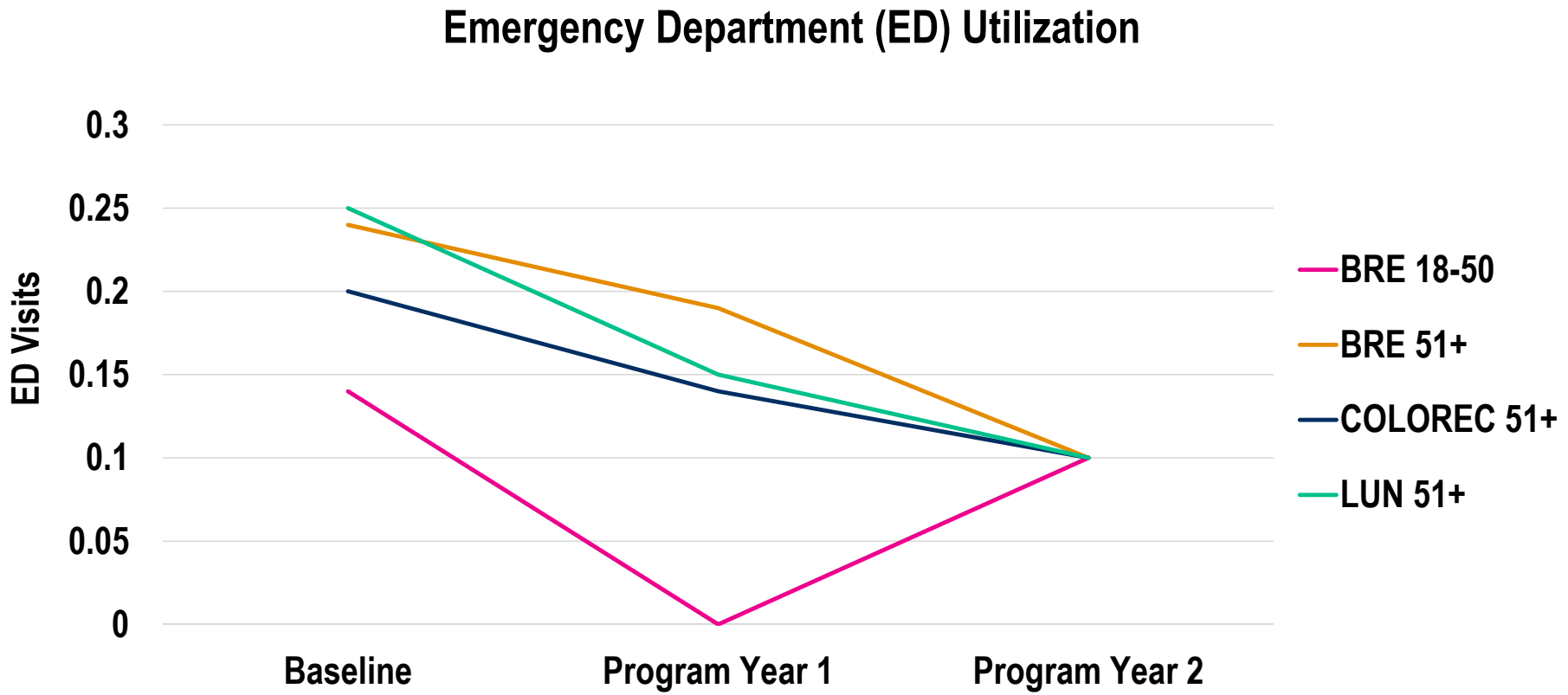
Chawla A, et al. *Am J Manag Care*. 2016;22:53-62.

Most MCOs Perceive Pathways Programs to be Moderately or at Least Slightly Effective in Impacting Care Quality and Cost



2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

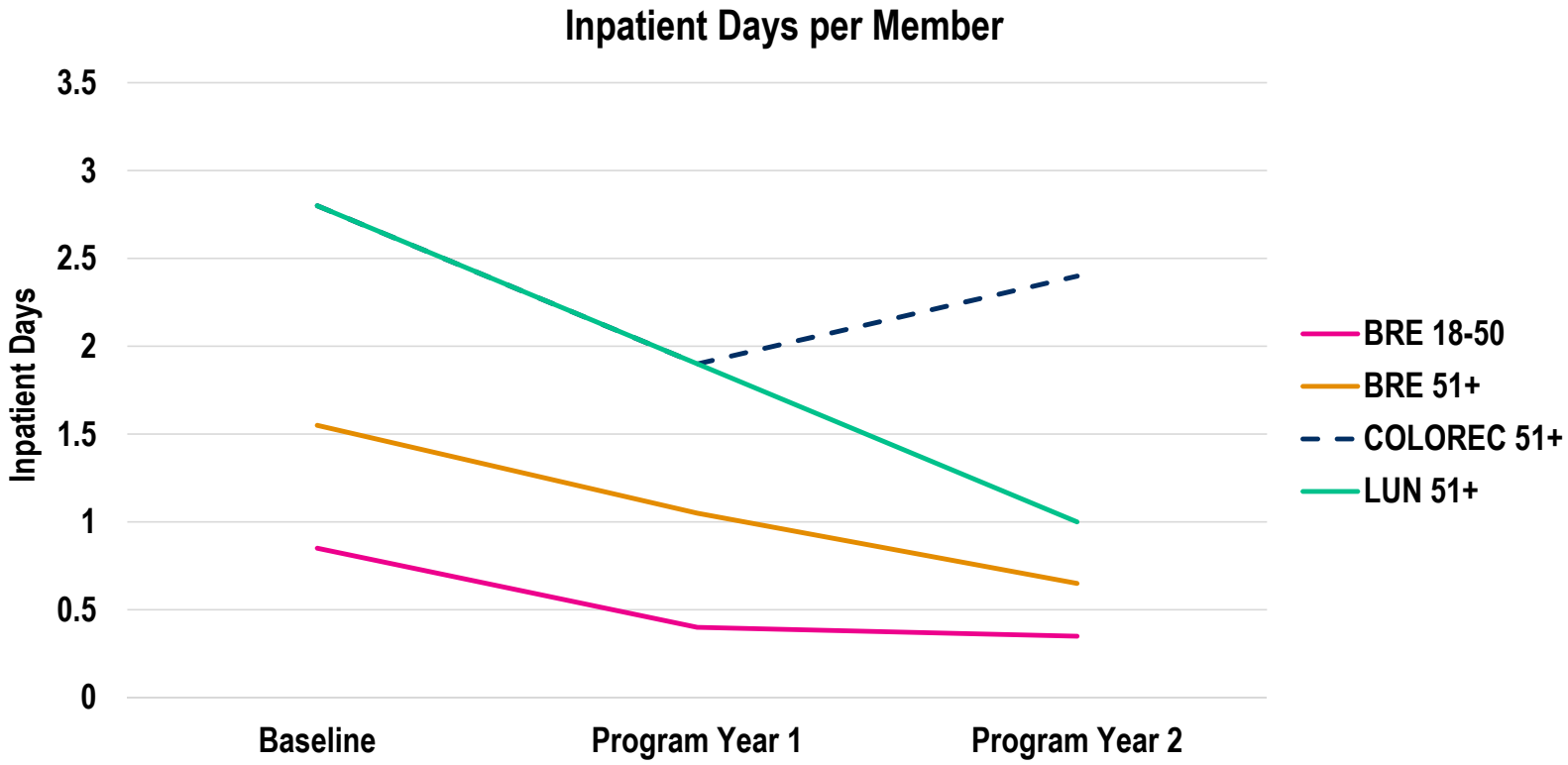
Pathway Programs Have Generated Real-life Reductions in Health Care Resource Utilization for Leading Tumor Types



BRE 18-50=Patients aged 18-50 years with breast cancer; BRE 51+=Patients aged 51+ years with breast cancer; COLOREC 51+=Patients aged 51+ years with colorectal cancer; LUN 51+=Patients aged 51+ years with lung cancer

Klein IM, et al. *Am J Manag Care.* 2014;20:S45-S60.

Pathway Programs Have Generated Real-life Reductions in Health Care Resource Utilization for Leading Tumor Types



Klein IM, et al. *Am J Manag Care.* 2014;20:S45-S60.

BRE 18-50=Patients aged 18-50 years with breast cancer; BRE 51+=Patients aged 51+ years with breast cancer; COLOREC 51+=Patients aged 51+ years with colorectal cancer; LUN 51+=Patients aged 51+ years with lung cancer

ASCO Policy Statement on Clinical Pathways in Oncology

RECOMMENDATIONS

1) A collaborative, national approach is necessary to remove the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways.
2) Oncology pathways should be developed through a process that is consistent and transparent to all stakeholders.
3) Oncology pathways should address the full spectrum of cancer care, from diagnostic evaluation through medical, surgical and radiation treatments, and include imaging, laboratory testing, survivorship, and end-of-life care.
4) Oncology pathways should promote the best possible evidence-based care in a manner that is updated continuously to reflect the rapid development of new scientific knowledge, as well as insights gained from clinical experience and patient outcomes.

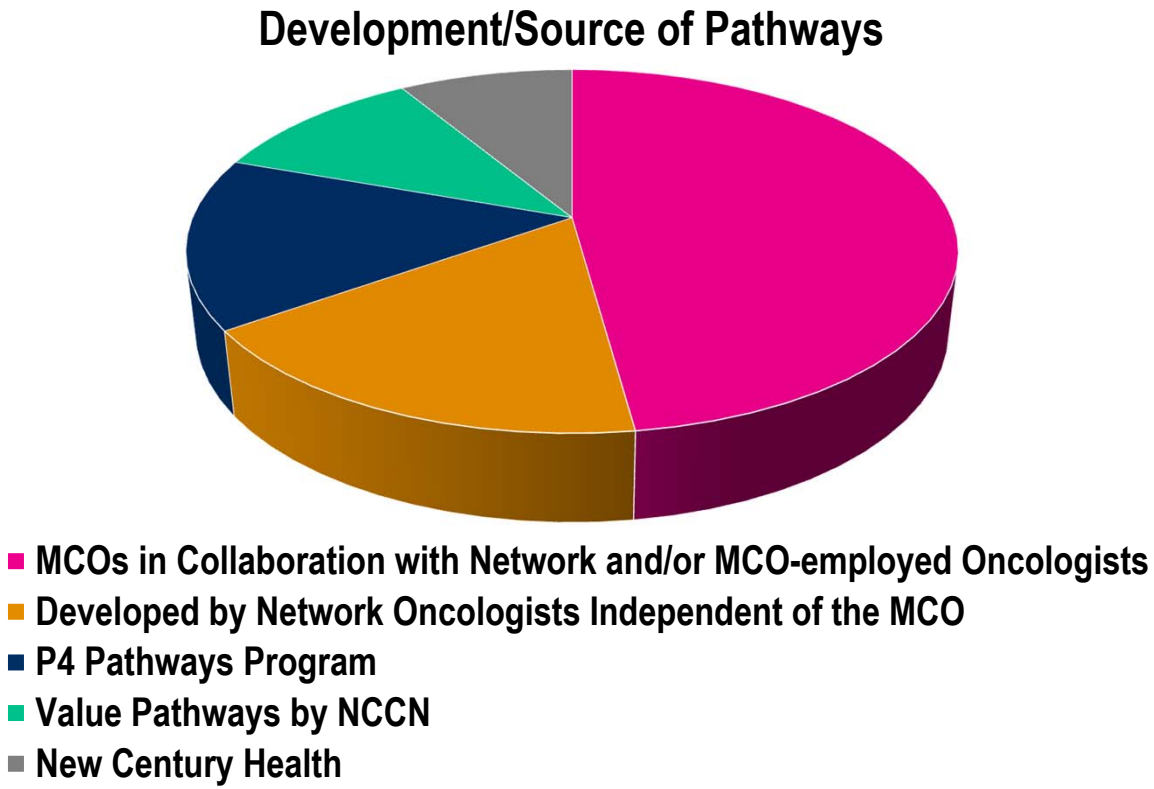
Zon RT, et al. *J Oncol Pract.* 2016;12:261-266.

ASCO Policy Statement on Clinical Pathways in Oncology (cont.)

5) Oncology pathways should recognize patient variability and autonomy and stakeholders must recognize that 100% concordance with oncology pathways is unreasonable, undesirable, and potentially unsafe.
6) Oncology pathways should be implemented in ways that promote administrative efficiencies for both oncology providers and payers.
7) Oncology pathways should promote education, research, and access to clinical trials.
8) Robust criteria must be developed to support certification of oncology pathway programs. Pathway programs should be required to qualify based on these criteria and payers should accept all oncology pathway programs that achieve certification through such a process.
9) Pathway developers, users, and private and governmental funding agencies should support research to understand pathway impact on care and outcomes.

Zon RT, et al. *J Oncol Pract.* 2016;12:261-266.

Network Oncologists are the Prevailing Developers of Pathways Initiatives



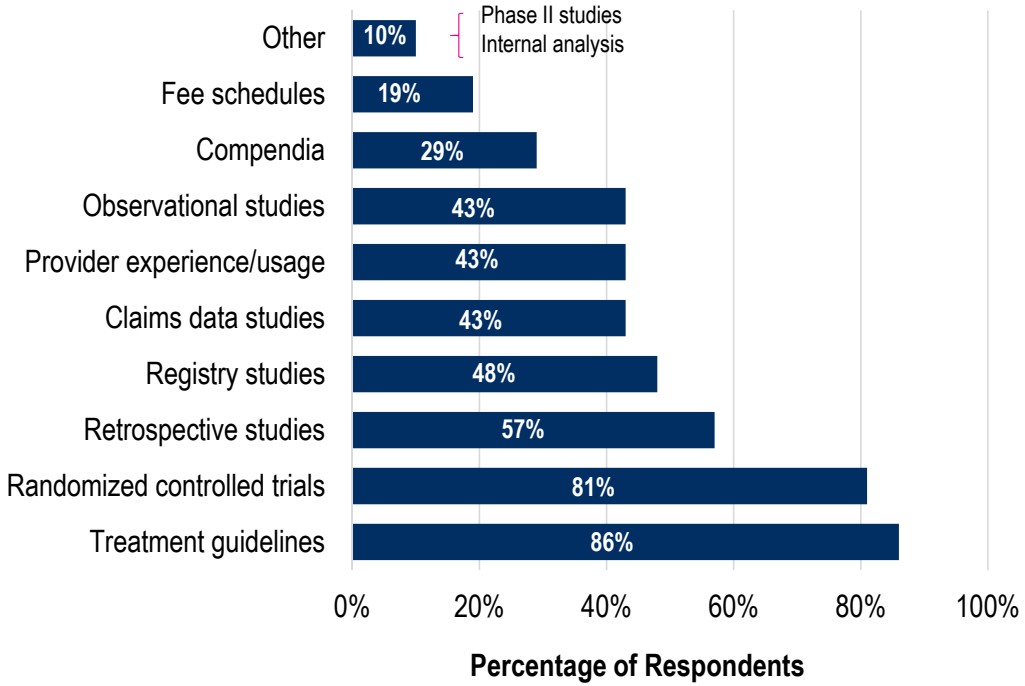
2016 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed March 2017.

Key Sources of Information for Pathway Development

Question:

"In developing a care pathway, different types of evidence or information may be used to develop the clinical algorithm. Please indicate which of the following types of evidence or information are typically used to develop the clinical algorithm."

Source: Online survey of 21 stakeholders (payers, providers, and vendors) who rated their level of experience/knowledge related to development of care pathways as 3, 4, or 5



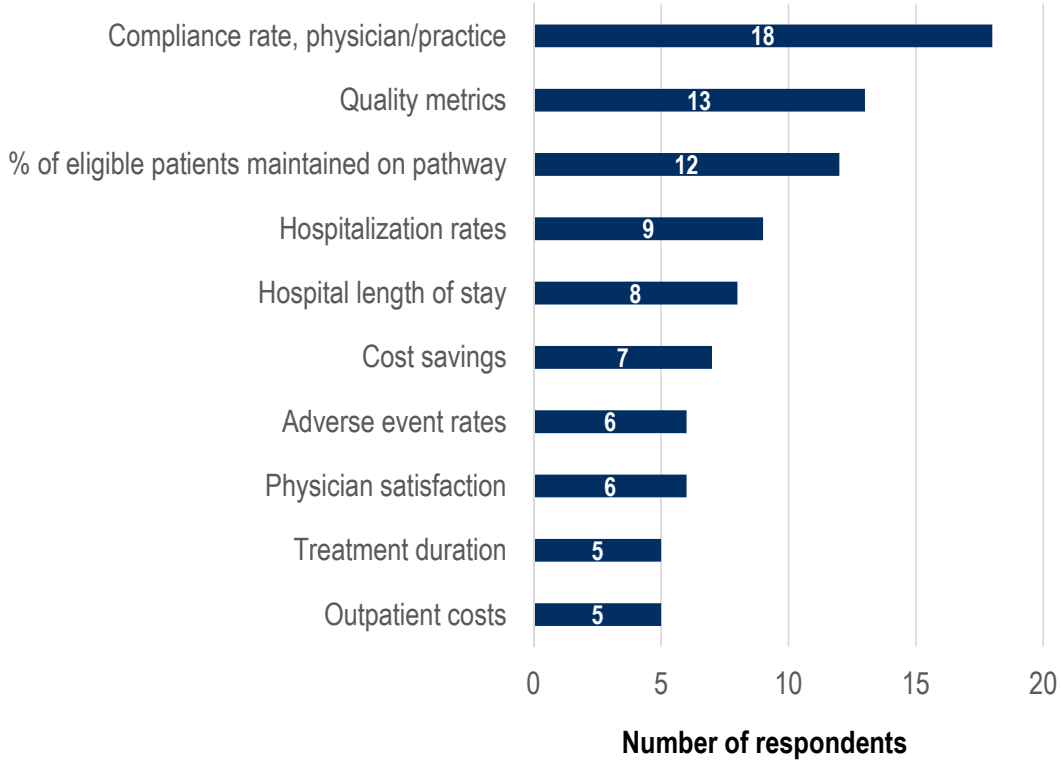
Chawla A, et al. *Am J Manag Care*. 2016;22:53-62.

Common Evaluation Metrics for Pathways Programs

Question:

"Which of the following metrics (if any) are typically used to evaluate care pathway performance? For the metrics that you selected, please indicate the 3 most important metrics when it comes to evaluating care pathway performance."

Source: Online survey of 19 payers, providers, and vendors who rated their level of experience/knowledge related to evaluating care pathway performance as 3, 4, or 5



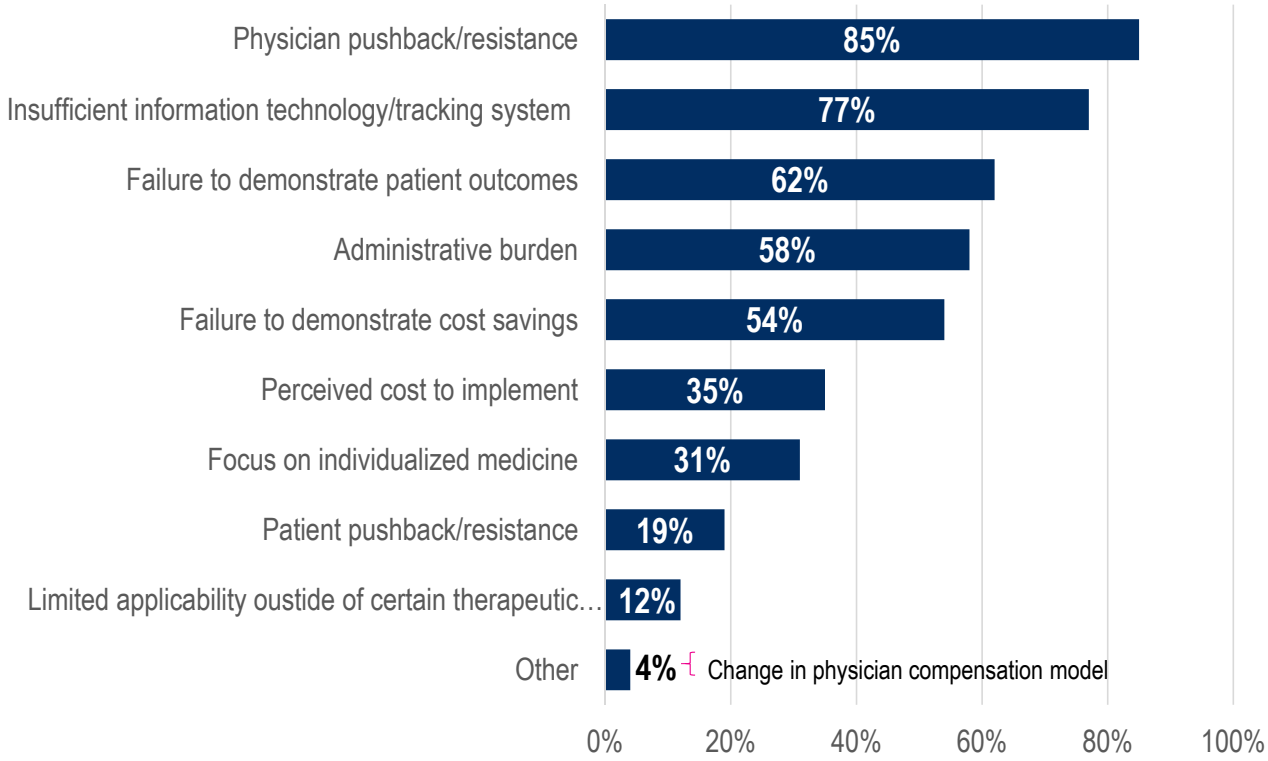
Chawla A, et al. *Am J Manag Care*. 2016;22:53-62.

Potential Barriers to Pathway Expansion

Question:

"What do you see as potential barriers to the expansion or uptake of care pathways?"

Source: Online survey of 26 payers, providers, and vendors who influence or are affected by care pathways



Chawla A, et al. *Am J Manag Care*. 2016;22:53-62.

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

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

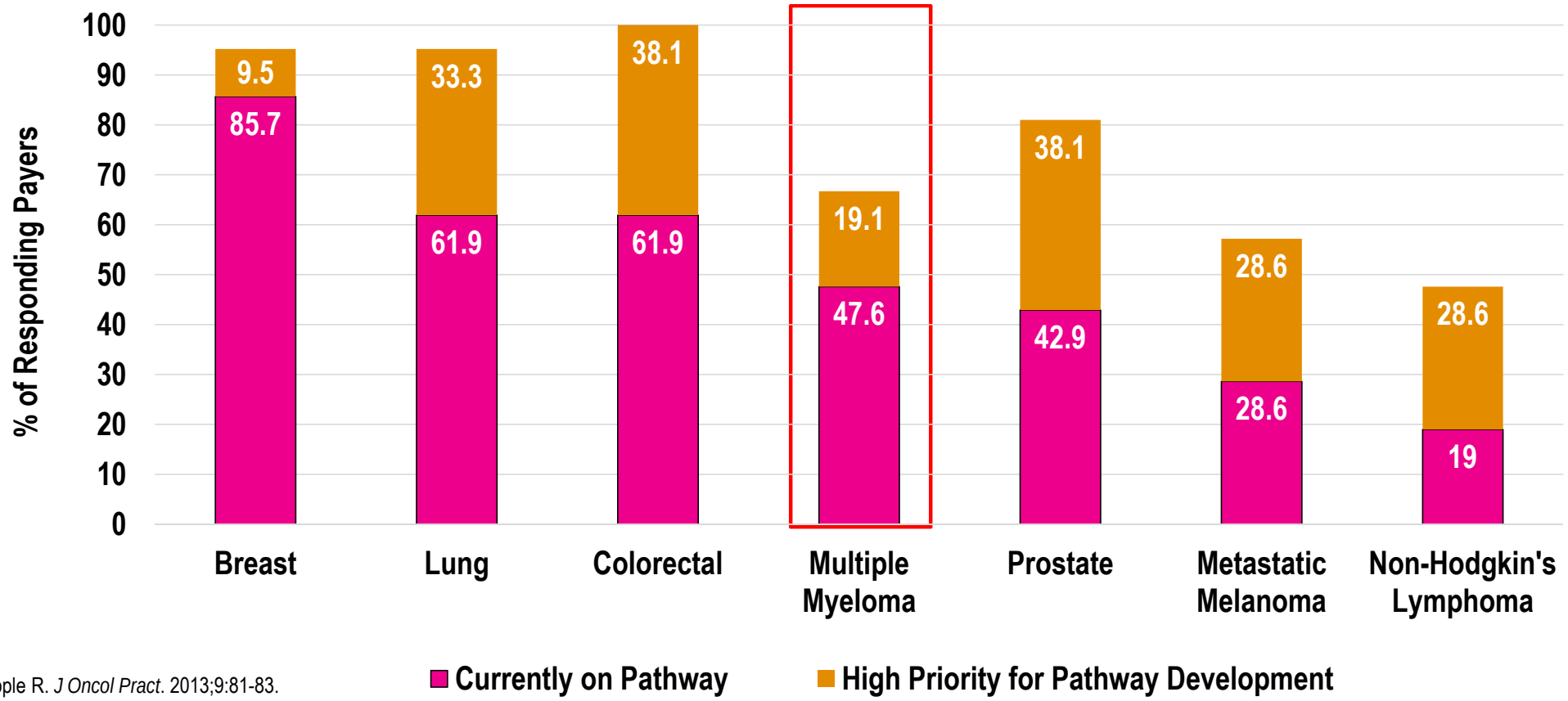
- Multidisciplinary approach with a strong dedicated team
- Physician knowledge about MM (ie, experienced, motivated, significant clinical expertise)
- ***Offering personalized care***
- ***Reviewing and following established guidelines (NCCN, ASCO)***
- Use of current therapies
- Established referral 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. http://www.accc-cancer.org/resources/MultipleMyeloma-Improving-Care-Project.asp. Accessed March 2017.

MM Represents a Key Area for Pathway Development



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.

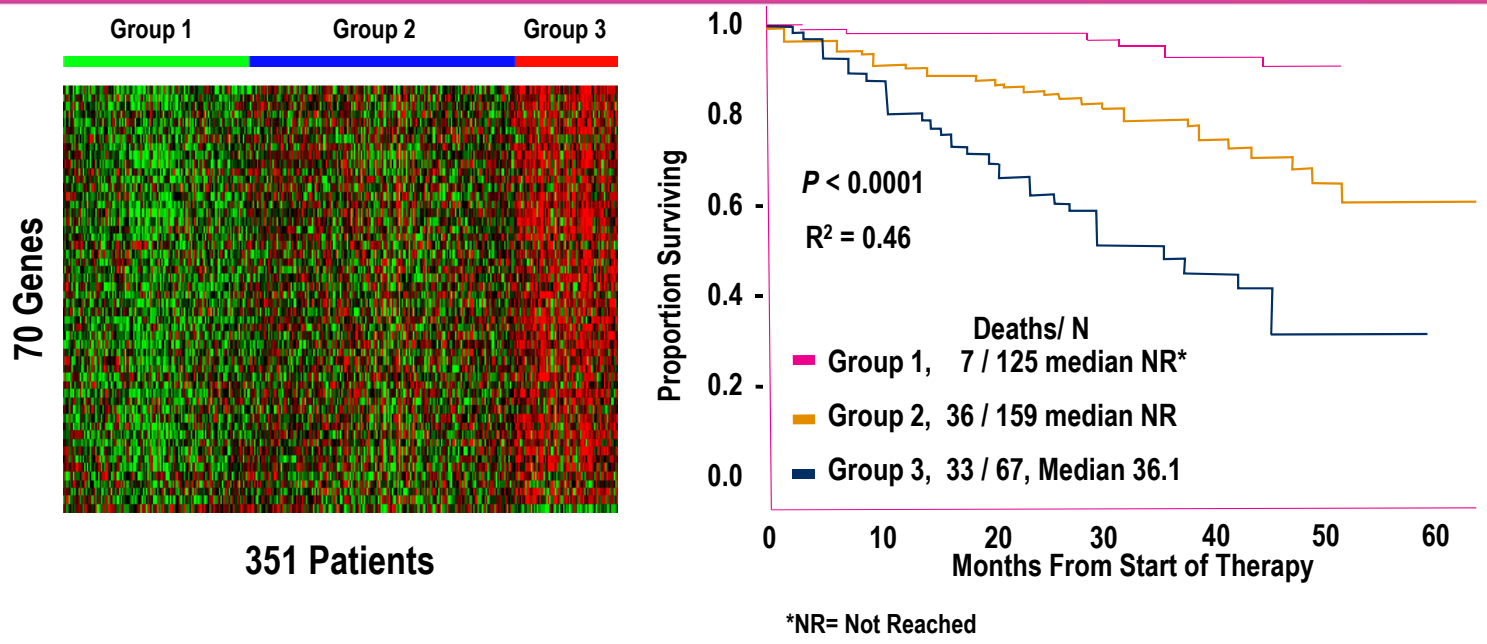
Pathways Programs May Guide Diagnosis, Surveillance, and Supportive Care in Addition to Active Treatment in MM

- 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.

Pathways in MM Must Ultimately Be Capable of Allowing Personalized Treatment Plans



Overall survival of MM patients from the start of therapy based on 70 highly overexpressed or underexpressed genes distinguished 3 groups of patients: good, intermediate, or poor prognosis

Shaughnessy JD et al. *Blood*. 2007;109:2276-2284.

Summary/Conclusion

- Oncology pathway programs are gaining traction among MCOs
  - Especially in areas of high cost and prevalence
  - Their effectiveness in impacting the quality and cost of care is perceived to be at least moderate, and data support decreased health care resource utilization associated with programs
- These initiatives must remain fixed on evidence-based guidelines but fluid enough to allow individualized care for members
- Approximately half of oncologists participate on a voluntary basis, with few programs tying mandatory participation to reimbursement
- As recommended by ASCO, most pathways are developed by MCOs in conjunction with network oncologists or by network oncologists working independent of MCOs
- Future directions include access to pathways (ie, integrated into electronic medical record [EMR]) for real-time for decision support

Innovative Oncology Pharmacy Benefit Models and Specialty Pharmacy Management Services

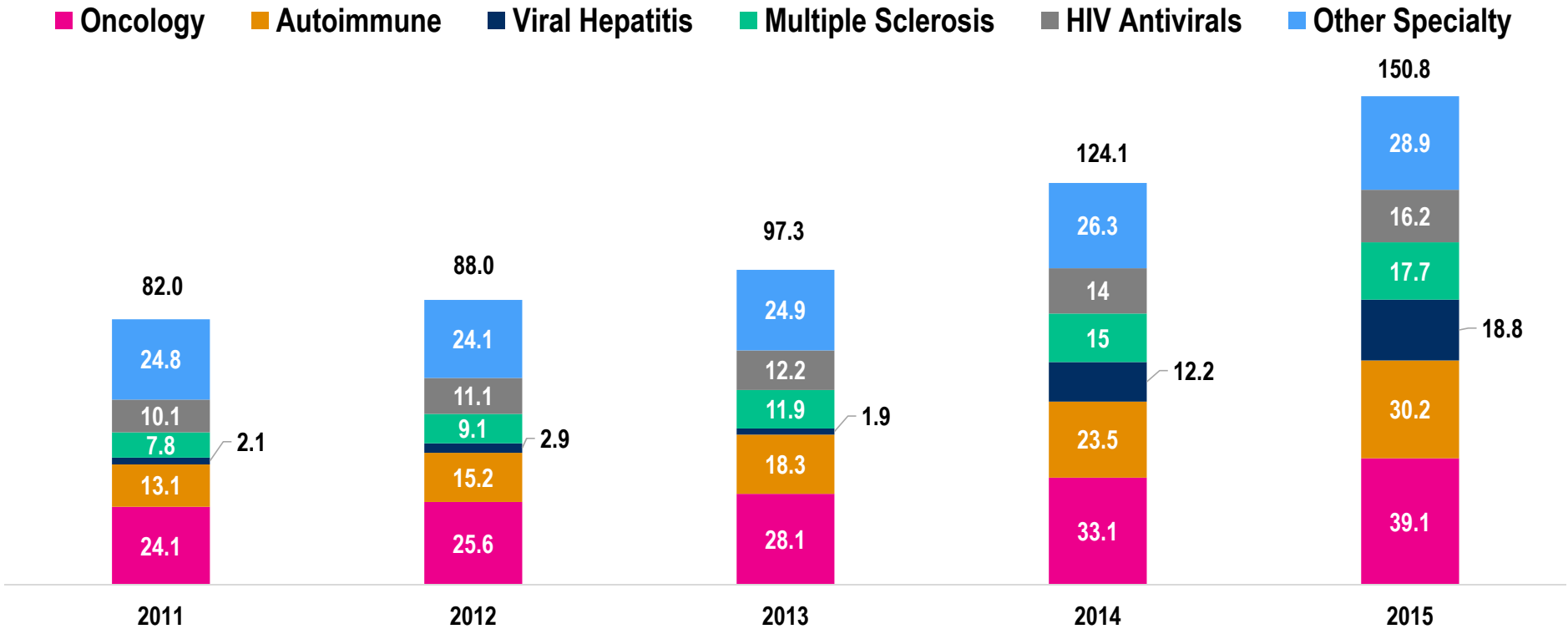
Jeffrey Dunn, PharmD, MBA
Chief Clinical Officer
Senior Vice President
VRx/MagellanRx

Specialty Utilization and Associated Costs are Increasing at an Unprecedented Rate

- Total spending on medicines in the US reached $310 billion in 2015 on an estimated net price basis, up 8.5% from the previous year
- Specialty drug spending reached $121 billion on a net price basis, up more than 15% from 2014
- Spending on specialty medicines has nearly doubled in the past five years, contributing more than two-thirds of overall medicine spending growth between 2010 and 2015
- Increased specialty spending was driven primarily by treatments for hepatitis, autoimmune diseases, and oncology, which accounted for $19.3 billion in incremental spending
- Overall, 2015 saw a 21.5 percent spending increase for specialty medicines to $150.8 billion on an invoice price basis

IMS Health. Medicines Use and Spending in the US. April 2016.

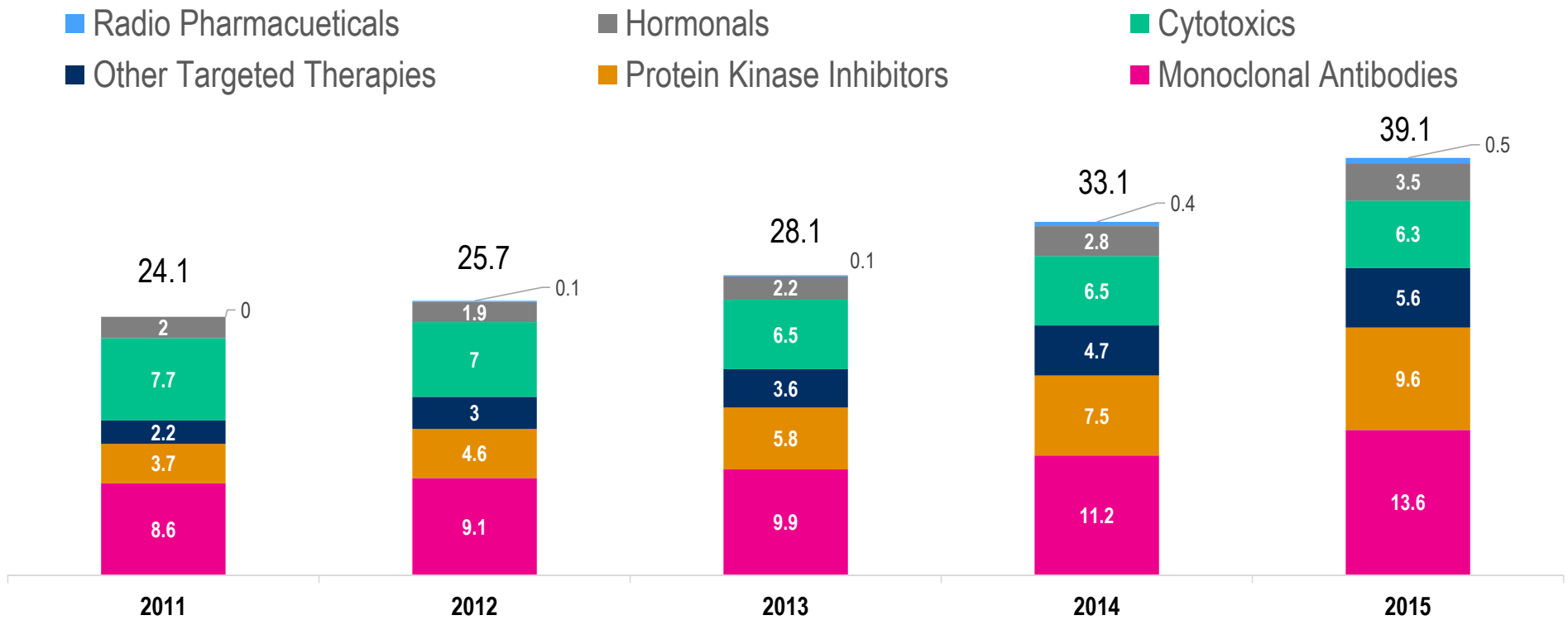
Oncology Remains a Key Driver of the Specialty Drug Trend



Source: IMS Health, National Sales Perspective, Jan. 2016

IMS Health. Medicines Use and Spending in the US. April 2016.

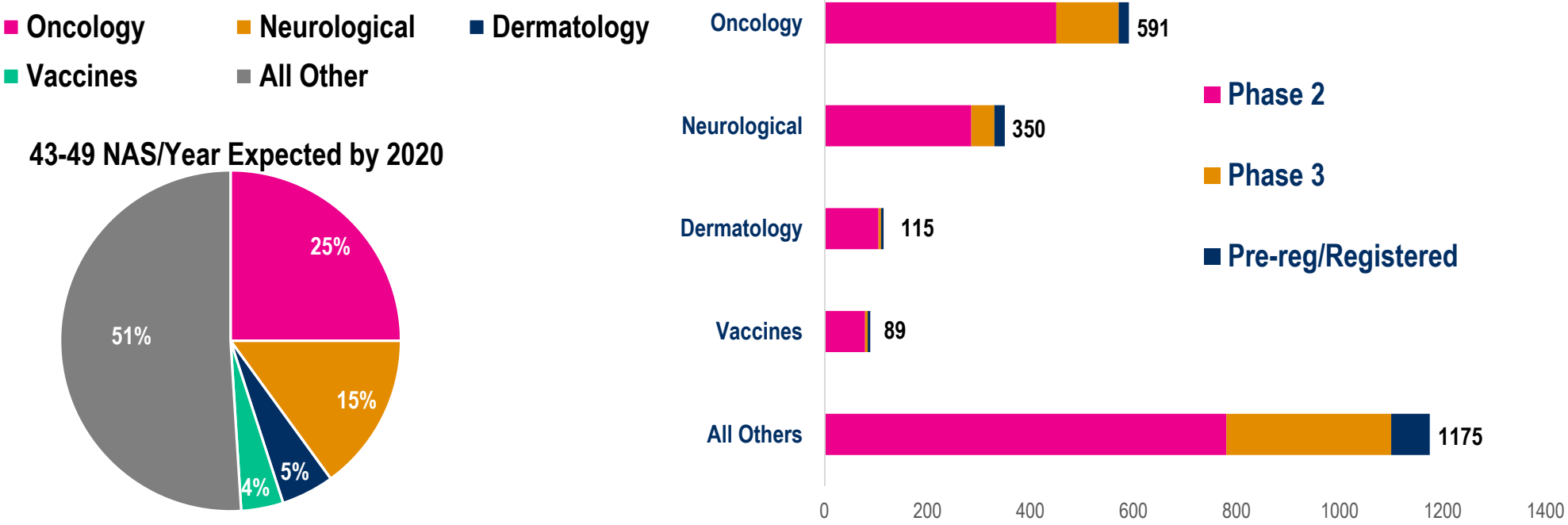
Oncology Spending Increased 18.0% to $39.1Bn in 2015, Driven by Biologics and Targeted Therapeutics



Source: IMS Health, National Sales Perspectives, Jan 2016

IMS Health. Medicines Use and Spending in the US. April 2016.

An Estimated $282Bn of Growth is Anticipated by 2020 from Branded Specialty Products with $91Bn Resulting from New Launches, Largely in Oncology



Source: IMS Health, LifeCycle R&D Focus, Dec 2015, IMS Institute for Healthcare Informatics, Mar 2016

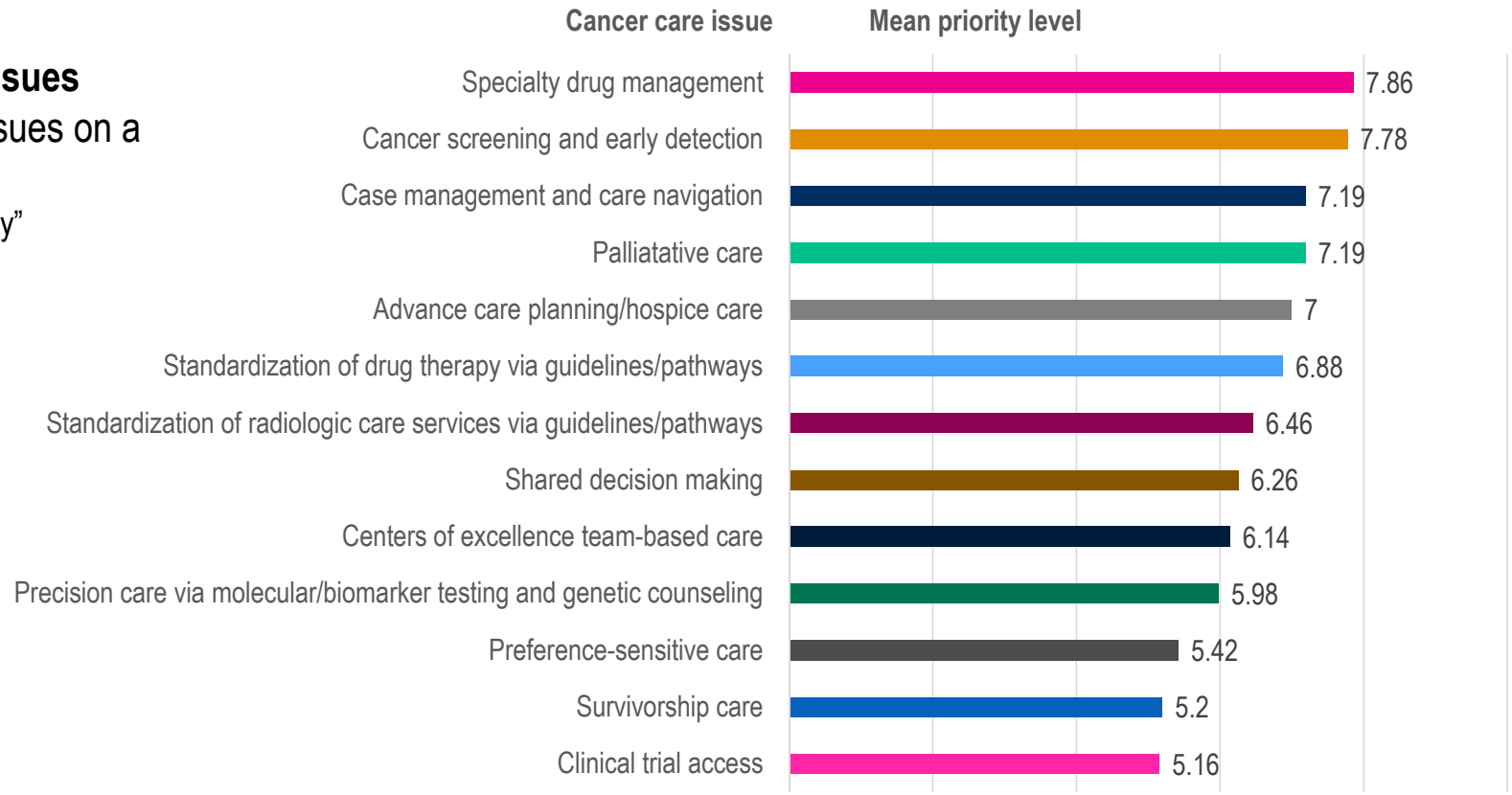
IMS Health. Medicines Use and Spending in the US. April 2016.

Specialty Drug Management Continues to Top the List of Cancer Care Priorities Among Managed Care Stakeholders

Level of Priority MCOs Place on Cancer Care Issues

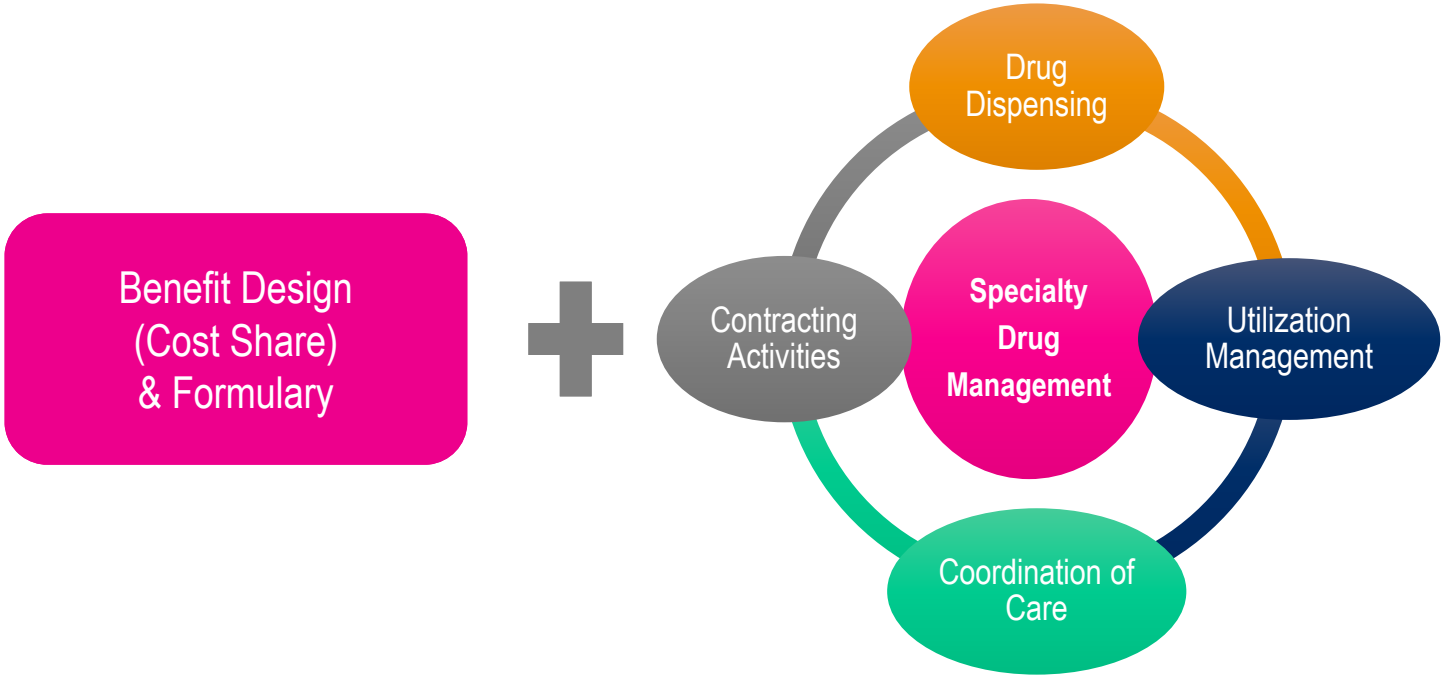
- Respondents rated issues on a 10-point scale:
  - 10 = "very high priority"
  - 1 = "very low priority"

N=100; Pharmacy directors (58.0%)
Medical Directors (23.0%)
Clinical Pharmacists/Clinical Program Managers (13.0%)
Other (6.0%)



2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

Innovative Payer Oncology Models Require Multifaceted Specialty Drug Management Initiatives in Addition to Traditional Approaches Based on Benefit and Formulary Considerations



Current and Future Oncology Formulary and Benefit Design Strategies

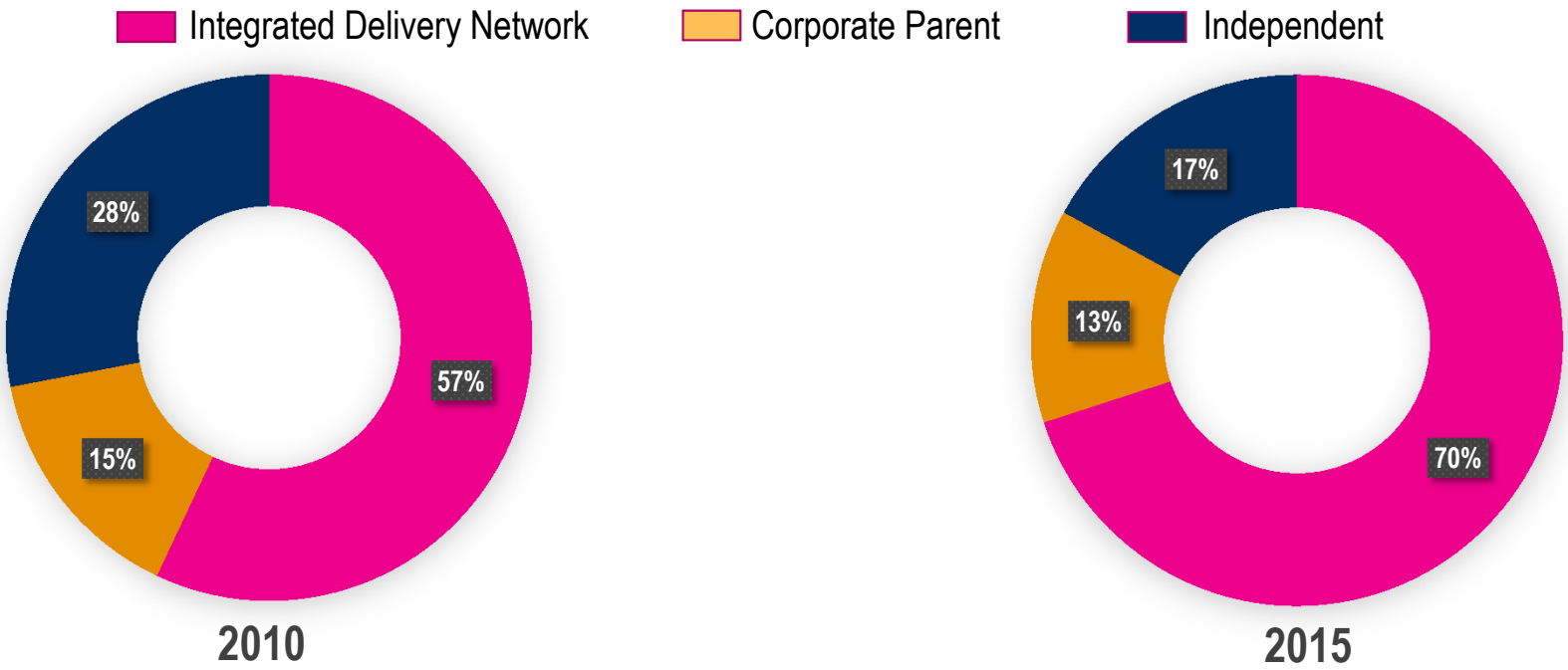
	Currently Implemented	Mean likelihood of implementation over the next 12-18 months*
Introduce testing for preferred and nonpreferred generics	**31.0%**	**3.97**
Introduce a fourth or fifth tier for commercial plans that includes high-cost specialty drugs for cancer	28.0%	**3.74**
Develop a separate specialty drug benefit	26.0%	**3.0**
Equalize cost sharing for drugs covered under both the medical and pharmacy benefits	22.0%	**4.15**
Set a maximum dollar copay for oncology drugs	20.0%	**3.34**
Institute formulary exclusions regarding select products	17.0%	**4.10**
Increase patient OOP maximums	9.0%	**4.26**
Introduce a separate tier for oncology drugs	5.0%	**2.39**
Shift coverage of parenteral oncology drugs from the medical to the pharmacy benefit	3.0%	**3.08**

N=100; Pharmacy directors (58.0%), medical directors (23.0%), clinical pharmacists/clinical program managers (13.0%), other (6.0%)

*8-point scale: 1 = not at all likely, 8 = very likely

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

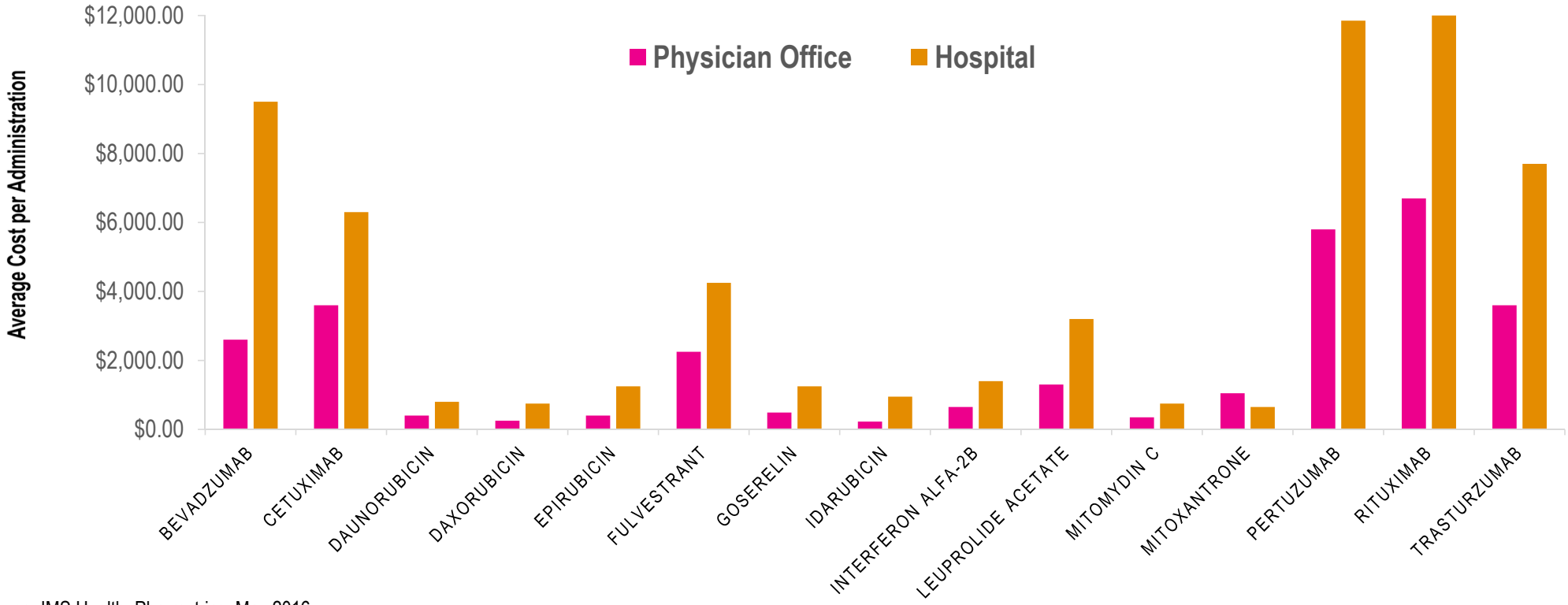
US Oncology Provider Affiliations have Shifted Significantly toward Integrated Delivery Networks



Source: IMS Health, Healthcare Organizational Services; May 2016

IMS Health. Global Oncology Trend Report. June 2016.

This Change Comes with Increased Facility Distribution Where Costs are Invariably Higher, Resulting in Further Attention to Channel Management



Source: IMS Health, Pharmetrics, May 2016

IMS Health. Global Oncology Trend Report. June 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**

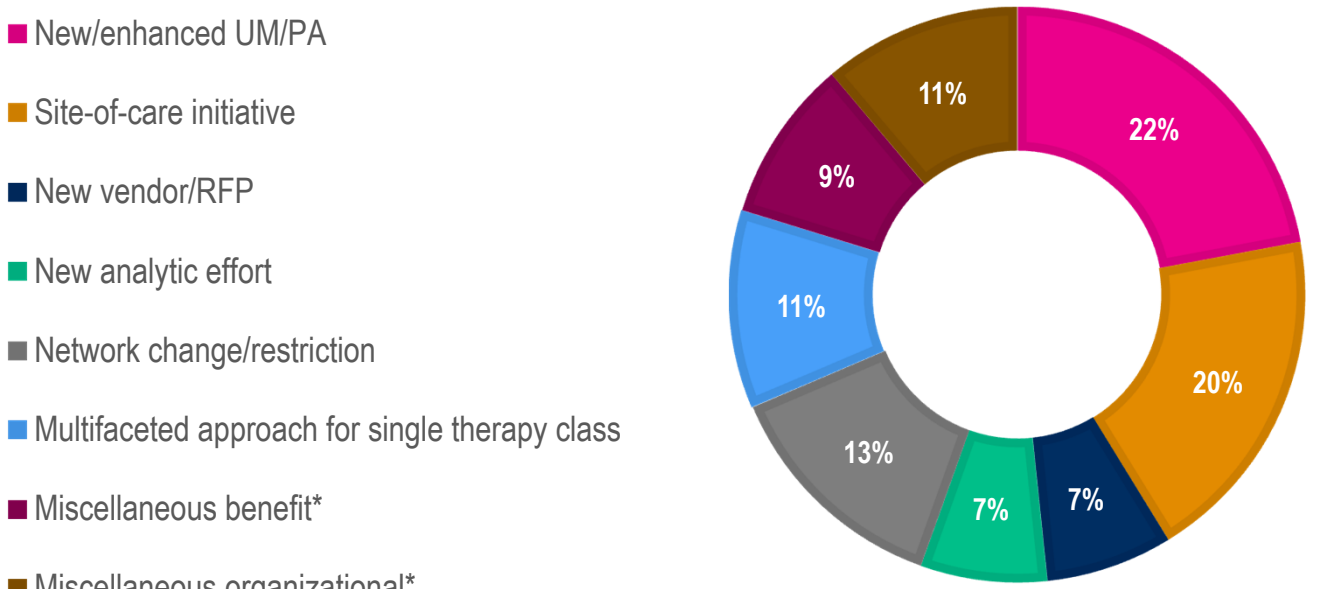
HOPD=hospital outpatient department.

Internal Utilization and Pricing Data.

Utilization/PA and Site-of-care Initiatives Consistently Rank as the Most Important Specialty Drug Management Interventions

What is your single most important specialty drug management activity?

N=58; Pharmacy directors (82%), medical directors (9%), others (9%)



*Miscellaneous benefit initiatives=clinical program, formulary change, increased cost sharing; Miscellaneous organizational initiatives=billing requirement enhancement, coordination initiatives, staff resource increase, pricing.

EMD Serono Specialty Digest, 12th Ed. 2016. http://specialtydigest.emdserono.com/digest.aspx. Accessed March 2017.

Utilization Management via Traditional Prior Authorization Remains the Most Common Intervention

Management strategies	Percentage of MCOs	Effectiveness rating*
Prior authorization protocols	92.0%	3.35
Drug quantity/days' supply limitations	86.0%	2.92
Formulary tiering	77.0%	2.83
Member cost sharing via dollar copays and percent coinsurance	71.0%	2.79
Step therapy	71.0%	3.04
Preferred drug therapy	69.0%	2.94
Benefit design recommendations regarding site-of-care/service	65.0%	2.69
Integration of management across the medical and pharmacy benefits	57.0%	3.04
Claims editing/repricing	56.0%	2.98
Site of care/service management	48.0%	2.73
Fee schedule management to lower drug expenditures	47.0%	3.02
Split-fill (ie, short fill) for oral oncology drugs	39.0%	2.77

N=100; Pharmacy directors (58.0%), medical directors (23.0%), clinical pharmacists/clinical program managers(13.0%), other (6.0%)

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

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

Current and Future Oncology Utilization Management Strategies

	Currently Implemented	Mean likelihood of implementation over the next 12-18 months*
Integrate case management across medical and pharmacy benefits	47.0%	5.11
Offer a care management program for any cancer diagnosis	31.0%	4.76
Require a prior authorization/precertification for molecular/biomarker tests	30.0%	5.04
Restrict drug coverage to favorable molecular/biomarker test results	28.0%	4.72
Integrate oncology drug data across medical and pharmacy benefits to improve UM and clinical care management	25.0%	5.51
Restrict molecular/biomarker test coverage based on evidence supporting their validity and cost-effectiveness	24.0%	5.12
Require evidence of disease progression before approving use of a nonpreferred drug	21.0%	4.71
Institute/increase peer-to-peer consultations with oncologists	11.0%	4.51

N=100; Pharmacy directors (58.0%), medical directors (23.0%), clinical pharmacists/clinical program managers(13.0%), other (6.0%)

***8-point scale: 1 = not at all likely, 8 = very likely**

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

Current and Future Oncology Provider Incentive and Reimbursement Strategies

	Currently Implemented	Mean likelihood of implementation over the next 12-18 months*
Incentivize physicians to use generic drugs	15.0%	4.34
Change oncologist drug reimbursement from ASP-plus to drug acquisition cost plus care management fee	9.0%	3.80
Contract with oncology practices for services using global payments (ie, full capitation)	9.0%	3.74
Contract with oncology practices using a bundled payment or episode-of-care approach	8.0%	4.42
Contract with oncology practices for services using global payments (ie, partial capitation)	7.0%	3.96
Implement and/or expand a clinical pathway incentive payment program	6.0%	3.90
Incentivize physicians to use lower-cost biosimilars indicated in cancer care/supportive care	5.0%	4.43
Contract with oncology medical homes and/or oncology accountable care organizations (ACOs) using a bundled payment or episode-of-care approach	5.0%	4.21
Apply different physician reimbursements for use of preferred oncology drugs	4.0%	4.02

N=100; Pharmacy directors (58.0%), medical directors (23.0%), clinical pharmacists/clinical program managers (13.0%), other (6.0%)

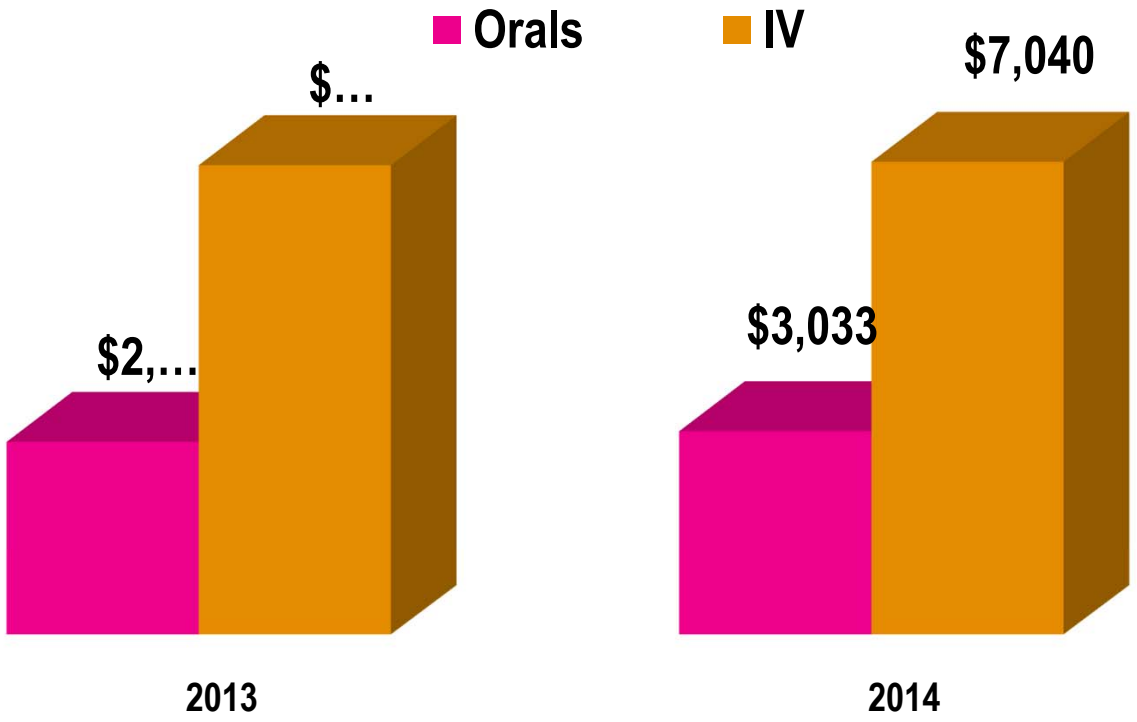
***8-point scale: 1 = not at all likely, 8 = very likely**

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

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

Patient Responsibility for Cost is Rising, but Partially Offset by Coupons and Other Forms of Assistance



Source: IMS Health, Pharmetrics, May 2016

IMS Health. Global Oncology Trend Report. June 2016.

Specialty Care Management

Program

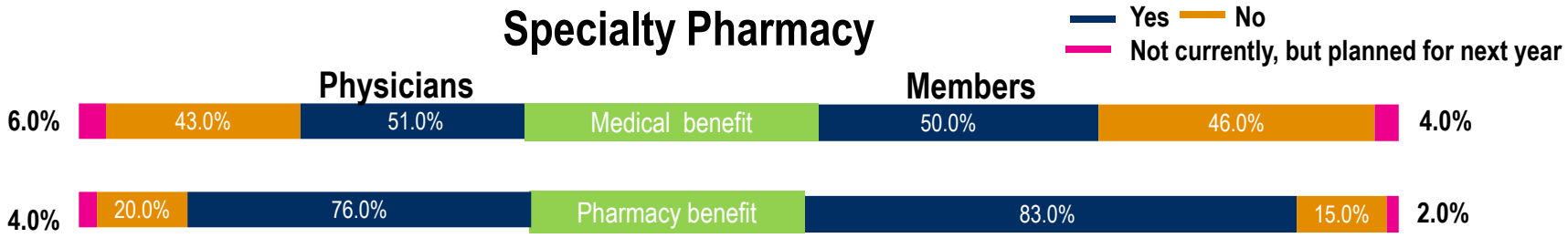
- Specialty Pharmacy MTM
  - Integration with care management
  - Coordinate site of care
  - Ensure appropriate dosing
  - Adherence
  - Education on use
  - Expectation management

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

Payer SP Management Requirements for Patients and Providers Vary According to Benefit and Drug Type

Percentage of MCOs requiring physician and member use of designated SPs (N=100)

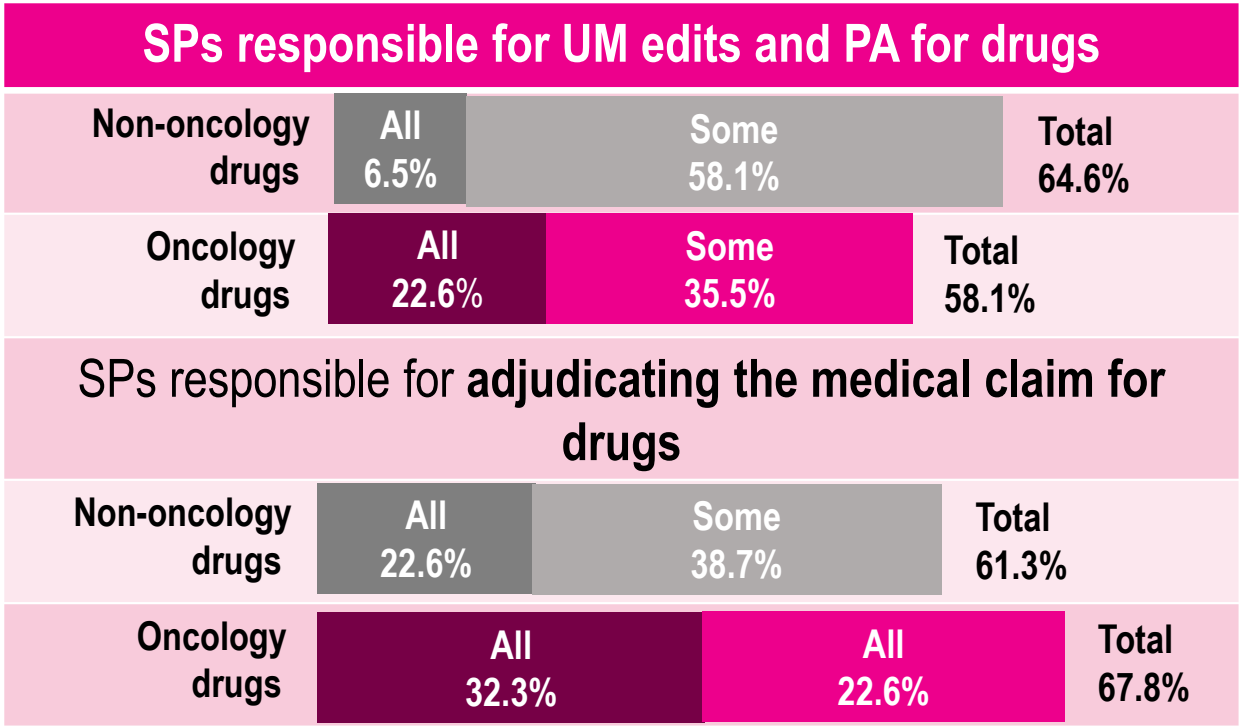


	Oral agents	Self-injectables	In-practice infused/ injected agents	Adjunctive/supportive agents
	Required PHYSICIANS use of SPs for *some* or *all* oncology agents			
Medical benefit (n=57)	50.9%	56.1%	71.9%	68.4%
Pharmacy benefit (n=80)	71.3%	70.0%	53.8%	58.8%
	Required MEMBER use of SPs for *some* or *all* oncology agents			
Medical benefit (n=54)	51.9%	63.0%	72.2%	74.1%
Pharmacy benefit (n=85)	80.0%	82.4%	56.5%	71.8%

N=100; Pharmacy directors (58.0%), medical directors (23.0%), clinical pharmacists/clinical program managers (13.0%), other (6.0%)

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

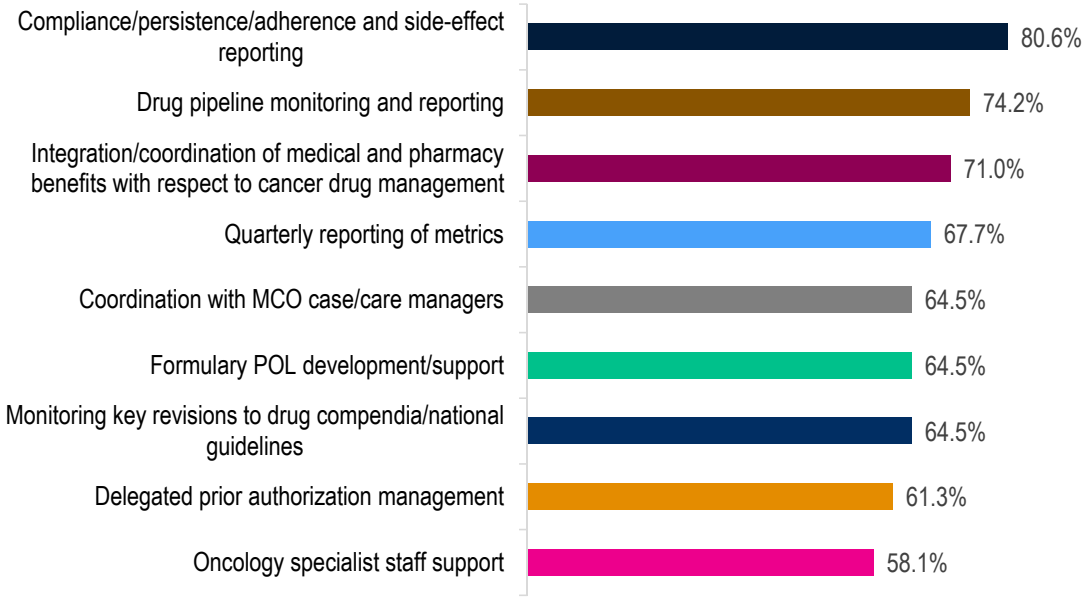
SP Management of UM Edits and PA for Drugs is Heightened in the Oncology Therapeutic Class



N=31; SP professionals; Vice presidents (22.6%), pharmacy directors (16.1%), pharmacy managers (12.9%), clinical staff (12.9%), presidents (12.9%), directors (9.7%), other (12.9%)

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

Specialty Pharmacy Management Involves a Variety of Payer-focused Noncore Services



N=31; SP professionals; Vice presidents (22.6%), pharmacy directors (16.1%), pharmacy managers (12.9%), clinical staff (12.9%), presidents (12.9%), directors (9.7%), other (12.9%)

*"Noncore" services refer to services provided *in addition to* basic/universally provided plan/payer-focused services, such as utilization and costs reporting/trending, adjudication, contracting, compliance monitoring, 24/7 support, and delivery.

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

The Role of Specialty Pharmacy Management is Expected to Increase

Among 31 SP managers 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%	22.6%	77.5%	Oral	0.0%	16.1%	83.9%
3.2%	48.4%	48.4%	Patient self-injectable	6.5%	35.5%	58.1%
12.9%	77.4%	9.7%	In-practice injectable/infused	12.9%	54.8%	32.3%
3.2%	51.6%	45.2%	Adjunctive/supportive	0.0%	41.9%	58.1%

N=31; SP professionals; Vice presidents (22.6%), pharmacy directors (16.1%), pharmacy managers (12.9%), clinical staff (12.9%), presidents (12.9%), directors (9.7%), other (12.9%)

2016 Oncology Trend Report. Available at: http://www.genentech-forum.com/annual-genentech-oncology-trend-report. Accessed March 2017.

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

NCCN Clinical Practice Guideline

Example: Previously Treated MM

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

NCCN Clinical Practice Guidelines: Multiple Myeloma. v3.2017.

Clinical Pathways Program

Plan-derived Criteria

Plan-derived Criteria

Options for First Relapse

Options for Second Relapse

Options for Salvage

Summary

- A precipitous rise in the specialty trend is characterized by increased utilization and associated spending in oncology, which includes a wealth of biologics and targeted agents managed under both the medical and pharmacy benefits in MM and other cancer types
- In addition to long-standing utilization management initiatives, further attention is being given to channel management interventions due to increased facility dispensation, which is invariably associated with higher costs
- Plans need to find a balance between outcomes, cost shifting to patients, and compliance to therapy
- Multifaceted MM utilization management interventions, benefit design strategies, and other key considerations, such as site-of-care, all serve an important role in innovative specialty drug management on the part of payers

Patient Perspective

Yelak Biru

Patient Champion

International Myeloma Foundation, Board Member

ECOG-ACRIN Patient Advocate and Myeloma Core Committee Member

Story in the Making

Diagnosis
- 3.4IgG, λ light chain
- M-Spike
- 4.3 M-spike
- **70% plasma cell**
- **Numerous lytic lesions**
- Stage III Myeloma

Induction therapy
- VAD, CVAD, VAD
- Cyclophosphamide
- Cisplatin, etoposide

Thalidomide

→50 mg ↑100 mg ↓ 50 mg

+/-

dexamethasone 20 mg

cyclophosphamide 50 mg

clarithromycin 500 mg

Bisphosphonates

>24 months

Lenalidomide

→25 mg ↓15 mg

+/-

dexamethasone 20 mg

>24 months

Tests:

Blood Tests – Bone Marrow Biopsies – PET/CTs – MRIs

Supporting Therapies:

Radiation

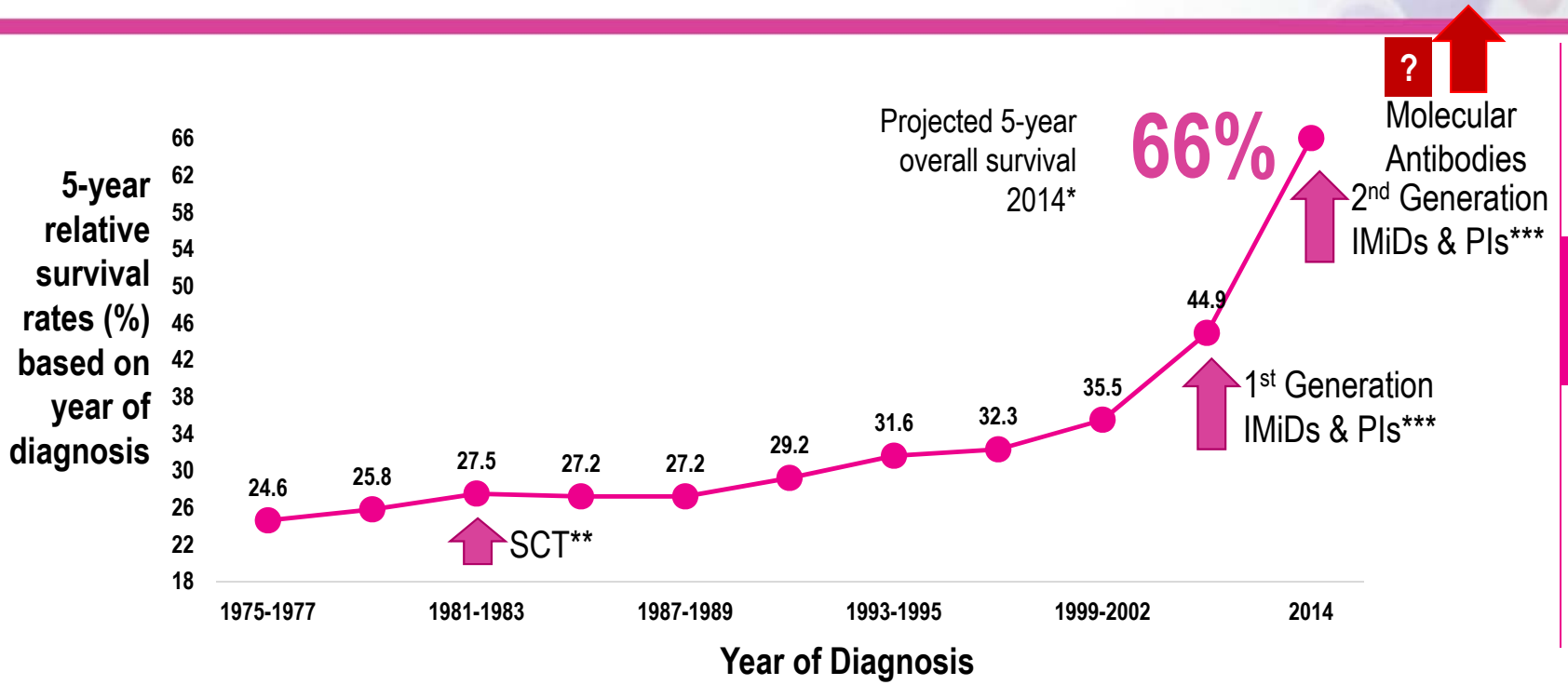
Sub-Q Bortezomib — **Day 1 4 8 11** — **1.3 mg/m2**

Sub-Q Bortezomib — **Day 1 8 15** — **1.3 mg/m2**

Oral Ixazomib — **Day 1 8 15** — **4 mg**

PIs = Proteasome Inhibitors Imids = Immunomodulatory Agents HDAC = Histone deacetylase inhibitors mab = Molecular Antibodies

Relative Survival Rate for Multiple Myeloma



Standard Risk Vs High Risk

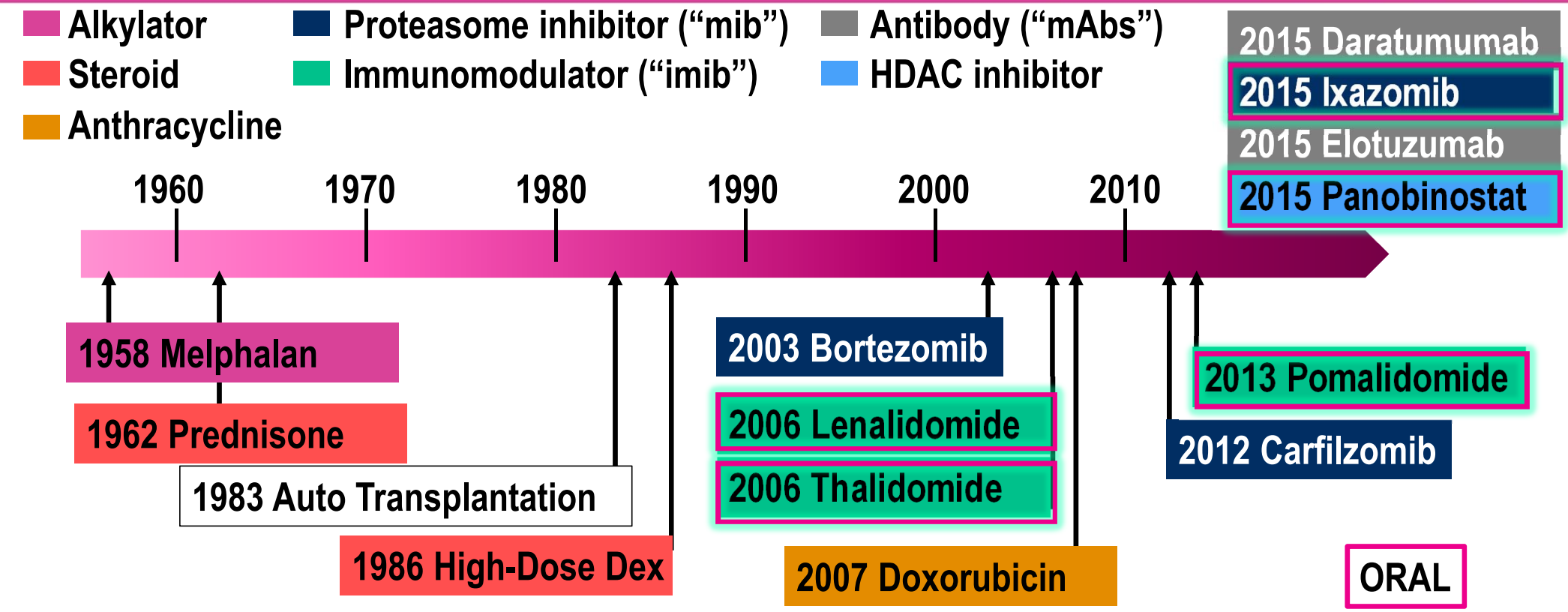
* Based on recent trends in the 5-year relative survival rate, for myeloma patients diagnosed in 2014, the relative overall survival rate may have reached as high as 66%

** SCT = Autologous Stem Cell Transplant; *** IMiD = Immunomodulatory agents, PI = Proteasome Inhibitors

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER Cancer Statistics Review, 1975-2010. Table 18.8: Myeloma, 5-Year Relative and Period Survival (Percent) by Race, Sex, Diagnosis Year and Age. Available at https://seer.cancer.gov/archive/csr/1975_2010/results_merged/sect_18_myeloma.pdf. Accessed February, 2017.

Bergsagel P. Where We Were, Where We Are, Where We Are Going: Progress in Multiple Myeloma. *ASCO 2014 Educational Book*. Available at: http://meetinglibrary.asco.org/content/114000199-144. Accessed February, 2017.

Myeloma Drug Approval History

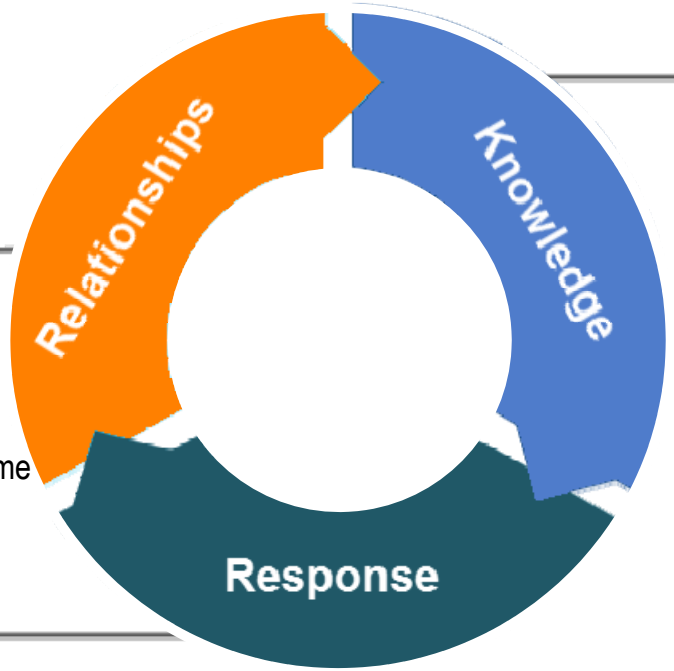


Auto = Autologous; Dex = Dexamethasone

Source: https://www.myeloma.org/multiple-myeloma-drugs

To Live With Myeloma for as Long as Possible With the Greatest Quality of Life Possible

- Taking ownership
- Building a survival team
- Enlisting a myeloma specialist



- Educating myself
- Advocating for others
- Ensuring treatment choices to maximize outcomes and QOL

- Choosing to get up
- Choosing to fight the right battle for me

Maximize Outcomes, Minimize Adverse Events ➔ Don't Close the Door on Future Treatment Options

Hematological

- Thrombocytopenia
- Neutropenia

Non Hematological

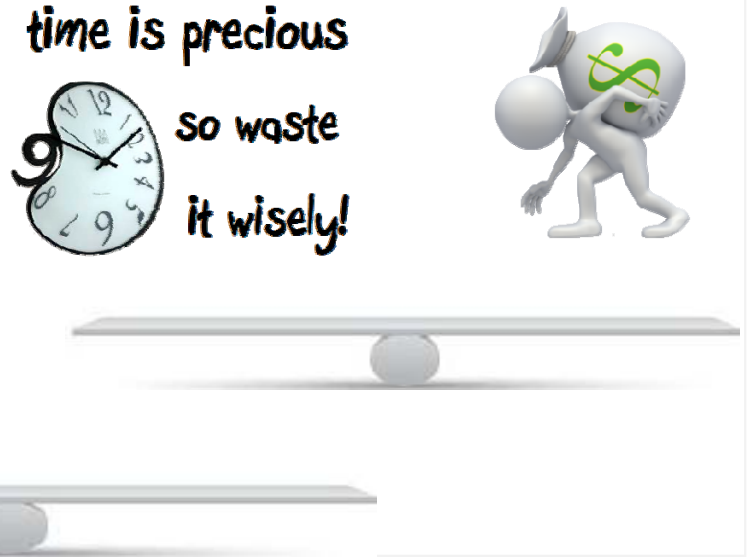
- Peripheral Neuropathy (PN)
- Fatigue
- Sleeplessness
- Rash
- Ecchymosis
- GI effect
- Glaucoma

- Cognitive Disorders
- Diabetics
- Cardiac Event

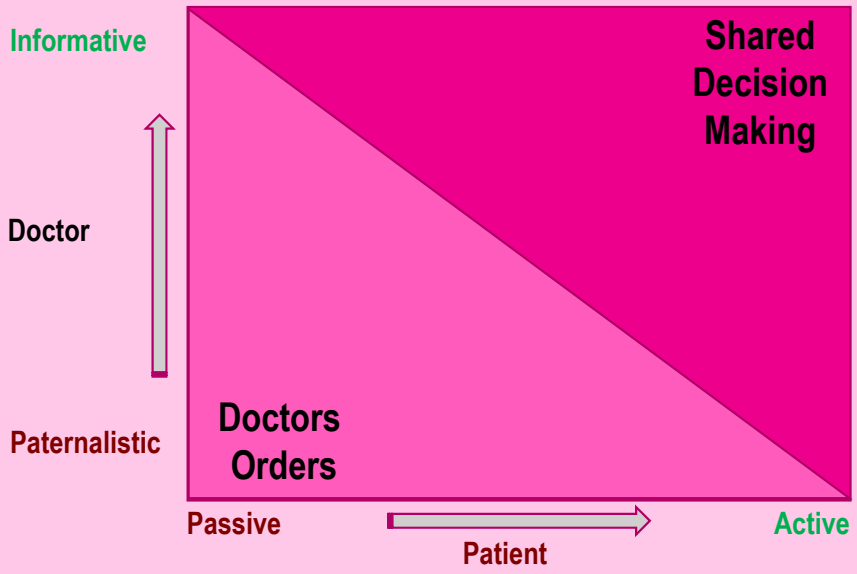
QOL

Does Limiting Current Treatment Alter Future Treatment?

Survival



Shared Decision Making (SDM)



https://www.medicalprotection.org/uk/practice-matters-issue-2/doctor-s-orders-vs-patient-choice

Benefits of shared decision making

- Increases patient involvement in decision making
- Increase patient knowledge and understanding
- More realistic expectations from treatment
- Higher satisfaction with treatment decisions
- In some cases better health outcomes

- Better adherence to treatment
- Improved Quality of Life

Patient Preference & QOL

Family Situation Social Status	Insurance coverage Ability to pay	Work Travel	Proximity to provider Oral vs IV	…

What ~~Myeloma~~ Cancer Patients Want

Maximum effectiveness | Minimal adverse events| Affordability

In essence, a treatment combination that will increase our progression-free or stable disease period and bridge us to the next best treatment already here or around the corner

Maximizing our individually defined quality of life

Reality

Most novel myeloma drugs ~$150,000 per drug per year

Monthly insurance premiums ↑ 27% since 2010

No oral drug coverage parity

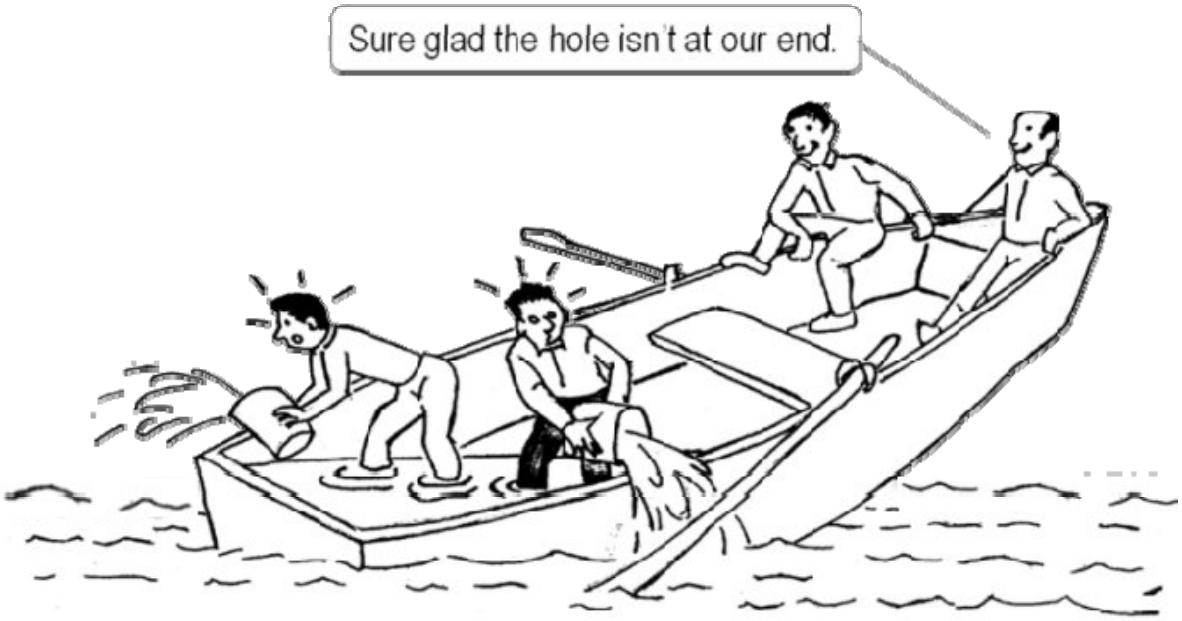
Average Annual Income $55,775

Source: http://kff.org/report-section/ehbs-2015-summary-of-findings/

Value Frameworks and Clinical Treatment Pathways

ASCO Value Framework | MSKCC Abacus NCCN Evidence Block | Anthem CCQP | ICER	→	All value frameworks perceived to be NON PATIENT Centric
Not many patients know about pathways	→	How do you infuse transparency so patients co-create pathways?
4 new drugs in 2015 New lines of Tx approved in 2016 Many more agents and trials under investigation	→	How do you keep value frameworks and oncology care pathways current?
60+ providers ➔ many pathways	→	How can providers stay current with the multiple pathways relevant to all of their patients and their respective providers?
More lines of treatment ➔ more unique patient Drugs, tests, supportive care, etc.		How do you maintain individualization of therapy while reducing treatment variation?

Patients, Payers, Providers, and Other Health Care and Industry Stakeholders Are All in the Same Boat



The Six Ps Need to Collaborate to Improve Outcomes and Manage Costs

- Approval and availability disparity across the country

➔ Survival disparity