MIDWEST
CEPAC
COMPARATIVE EFFECTIVENESS
PUBLIC ADVISORY COUNCIL

Treatment Options for Relapsed or Refractory Multiple Myeloma

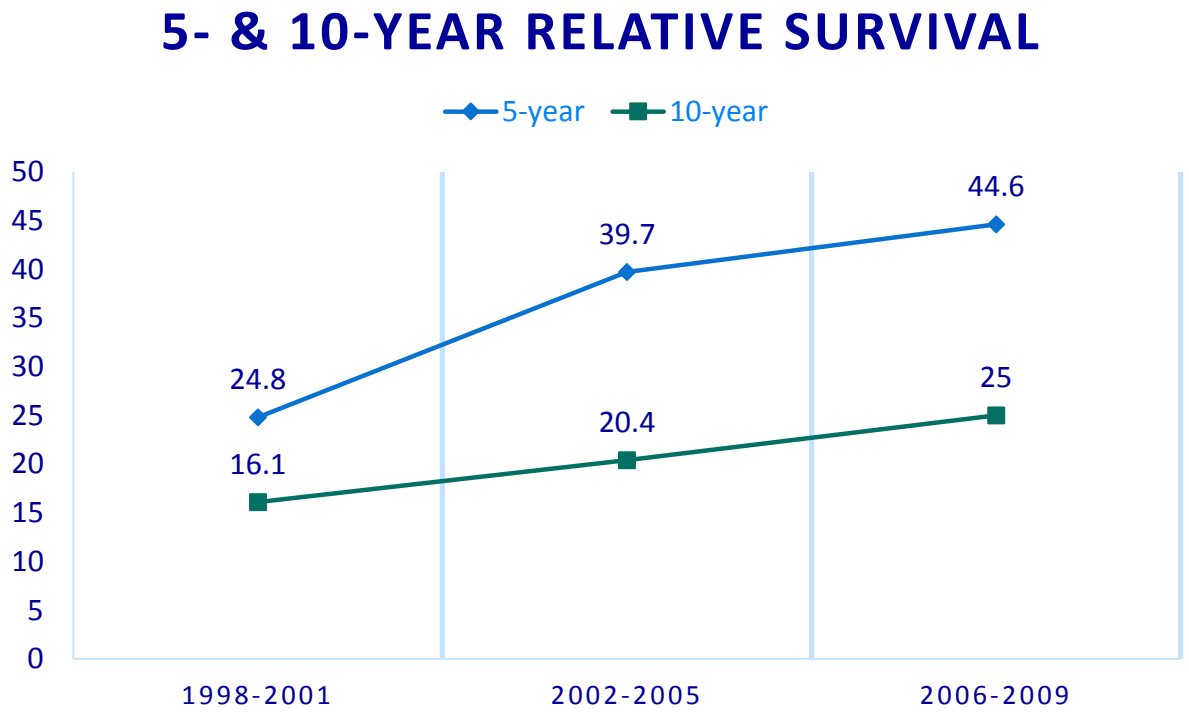
Public Meeting

May 26, 2016

Welcome and Introduction

- Why are we here today?

Multiple myeloma survival improvements



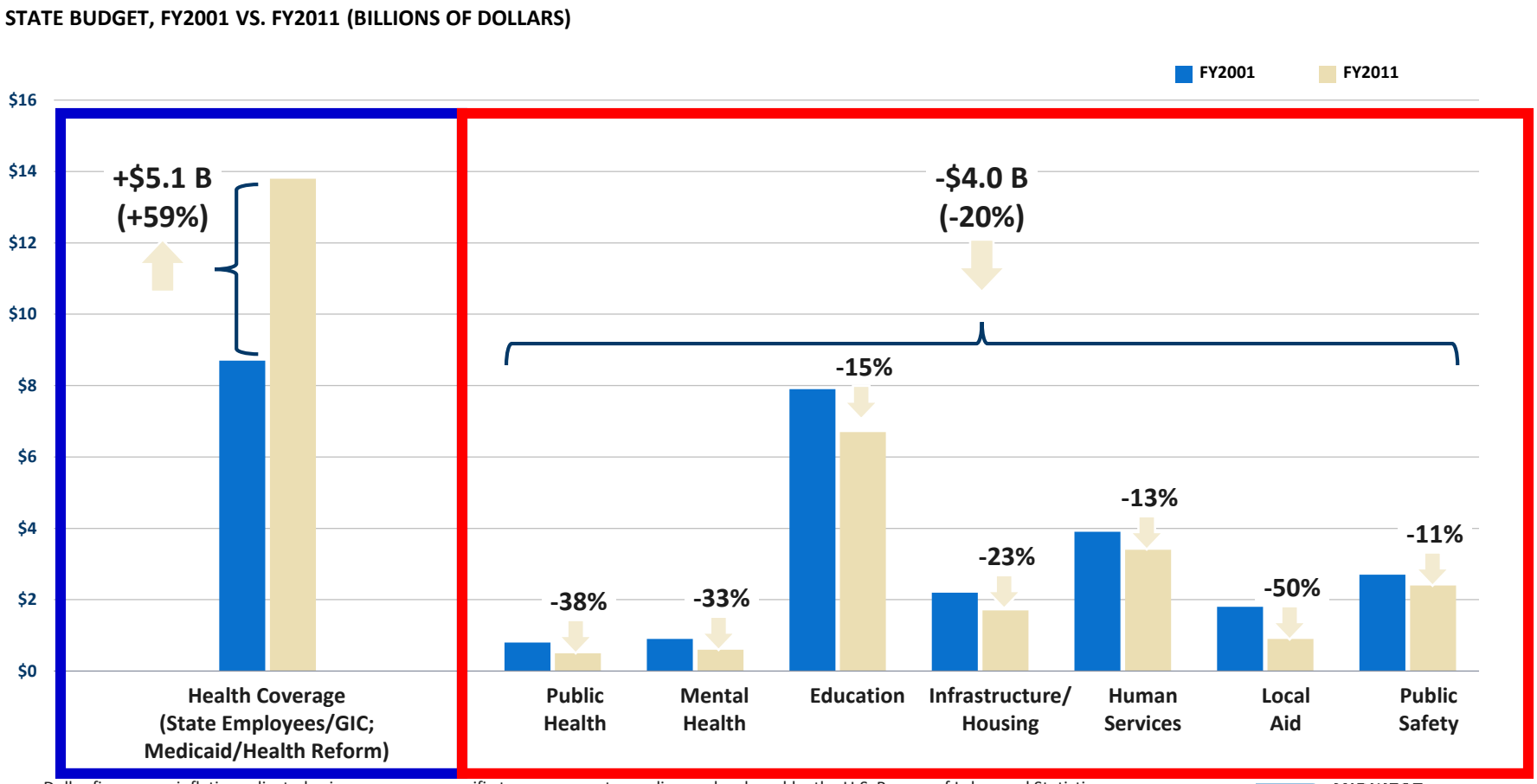
Recent improvement in survival of patients with multiple myeloma: variation by ethnicity Dianne Pulte , Maria Theresa Redaniel , Hermann Brenner , Lina Jansen , Mona Jeffreys Leukemia & Lymphoma Vol. 55, Iss. 5, 2014

Cancer drug costs and patients

- In 2012 the FDA approved 12 cancer drugs; 11 of them cost > $100,000 per year

- For all cancer drugs, average monthly costs doubled in the last decade from $5,000 per month to $10,000 per month

The Increasing Costs of Health Care Squeeze Out Other Public Spending Priorities, Too



NOTE: Dollar figures are inflation adjusted using a measure specific to government spending as developed by the U.S. Bureau of Labor and Statistics.
SOURCE: Massachusetts Budget and Policy Center Budget Browser.

MIDWEST CEPAC
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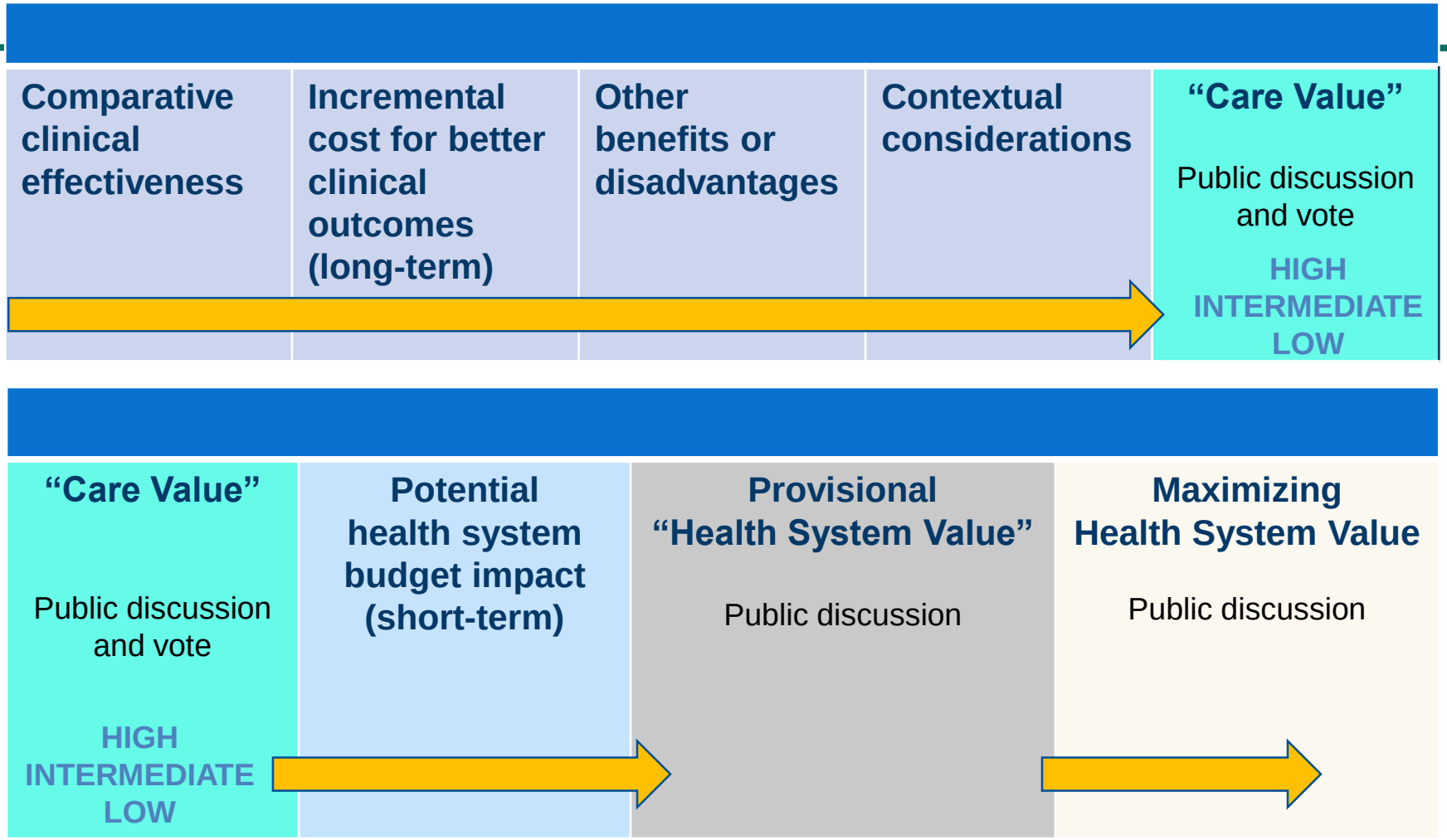
AN ICER PROGRAM

Welcome and Introduction

- Why are we here today?
- What are ICER and the Midwest CEPAC?
- How was the ICER multiple myeloma report developed?

ICER Value Assessment Framework



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- Why are we here today?
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- How was the ICER multiple myeloma report developed?
- What are the goals for the day?

Agenda

- Meeting Convened and Opening Remarks | 10:00 am
- Presentation of the Evidence | 10:15 am
- Public Comments | 11:30 am
- Lunch | 12:30 pm
- Midwest CEPAC Deliberation and Votes | 1:00 pm
- Policy Roundtable Discussion | 2:30 pm
- Meeting Adjourned | 4:15 pm

Evidence Review

Dan Ollendorf, PhD

Chief Scientific Officer

Institute for Clinical and Economic Review

Disclosures

I have no conflicts of interest.

Key review team members:

Elizabeth Russo, MD

Patricia Synnott, MS, MA

Topic in context

- Nearly 100,000 Americans are currently living with multiple myeloma (MM) in the U.S.; 75% > age 70
- No cure for MM; multiple rounds of remission and subsequent relapse
- Heterogeneous disease: prognosis depends on underlying genetic abnormalities, comorbid conditions, and response to initial treatment
- Prognosis greatly improved since introduction of new treatment options over past decade
- Variation in clinical practice/philosophy (“marathon vs. sprint”)
- Cost per treatment course in patients with relapsed/refractory MM: ~$75,000 - $250,000 and higher

Purpose of review

- To assess comparative clinical effectiveness and comparative value of newer treatment regimens for relapsed and/or refractory MM
- Focus on head-to-head comparative data (as available) as well as indirect comparisons of the newer regimens
  - Use established techniques of “network” meta-analysis for indirect comparisons
- Where available, used subgroup data to distinguish performance for 2nd- and 3rd-line or later use

Review scope (PICOTS)

- **Population:** adults 18 years or older with relapsed and/or refractory MM
- **Interventions:**
  - Carfilzomib + lenalidomide + dexamethasone **(CFZ+LEN+DEX)**
  - Daratumumab monotherapy **(DARA)**
  - Elotuzumab + lenalidomide + dexamethasone **(ELO+LEN+DEX)**
  - Ixazomib + lenalidomide + dexamethasone **(IX+LEN+DEX)**
  - Panobinostat + bortezomib + dexamethasone **(PAN+BOR+DEX)**
  - Pomalidomide with low-dose dexamethasone **(POM+LoDEX)**
- **Comparators:** LEN+DEX, BOR+DEX, or HiDEX

Review scope (PICOTS), *continued*

- **Outcomes**:
  - Overall survival
  - Progression-free survival
  - Overall response rate
  - Patient-reported outcomes (e.g., QoL, effects of oral vs. IV administration)
  - Adverse events
- **Timing/settings**: no limitations
- **Study types**: Phase II/III RCTs; single-arm studies if no comparative data available for regimen of interest

Overall evidence quality

- **6 key studies**: 5 Phase III trials, 1 Phase II single-arm study
- 2 placebo-controlled trials were rated as **good quality** (IX+LEN+DEX, PAN+BOR+DEX)
- 3 open-label randomized studies were rated as **fair quality** (CFZ+LEN+DEX, ELO+LEN+DEX, and POM+LoDEX)
- 1 single-arm, Phase II trial was rated **poor quality** due to the lack of comparator (DARA)

Patient and study characteristics

- Median age across studies: ~63-66
- CFZ, ELO, IX, and PAN
  - Similar inclusion criteria: adults with measurable relapsed/refractory MM, 1-3 prior therapies
  - Median 1-2 prior regimens
  - 6-21% prior LEN
  - Comparable ECOG performance status, ISS stage, receipt of prior stem cell transplant
- DARA and POM - *more advanced levels of disease*
  - Inclusion criteria: refractory to previous treatment, 2-3 prior therapies that included a PI and IMiD
  - ≥75% refractory to both LEN and BOR
  - Median of 5 previous treatments

CFZ+LEN+DEX (vs. LEN+DEX)

- Overall survival (OS): Interim analysis; hazard ratio (HR) for progression 0.79 (p=0.04)
- Progression-free survival (PFS): median 26.3 vs. 17.6 months, HR 0.69 (p=0.0001)
  - Comparable effects when stratified by 2nd- vs. 3rd- or later-line use
- Quality of life: Statistically- and clinically-significant improvements compared with LEN+DEX over 18 cycles of treatment (open-label RCT)
- Harms: rates of treatment-related death, discontinuation due to AEs, and rates of grade ≥3 hematologic AEs similar to those of most other regimens
  - Cardiac toxicity observed with CFZ (e.g., ischemic heart disease, cardiac failure)

DARA (no comparator)

- NOTE: FDA-approved for use as 4th-or later-line therapy
- Overall survival (OS): median 17.5 months
- Progression-free survival (PFS): median 3.7 months
  - No subgroup analyses of either OS or PFS by prior lines of therapy
- Quality of life: No data presented
- Harms: no treatment-related deaths, somewhat lower rates of discontinuation due to AEs and rates of some grade ≥3 hematologic AEs (but no comparator)

ELO+LEN+DEX (vs. LEN+DEX)

- Overall survival (OS): Interim analysis; median 43.7 vs. 39.6 months, HR 0.77 (p=0.03)
- Progression-free survival (PFS): median 19.4 vs. 14.9 months, HR 0.70 (p<0.001)
  - Comparable effects when stratified by 2nd- vs. 3rd- or later-line use
- Quality of life: No differences between treatment groups
- Harms: rates of treatment-related death, discontinuation due to AEs, and rates of grade ≥3 hematologic AEs similar to those of most other regimens

IX+LEN+DEX (vs. LEN+DEX)

- Overall survival (OS): Interim analysis—no difference between groups (follow-up for final analysis ongoing)
- Progression-free survival (PFS): median 20.6 vs. 14.7 months, HR 0.74 (p=0.012)
  - Observed difference in performance for 2nd-line (HR 0.88) vs. 3rd- or later-line (HR 0.58); no a priori explanation for this difference
- Quality of life: No differences between treatment groups
- Harms: treatment-related death not reported; rates of discontinuation due to AEs, and rates of grade ≥3 hematologic AEs similar to those of most other regimens

PAN+BOR+DEX (vs. BOR+DEX)

- NOTE: FDA Advisory Committee cited concerns with quality of evidence in overall trial population (e.g., death not due to progressive disease, d/c due to AEs)
  - Approval granted in subgroup with prior receipt of BOR and and IMiD (e.g., LEN); data presented below
- Overall survival (OS): median 25.5 vs. 19.5 months (neither HR nor p-value reported)
- Progression-free survival (PFS): median 12.5 vs. 4.7 months, HR 0.47 (p=0.0003)
  - Approved subgroup is 3rd- or later-line use by definition
- Quality of life: No data presented
- Harms: higher rates of grade ≥3 diarrhea, peripheral neuropathy, fatigue, thrombocytopenia and discontinuation due to AEs vs. other regimens

POM+LoDEX (vs. HiDEX)

- NOTE: FDA-approved for use as 3rd- or later-line therapy in patients who have received LEN and a PI (e.g., BOR) and were refractory to most recent course of treatment
- Overall survival (OS): median 12.7 vs. 8.1 months, HR 0.74 (p=0.03)
- Progression-free survival (PFS): median 3.6 vs. 1.8 months, HR 0.45 (p<0.001)
  - Approved subgroup is 3rd- or later-line use by definition
- Quality of life: Statistically-significant improvements in 7 of 8 QoL domains (open-label RCT)
- Harms: rates of treatment-related death, discontinuation due to AEs, and rates of grade ≥3 hematologic AEs (except neutropenia) similar to those of most other regimens
  - Black-box warning for POM and other IMiDs re: thromboembolism

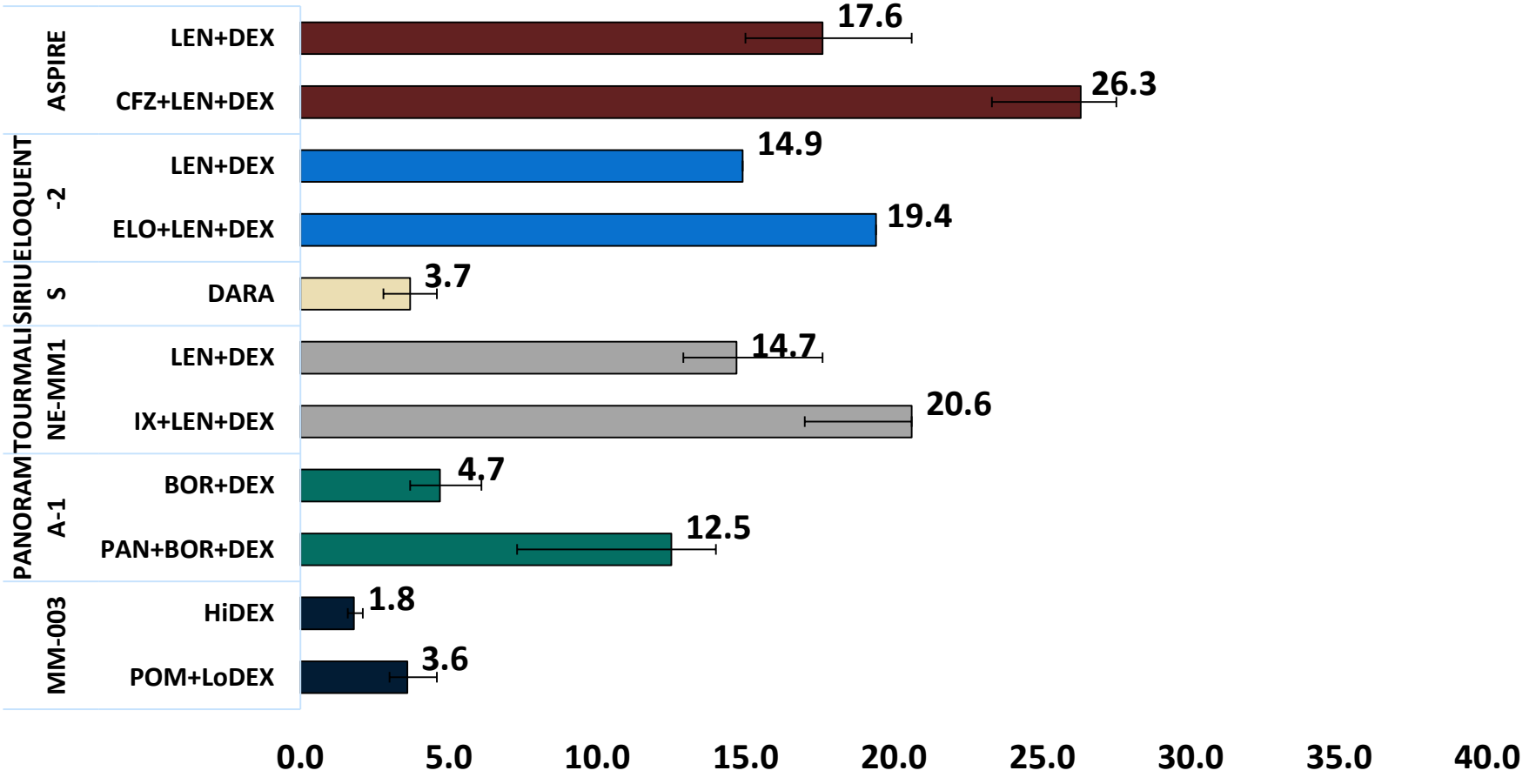
Controversies and uncertainties

- Final OS data demonstrating statistically significant improvement not yet available (with exception of POM+LoDEX); correlation of PFS with OS in relapsed/refractory MM not consistent
- Uncertainty about PAN+BOR+DEX: missing and censored data, drug-related toxicity, approval in subgroup of PANORAMA-1 trial
- Comparative evidence not yet available for DARA; uncertainty about role in earlier lines of therapy
- POM+LoDEX: HiDEX alone may no longer serve as a relevant comparator for salvage therapy
- No head-to-head data; limited and nonstandardized subgroup data

Overall summary

- **CFZ/ELO/IX** + **LEN+DEX**: Moderate certainty of incremental or better net health benefit for both 2nd- and 3rd-line or subsequent therapy
- **PAN+BOR+DEX**: Insufficient evidence for 2nd-line therapy; promising but inconclusive for 3rd-line and subsequent therapy
- **POM+LoDEX**: Insufficient evidence for 2nd-line therapy; promising but inconclusive for 3rd-line and subsequent therapy
- **DARA**: Insufficient evidence to determine net health benefit for 2nd- or 3rd- line and subsequent setting

Progression-free survival (PFS), months



Outcome summary

- OS: Final data indicating benefit for POM; interim data favoring CFZ and ELO
- PFS:
  - No significant differences from results of indirect comparisons (network meta-analyses)
  - Findings generally comparable when stratified by 2nd- vs. 3rd- or later-line use
- Overall response rate: findings generally followed those of PFS
- QoL: significant findings in favor of CFZ and POM from open-label trials
- Harms: similar rates of treatment-related deaths, discontinuation due to AEs, and grade ≥3 AEs across all regimens except for PAN+BOR+DEX

Public comments received

- Heterogeneous disease process and patient population—not a single disease, treatment must be personalized
- Premature timing of evidence review given emerging nature of therapies
- Need to incorporate patient experience as well as patient-centric valuation of important outcomes and costs
- Doublet comparator therapy outdated
- Analyses do not recognize substantial heterogeneity of trial populations

Cost Effectiveness Analysis

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Assistant Professor

Pharmaceutical Outcomes Research and Policy Program

University of Washington

Disclosures

Financial support provided to the University of Washington from the Institute for Clinical and Economic Review (ICER).

Key review team members:

Greg Guzauskas, MSPH, PhD

Rick Chapman, PhD, MS

Dan Ollendorf, PhD

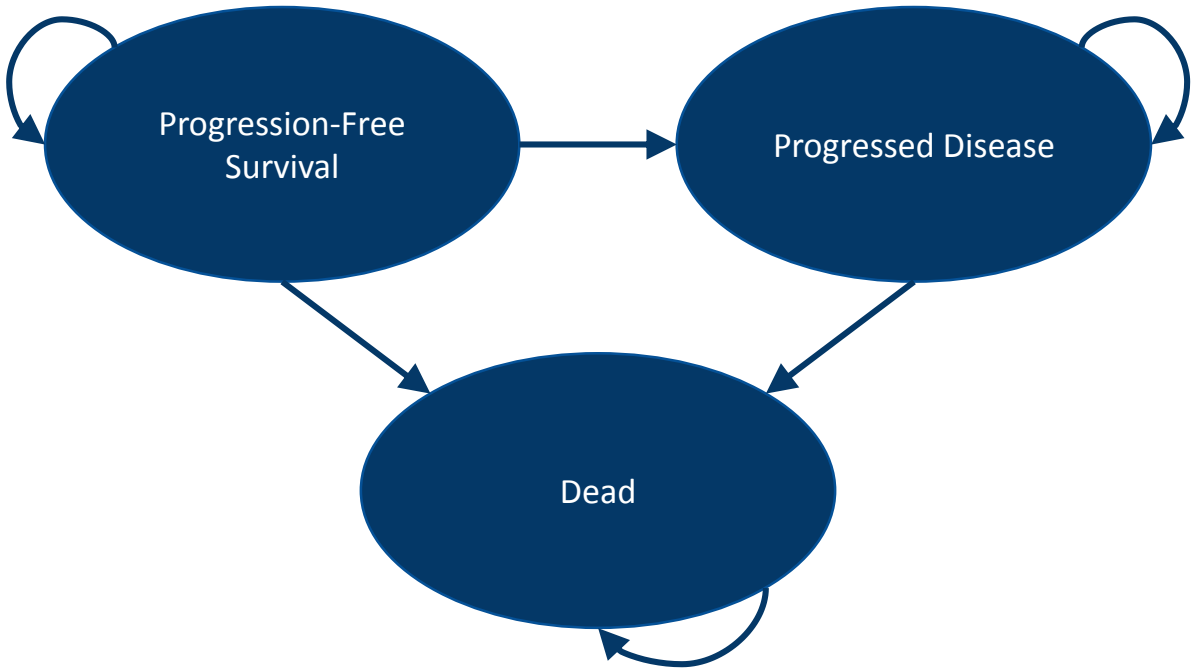
Objective

- Compare the cost-effectiveness of 2nd- and 3rd-line treatment strategies for relapsed and/or refractory multiple myeloma
- Baseline comparator = LEN+DEX (BOR+DEX for PAN)
- NOTE: POM+LoDEX and DARA not included in analysis due to advanced nature of disease vs. other studied populations

Overall approach

- Survival estimated using results of network meta-analysis conducted for evidence review and published estimate of relationship of PFS to OS in MM patients:
  - 2.5-month increase in OS for every month of PFS
- Survival was weighted by health state utilities to adjust for quality-of-life impacts
- The model included grade 3/4 adverse events occurring in at least 5% of patients in at least one of the included regimens
- Costs of disease progression based on estimates of the mix of subsequent treatments as well as best supportive care

Model structure



Key model assumptions

- Relative effects of treatment on PFS assumed to be the same for 2nd- and 3rd-line treatment
- Trial populations were sufficiently comparable for inclusion in model
- Hazard of progression assumed to be proportional for regimens of interest
- No vial sharing for infused/injected medications occurs between patients
- Treatment received after progression uniform for all regimens

Costs

- Drugs
  - Based on wholesale acquisition costs, dosing schedule, dosing intensity for each drug in regimen, weight/body surface area
  - If a regimen is treat-to-progression, the treatment utilization and cost were applied across all time spent in the PFS health state
  - If a finite number of cycles is used, patients may remain in the PFS state without active treatment
- Physician administration of in-office drugs
- Adverse events
- Supportive care and post-progression

Utilities

- Stratified for 2nd- and 3rd-line treatment
- Higher utilities for progression-free (e.g., 0.82-0.84 for 2nd-line, depending on being on or off treatment) than progressed (e.g., 0.65) states
- A reduction in utility assumed for any grade ≥3 adverse event

Model outcomes

- By intervention:
  - Quality adjusted life expectancy
  - Life expectancy
  - Mean time in the progression-free and post-progression health states
- Pairwise comparisons:
  - Incremental cost-effectiveness ratios for each intervention versus the standard comparators

Results by regimen: 2nd line

Regimen	Costs	QALYs	Cost/QALY gained (vs. LEN+DEX)
LEN+DEX	$284,400	2.59	--
CFZ+LEN+DEX	$457,350	3.45	$199,982
ELO+LEN+DEX	$638,144	3.41	$427,607
IX+LEN+DEX	$582,428	3.27	$433,794

Results by regimen: 3rd line

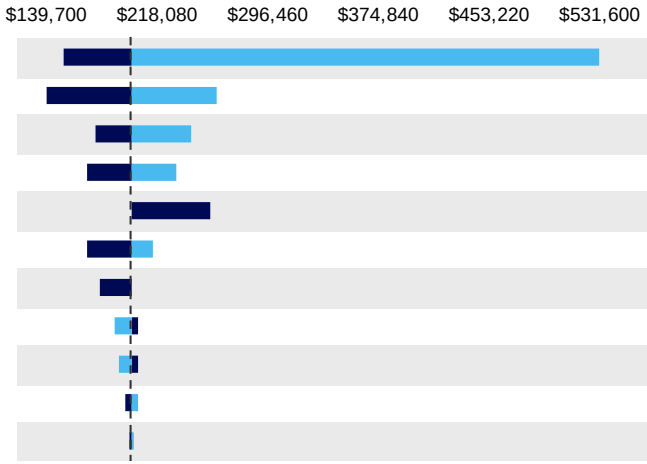
Regimen	Costs	QALYs	Cost/QALY gained (vs. LEN+DEX)
LEN+DEX	$258,609	2.04	--
CFZ+LEN+DEX	$427,027	2.74	$238,560
ELO+LEN+DEX	$583,531	2.71	$481,244
IX+LEN+DEX	$530,228	2.60	$484,582

Results by regimen: 3rd line

- PAN+BOR+DEX:
  - Costs: $196,021
  - QALYs: 3.46
  - Cost/QALY gained vs. BOR+DEX: $10,230
- Results should be interpreted with caution given concerns with clinical data

Sensitivity analysis “tornado” example

CFZ+LEN+DEX vs. LEN+DEX, 2nd-line



Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, CL+Dex	0.53	0.91	$151,437	$531,598	$380,161
Dose Intensity: CL+Dex Lenalidomide	64.4%	96.6%	$139,764	$260,200	$120,436
Felix Hazard Ratio	0.31	0.58	$174,454	$243,041	$68,588
Cost: Carfilzomib 60 mg vial	$1,489.56	$2,234.34	$168,677	$231,288	$62,611
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$255,562	$199,982	$55,580
Dose Intensity: CL+Dex Carfilzomib	72.8%	100.0%	$168,677	$215,463	$46,786
Cost: Carfilzomib vial sharing?	Yes	No	$177,493	$199,982	$22,489
2nd Line Utility, Progressed Disease	0.62	0.74	$204,512	$188,559	$15,952
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$205,323	$191,501	$13,822
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$195,344	$204,620	$9,276
Cost: Carfilzomib administration	$167.39	$251.09	$198,045	$201,919	$3,874

Scenario analyses

- Cost-effectiveness ratios uniformly higher when other regimens compared to BOR+DEX
- Ratios declined slightly when PFS-to-OS relationship based on data from available trials (~3.3 vs. 2.5 mo from published study)
- Findings similar when LEN+DEX survival curves adjusted for more recent experience in available trials
- Ratios declined slightly when additional utility benefit from using triplet vs. doublet therapy considered

Cost effectiveness summary

- The additional new agents in the treatment of multiple myeloma improves outcomes for patients but at substantial additional cost
- The estimated cost-effectiveness for these treatments is above commonly used cost-effectiveness thresholds in the U.S.
- There remains considerable uncertainty in these findings, but the model conclusions remained relatively constant across various sensitivity analyses

Cost-effectiveness: public comments received

- Did not explicitly incorporate differences between regimens and comparators in QoL measures from available clinical trials
- Cost-effectiveness thresholds between $50,000 and $150,000 per QALY gained were challenged as outdated and not reflective of cancer patients' values
- Survival data came from older trials of LEN+DEX and are not reflective of contemporary experience
- QALY measure does not adequately capture full breadth of values that cancer patients consider important

Potential Budget Impact Analysis

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Director of Health Economics
Institute for Clinical and Economic Review

Disclosures

I have no conflicts of interest.

Key review team members:

Dan Ollendorf, PhD

Potential budget impact: methods

- Total incremental cost of therapy for treated population
  - Calculated as incremental health care costs minus any offsets in costs from averted health care events
- Note: this analysis is performed from an *ex ante* perspective
  - Treats all drugs being evaluated as though new to market, whether or not already launched
- Estimated net costs of adding each drug to LEN+DEX, assuming no current use of the drug, over 5 year time horizon

Potential budget impact: methods

- Estimated entire candidate populations for treatment:
  - Adults with MM who have relapsed or not responded to ≥1 prior line of therapy, not currently on maintenance treatment, and not being considered for stem cell transplant
  - 2nd line treatment = 33,900
  - 3rd line treatment = 11,900
- Assumed uptake:
  - 2nd line treatment: 25% for each of 3 regimens
  - 3rd line treatment: 18.75% for each of 4 regimens
- Year 5 treated estimates:
  - 2nd line treatment = 8,485
  - 3rd line treatment = 2,237

Potential budget impact: methods

- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug/device approvals annually
  - Contribution of drug/device spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 threshold is $904 million for each new drug

Potential budget impact: 2nd line results at 5 years (eligible population: 33,900)

Regimen	Number Treated	Weighted BI per Patient	Average BI per year (millions)
CFZ+LEN+DEX	8,500	$133,100	$225.9
ELO+LEN+DEX	8,500	$232,800	$395.1
IX+LEN+DEX	8,500	$194,400	$329.9
Total	25,500	$186,800	$950.9

Potential Budget Impact: 3rd Line Results at 5 Years

Regimen	Eligible Population	Number Treated	Weighted BI per Patient	Average BI per year (millions)
CFZ+LEN+DEX	11,900	2,240	$132,400	$59.2
ELO+LEN+DEX	11,900	2,240	$222,400	$99.4
IX+LEN+DEX	11,900	2,240	$185,400	$82.9
PAN+BOR+DEX*	11,900	2,240	$26,400	$11.8
Total	11,900	8,960	$141,600	$253.3

*Compared to BOR+DEX

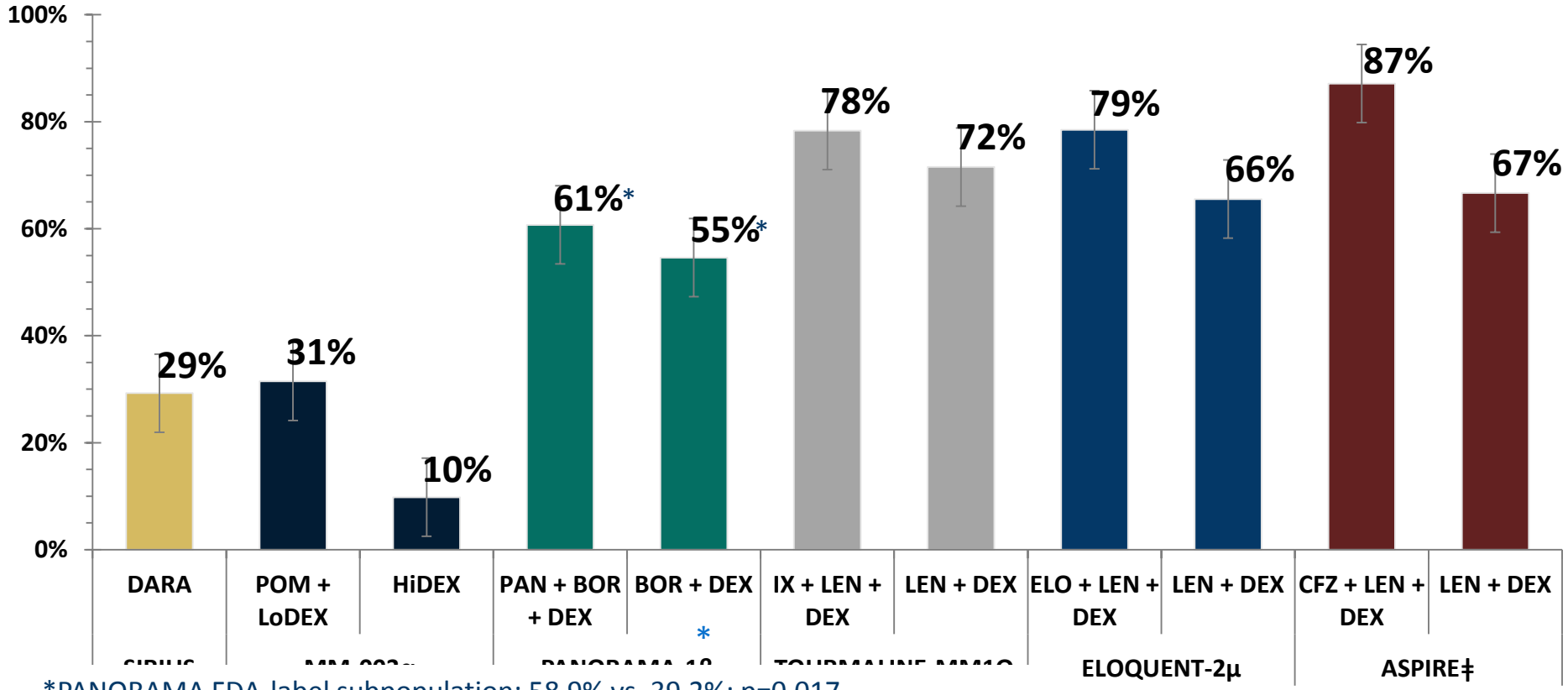
Potential budget impact: public comments

- Establishment of arbitrary budget “caps”
- Lack of rationale for uptake assumptions
- Incorrect interpretation of published data on % of patients receiving chemotherapy for invasive MM

APPENDIX

Overall response rate (ORR)

‡ p<0.001; µ p-value not reported; Ω p=0.04; β p=0.09; α p<0.0001



*PANORAMA FDA-label subpopulation: 58.9% vs. 39.2%; p=0.017

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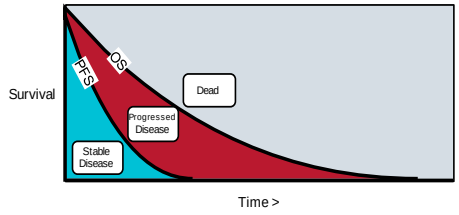
Approach: partition survival model

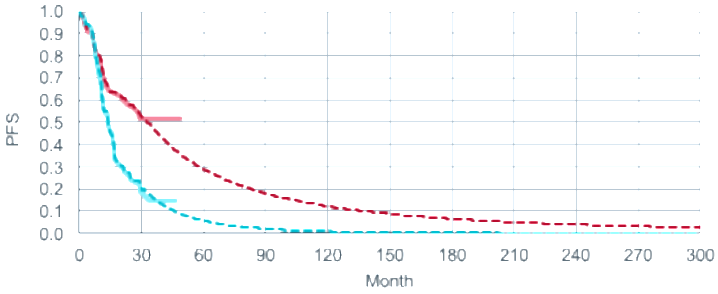
- Patient outcomes are modeled using a partition survival model that utilizes PFS and OS Kaplan-Meier curves, and parametric extrapolations of these curves to model beyond follow-up time.[1]
  - Commonly used approach in advanced oncology indications
  - Uses the area under the survival curves (both PFS and OS) to calculate the proportion of patients at a given time point in each health state
- Bypasses the need to estimate discreet transition probabilities
- Simple, straightforward, directly modeling survival using trial results
- Avoids the need for additional assumptions



1. Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Stat Med. 1990;9(11):1259-1276.

Parametric curve fits to K-M data

- Ideal estimates are obtained from fitting an appropriate parametric model to individual patient data.
  - However, such data are usually not available to independent researchers.
  - It is common to fit curves to summary Kaplan-Meier graphs, either by regression or by least squares.



- Instead, we estimated the underlying individual patient data from the numbers of patients at risk (or other published information) and from the Kaplan-Meier graph.[1]
- The survival curve can then be fit by maximum likelihood estimation.[1]
- The model curves included the distributional forms Weibull, exponential, log-normal, log-logistic, gamma, and Gompertz. The base case parametric function was selected based on best model fit using AIC values and visual comparison.

1. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011 Oct10;11:139.

Hazard ratios for PFS

Regimen	vs. Comparator*		
	HR	Range: Low	Range: High
PAN-BOR-DEX	0.58	0.48	0.71
CFZ-LEN-DEX	0.69	0.57	0.83
ELO-LEN-DEX	0.70	0.57	0.86
IX-LEN-DEX	0.74	0.59	0.93

*LEN+DEX for all regimens except PAN (BOR+DEX)

Treatment regimens and dosing

	Treatment Initiation				Subsequent Treatment (if different)			
	Days/Cycle	Cycle 1 Dose	To Cycle:	Admin. Days	Days/Cycle	Subs. Doses	To Cycle:	Admin. Days
Lenalidomide with dexamethasone								
Lenalidomide	28	25 mg	to progression	1-21				
Dexamethasone	28	40 mg	to progression	1,8,15,22				
Carfilzomib with lenalidomide and dexamethasone								
Carfilzomib	28	27 mg/m^2	13	1,2,8,9,15,16	28	27 mg/m^2	18	1,2,15,16
Lenalidomide	28	25 mg	to progression	1-21				
Dexamethasone	28	40 mg	to progression	1,8,15,22				
Elotuzumab with lenalidomide and dexamethasone								
Elotuzumab	28	10 mg/kg	2	1,8,15,22	28	10 mg/kg	to progression	1,15
Lenalidomide	28	25 mg	to progression	1-21				
Dexamethasone (oral)	28	28 mg	2	1,8,15,22	28	28 mg (40 mg if no Elo.)	to progression	1,8,15,22
Dexamethasone (IV)	28	8 mg	2	1,8,15,22	28	8 mg (0 mg if no Elo.)	to progression	1,15
Ixazomib with lenalidomide and dexamethasone								
Ixazomib	28	4 mg	to progression	1,8,15				
Lenalidomide	28	25 mg	to progression	1-21				
Dexamethasone	28	40 mg	to progression	1,8,15,22				
Panobinostat with bortezomib and dexamethasone								
Panobinostat	21	20 mg	16	1,3,5,8,10,12				
Bortezomib	21	1.3 mg/m^2	8	1,4,8,11	21	1.3 mg/m^2	16	1,8
Dexamethasone	21	20 mg	8	1,2,4,5,8,9,11,12	21	20 mg	16	1,2,8,9

Drug unit costs

Drug	Formulation		Cost‡
Bortezomib	vial	3.5 mg	$1,612.00
Carfilzomib	vial	60 mg	$1,861.95
Dexamethasone	per mg	varied	$0.32
Elotuzumab	vial	300 mg	$1,776.00
	vial	400 mg	$2,368.00
Ixazomib	capsule	2.3 mg	$2,890.00
	capsule	3 mg	$2,890.00
	capsule	4 mg	$2,890.00
Lenalidomide	capsule	2.5 mg	$502.69
	capsule	5 mg	$502.69
	capsule	10 mg	$502.69
	capsule	15 mg	$502.69
	capsule	20 mg	$502.69
	capsule	25 mg	$502.69
Panobinostat	capsule	10 mg	$1,222.22
	capsule	15 mg	$1,222.22
	capsule	20 mg	$1,222.22

‡ Cost reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed February 29, 2016).

Adverse events

Grade 3/4 Adverse Events	LEN-DEX n = 353	BOR-DEX n = 64	CFZ-LEN-DEX n = 392	ELO-LEN-DEX n = 318	IX-LEN-DEX n = 360	PAN-BOR-DEX n = 381
Anemia	17.0%	19.5%	14.8%	18.9%	11.7%	17.8%
Arrythmias	1.0%	2.0%	*	*	5.5%	3.0%
Back Pain	2.3%	3.0%	*	5.0%	0.8%	0.8%
Cataract	0.8%	*	*	6.3%	*	*
Deep Vein Thrombosis	3.3%	*	4.1%	5.7%	3.0%	*
Diarrhea	3.6%	8.0%	3.8%	5.0%	6.4%	25.5%
Fatigue	6.3%	11.9%	7.7%	12.6%	4.0%	23.9%
Hyperglycemia	6.3%	*	4.6%	17.0%	2.2%	*
Hypocalcemia	3.6%	2.0%	2.6%	11.3%	4.4%	5.0%
Hypokalemia	5.5%	7.0%	10.5%	11.3%	4.4%	18.0%
Lymphopenia	33.6%	40.2%	46.4%	76.7%	32.5%	53.6%
Nausea	0.5%	0.5%	0.2%	0.9%	1.7%	5.5%
Neutropenia	35.2%	11.4%	38.8%	33.6%	21.9%	34.5%
Peripheral/Sensory Neuropathy	1.5%	14.6%	1.7%	3.8%	2.5%	17.6%
Pneumonia	8.1%	10.3%	8.9%	14.2%	6.0%	12.6%
Thrombocytopenia	15.0%	31.4%	25.8%	19.2%	25.3%	67.3%
Vomiting	0.5%	1.3%	*	0.3%	1.1%	7.3%

* Not reported

Cost per adverse event

Adverse Event	Cost per event	Source
Anemia	$971	Roy et al.
Arrhythmias	$6,998	Roy et al.
Back Pain	$10,728	Roy et al.
Cataract	$3,700	CMS
Deep Vein Thrombosis	$31,645	Roy et al.
Diarrhea	$9,738	Roy et al.
Fatigue	$8,437	Roy et al.
Hyperglycemia	$166	Roy et al.
Hypocalcemia	$1,155	Roy et al.
Hypokalemia	$1,707	Roy et al.
Lymphopenia	$166	Roy et al.
Nausea	$11,934	Roy et al.
Neutropenia	$166	Roy et al.
Peripheral/Sensory Neuropathy	$783	Roy et al.
Pneumonia	$14,855	Roy et al.
Thrombocytopenia	$166	Roy et al.
Vomiting	$11,934	Roy et al.
Abbreviations: DRG: Diagnosis related group; CMS: Center for Medicare and Medicaid Services		

Utilities

Second-Line	Base Case	Distribution	Source
Progression-free disease, on treatment	0.82	Beta	AMGEN/ASPIRE
Progression-free disease, off treatment	0.84	Beta	AMGEN/ASPIRE
Progressed disease	0.65	Beta	AMGEN/ASPIRE
Third-Line			
Progression-free disease, on treatment	0.65	Beta	MM-003/NICE
Progression-free disease, off treatment	0.72	Beta	Acaster et al.
Progressed disease	0.61	Beta	MM-003/NICE
Disutility for any grade 3-4 adverse event	-0.076	Beta	MM-003/NICE

Threshold analysis for price per drug

2nd Line

Willingness-to-pay	CFZ	ELO (400 mg)	IX
$50,000	$78	$0	-$203
$100,000	$673	$267	$181
$150,000	$1,267	$588	$587
WAC price per vial/capsule	$1,862	$2,368	$2,890

3rd Line

Willingness-to-pay	CFZ	ELO (400 mg)	IX
$50,000	$0	$0	-$270
$100,000	$432	$178	$74
$150,000	$974	$466	$440
WAC price per vial/capsule	$1,862	$2,368	$2,890

LUNCH

Meeting will resume at 1:00 PM CT

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Questions for Deliberation

Treatment Options for Relapsed or Refractory Multiple Myeloma

Comparative *Clinical Effectiveness* Example Question

Is the evidence "**adequate**" to demonstrate that "**intervention A**" is superior to "**comparator B**" for patients with "**condition X**"?

- **Yes**
- **No**

Care Value Example Question

What is the care value of "**intervention A**" vs "**comparator B**"?

A. **Low**
B. **Intermediate**
C. **High**

Practice Question

What is the best way to spend Memorial Day Weekend?

A. A day at the beach

B. Camping in the woods

C. Taking a trip into the city

D. Hosting a BBQ

Comparative Clinical Effectiveness

Comparative Clinical Evidence: Second Line Therapy – CFZ+LEN+DEX

Q1. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Second Line Therapy – ELO+LEN+DEX

Q2. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Second Line Therapy – IX+LEN+DEX

Q3. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Second Line Therapy

Q4. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Is the evidence **adequate to distinguish** the net health benefit of treatment **among the following three regimens:** carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX), elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX), or ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)?

- Yes
- No

Comparative Clinical Evidence: Third Line Therapy – CFZ+LEN+DEX

Q5. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Third Line Therapy – ELO+LEN+DEX

Q6. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Third Line Therapy – IX+LEN+DEX

Q7. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)** is greater than that of treatment with **lenalidomide and dexamethasone?**

- Yes
- No

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Comparative Clinical Evidence: Third Line Therapy – PAN+BOR+DEX

Q8. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Is the evidence adequate to demonstrate that the net health benefit of treatment with **panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)** is greater than that of treatment with **bortezomib and dexamethasone?**

- Yes
- No

Comparative Clinical Evidence: Third Line Therapy

Q9. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Is the evidence **adequate to distinguish** the net health benefit of treatment **among the following three regimens:** carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX), elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX), or ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)?

- Yes
- No

Comparative Clinical Evidence: Daratumumab

Q10. For adults with relapsed and/or refractory multiple myeloma who are not currently on maintenance treatment and are not being considered for stem cell transplant, is the evidence adequate to determine the net health benefit of treatment with **daratumumab** in patients with **less than three prior lines of therapy**?

- Yes
- No

Comparative Care Value

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Comparative Care Value: Second Line Therapy

Q11. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Given the available evidence, what is the ***care value*** of treatment with **carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High

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Comparative Care Value: Second Line Therapy

Q12. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Given the available evidence, what is the ***care value*** of treatment with **elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High

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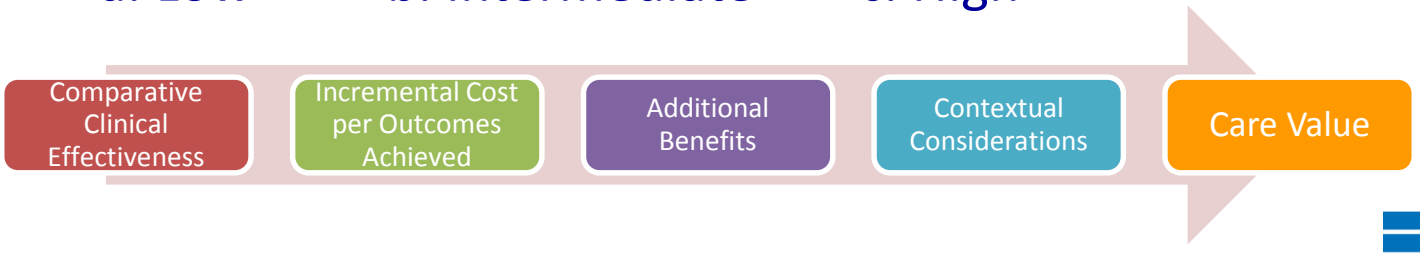
Comparative Care Value: Second Line Therapy

Q13. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, one line of therapy:

Given the available evidence, what is the ***care value*** of treatment with **ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High



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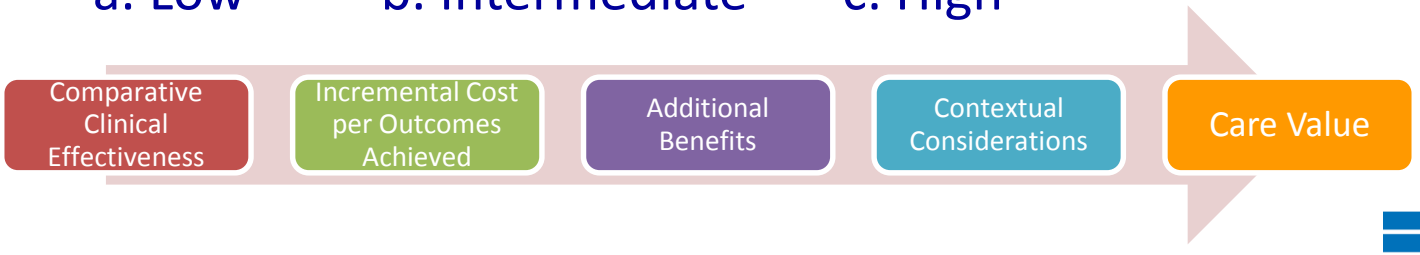
Comparative Care Value: Third Line Therapy

Q14. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Given the available evidence, what is the ***care value*** of treatment with **carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High



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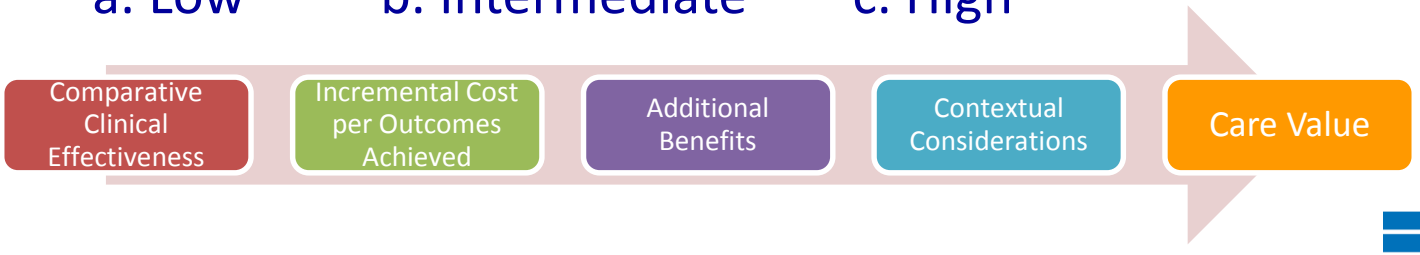
Comparative Care Value: Third Line Therapy

Q15. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Given the available evidence, what is the ***care value*** of treatment with **elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High



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Comparative Care Value: Third Line Therapy

Q16. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Given the available evidence, what is the ***care value*** of treatment with **ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)** versus treatment with lenalidomide and dexamethasone:

a. Low b. Intermediate c. High

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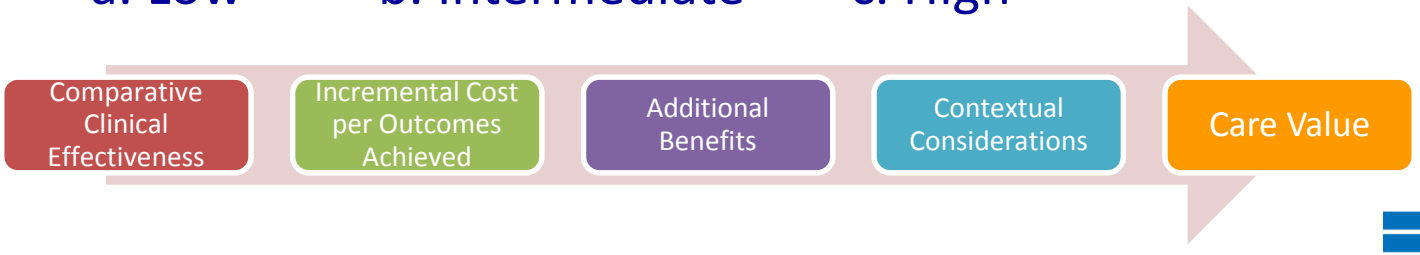
Comparative Care Value: Third Line Therapy

Q17. For adults with multiple myeloma who are not currently on maintenance treatment, are not being considered for stem cell transplant, and whose disease has not responded to, or has relapsed following, two or more lines of therapy:

Given the available evidence, what is the ***care value*** of treatment with **panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)** versus treatment with bortezomib and dexamethasone:

a. Low b. Intermediate c. High



Policy Roundtable

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Policy Roundtable Participants

- **Yelak Biru,** North Texas Myeloma Support Group, International Myeloma Foundation Board member
- **Deborah Collyer,** President and Founder, Patient Advocates in Research
- **Adam Kautzner, PharmD,** Vice President Drug Trend and Formulary, Express Scripts
- **Ed Pezalla, MD, MPH,** Vice President and National Medical Director for Pharmaceutical Policy and Strategy, Aetna
- **S. Vincent Rajkumar, MD,** Professor of Medicine, Hematology & Laboratory Medicine and Pathology; Chair, ECOG Myeloma Committee; Mayo Clinic
- **Ravi Vij, MD,** Professor of Medicine, Oncology Division, Bone Marrow Transplantation & Leukemia Section; Washington University School of Medicine in St. Louis

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Meeting Adjourned

Next Steps

- Final Report and accompanying materials expected on or before June 10, 2016.
- Meeting materials and outputs: http://icer-review.org/meeting/multiple-myeloma/

For more information please visit

http://icer-review.org/programs/midwest-cepac/

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