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Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks

Final Evidence Report and Meeting Summary

June 9, 2016

Institute for Clinical and Economic Review

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DATE OF PUBLICATION: June 9, 2016

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External Input

The following organizations, companies, and individuals provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these groups is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

External Input Received from:

Amgen
Anthem
Beth Israel Deaconess Medical Center
Bristol-Myers Squibb Company
Celgene Corporation
Express Scripts
Janssen Scientific Affairs
Memorial Sloan Kettering Cancer Center
Multiple Myeloma Research Foundation
Novartis
Takeda Oncology
Washington University School of Medicine in St. Louis

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List of Acronyms Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
BI	Budget impact
BOR	Bortezomib
BSA	Body surface area
CEA	Cost-effectiveness analysis
CFZ	Carfilzomib
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CR	Complete response
DARA	Daratumumab
DEX	Dexamethasone
ECOG PS	Eastern Cooperative Oncology Group Performance Status score
ELO	Elotuzumab
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire
FDA	U.S. Food and Drug Administration
FLC	Free light chain
HDAC	Histone deacetylase
HiDEX	High-dose dexamethasone
HR	Hazard ratio
HrQoL	Health-related quality of life
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
ISS	International Staging System
IX	Ixazomib
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LoDEX	Low-dose dexamethasone
MM	Multiple myeloma
MMRF	Multiple Myeloma Research Foundation
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PAN	Panobinostat
PFS	Progression-free survival
PI	Proteasome inhibitor
POM	Pomalidomide
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SAE	Severe adverse event
SCT	Stem cell transplant
TTP	Time to progression
Tx	Treatment
WAC	Wholesale acquisition price

Executive Summary

Background

Normally, plasma cells make up less than one percent of cells in the bone marrow. Multiple myeloma (MM) is a hematological cancer in which the bone marrow produces an overabundance of malignant plasma cells. Ultimately, the proliferation of plasma cells can cause bone and skeletal damage, anemia, hypercalcemia, neutropenia, and renal failure.[1] Like all cancers, MM is also a heterogeneous condition; prognosis varies depending on a number of variables, including the profile of the underlying genetic abnormalities, comorbid conditions, and the degree of response to initial treatment. There is no cure for MM, but its progression can be relatively slow in many individuals, often involving multiple rounds of remission after treatment followed by subsequent relapse. Over the past decade, the introduction of the proteasome inhibitor (PI) bortezomib (Velcade®, Takeda Millennium) and immunomodulatory drug (IMiD) lenalidomide (Revlimid®, Celgene) to MM treatment have greatly improved disease prognosis. Nearly half of all patients will survive at least five years after diagnosis, and nearly 100,000 individuals are currently living with the disease in the U.S.[2] The recent approvals of newer-generation PIs and IMiDs as well as new classes of agents have the potential to further extend survival gains.

Topic in Context

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other, equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

As noted previously, survival in MM has greatly improved since the introduction of PI and IMiD therapy. However, survival among patients with inadequate response or relapse while receiving treatment with PI and/or IMiD therapy remains poor, averaging approximately six months.[3] In the setting of MM that has relapsed (progression of disease following a period of initial response) and/or that is refractory (progression of disease while on, or shortly after, completing treatment), further treatment is guided largely by four major factors: (1) the presence of "aggressive" or "high-risk" disease characteristics; (2) the level and duration of response as well as toxicity experienced with prior treatment; (3) patient overall functional status and comorbidities that raise risks of treatment; and (4) patient values regarding the trade-offs between the potential benefits and side

effects of additional treatment options.[4,5] Aggressive, high-risk disease less likely to respond well to treatment is characterized by cytogenetic abnormalities, extensive skeletal disease, the presence of plasma cell leukemia in addition to MM, and other factors. With the availability of PI and IMiD therapy, median survival is now 8-10 years among patients with standard-risk disease, but is typically only 2-3 years in those whose disease has high-risk features.[6,7]

There remains a debate among oncologists about the appropriate intensity of treatment in relation to risk, however, with some preferring to employ multiple available active agents as early in the disease course as possible to achieve prolonged initial response, whereas other clinicians prefer a slower escalation of treatment, reserving aggressive early therapy for high-risk patients and otherwise using a "disease control" approach that seeks to maximize quality of life and minimize toxicity. This distinction in approach to practice has been termed the "sprint" approach to treatment versus the "marathon" approach.[8]

Recently-approved agents for MM include the newer-generation PIs carfilzomib (Kyprolis®, Amgen/Onyx) and ixazomib (Ninlaro®, Takeda Millennium), newer-generation IMiD pomalidomide (Pomalyst®, Celgene), the histone deacetylase inhibitor panobinostat (Farydak®, Novartis), and targeted antibodies elotuzumab (Empliciti™, Bristol-Myers Squibb) and daratumumab (Darzalex™, Janssen Biotech). Detailed descriptions of each class of agent can be found in the full report. These new agents have greatly expanded treatment options for patients and clinicians, leading to substantial variation in the care pathways for individual patients. In addition to differences in treatment philosophy around the use of aggressive treatment in the early stages of MM, guidelines from multiple clinical societies suggest many potentially appropriate treatment regimens and combinations for any given type of patient and sequence of treatment.[9,10]

The newest agents have also become available in an era in which the costs of managing the condition and the financial burden borne by patients are substantial. The cost of a single course of drug therapy for MM in the United States has been estimated to range from $75,000 - $250,000 for patients with relapsed or refractory disease; these estimates are likely conservative, given the increasing use of triplet therapy (i.e., combinations of new agents with lenalidomide or bortezomib as well as the steroid dexamethasone) and "treat to progression" labeling for the newest agents.[11] Out-of-pocket expenses for a single new cancer drug are estimated to reach $20,000-$30,000 annually for some patients, approximately half of the average annual household income in the U.S.[12,13] Recent surveys indicate that one-third of working-age cancer patients have had to borrow money or go into debt to pay for treatment, and bankruptcy rates for cancer patients are 2-3 times higher than individuals of comparable age, sex, and location.[14,15]

In this review, we sought to assess the comparative clinical effectiveness and comparative value of the newest regimens for second-line or third-line or later use in patients with relapsed and/or refractory MM, as compared to historical standard treatment with lenalidomide or bortezomib in combination with dexamethasone.

Comparative Clinical Effectiveness

Regimens of interest included the following:

- Carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- Daratumumab monotherapy (DARA)
- Elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- Ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)
- Panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)
- Pomalidomide with low-dose dexamethasone (POM+LoDEX)

Our literature search identified 1,254 potentially relevant references (see Appendix B, Figure B1), of which 38 references met our inclusion criteria; these citations related to nine individual studies. Six of these were identified as key studies, including single Phase III trials of each regimen of interest except for DARA, which was approved by the FDA based primarily on a single-arm Phase II study. Details of each key trial as well as major findings are summarized in Table ES1. All studies used standard and comparable methods to assess the primary outcomes of interest (i.e., progression-free and overall survival as well as response rate). The placebo-controlled trials of PAN+BOR+DEX and IX+LEN+DEX were rated as good quality, while the others were considered fair quality due to open-label design. The single-arm DARA trial was rated poor quality due to the lack of comparator.

The trials evaluating CFZ, ELO, IX, and PAN in combination with LEN or BOR plus DEX[1] specified similar inclusion criteria. Each trial included adult patients (≥18 years of age) with measurable relapsed and/or refractory multiple myeloma. All patients had received 1-3 prior therapies and had adequate renal, hepatic, and hematologic function to tolerate further treatment. Trial populations were similar with respect to age, ECOG performance status, ISS stage, receipt of prior stem cell transplant (SCT), and number and distribution of prior regimens. Definitions of disease risk varied (see Appendix C, Table C6), but the percentage of patients with high-risk disease ranged from 13-32% across studies reporting this element.[16-19]

[1] Patients in the comparator arms of the double-blind trials that evaluated IX and PAN were given a placebo in addition to LEN+DEX or BOR+DEX

Table ES1. Key trials

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Treatment Arm)
ASPIRE[16] **Open-label RCT** **Phase III** **Carfilzomib (CFZ)**	• Median age: 64 • ECOG=2: 9.5% • ISS Stage III: 20% • Previous SCT: 57% • High risk: 12.6% • Prior regimens (median): 2 • Prior BOR: 65.8% • Prior LEN: 19.8%	**CFZ+LEN+DEX** (n=396) • Median f/u: 32.3 m	**LEN+DEX** (n=396) • Median f/u: 31.5 m	• D/C due to AEs: 15% • SAEs: 60% • Tx-related deaths: 2%
		• OS HR: 0.79 (95% CI: 0.63-0.99; p=0.04) • PFS HR: 0.69 (95% CI: 0.57-0.83)		
		• Median PFS: 26.3 m • ORR: 87.1%	• Median PFS: 17.6 m • ORR: 66.7%, p<0.001	
SIRIUS[20] **Open-label single-arm study** **Phase II** **Daratumumab (DARA)**	• Median age: 63.5 • ECOG=2: 8% • ISS Stage III: 38% • Previous SCT: 80% • del(17p): 17% • Prior regimens (median): 5 • Refractory to LEN & BOR: 82%	**DARA** (n=106)	**None**	• D/C due to AEs: 5% • SAEs: 30% • Tx-related deaths: 0
		• Median f/u: 9.3 m • Median OS: 17.5 m (95% CI: 13.7-NE) • Median PFS: 3.7 m • ORR: 29.2%		
ELOQUENT-2[17] **Open-label RCT** **Phase III** **Elotuzumab (ELO)**	• Median age: 66 • ECOG=2: 9% • ISS Stage III: 21% • Previous SCT: 54% • del(17p): 32% • Prior regimens (median): 2 • Prior BOR: 70% • Prior LEN: 6%	**ELO+LEN+DEX** (n=321)	**LEN+DEX** (n=325)	• D/C due to AEs: 13% • SAEs: 65% • Tx-related deaths: 2%
		• Median f/u: 24.5 m • OS HR: 0.77 (95% CI: 0.61-0.97) • PFS HR: 0.70 (95% CI: 0.57-0.85; p<0.001)		
		• Median PFS: 19.4 m • ORR: 79%	• Median PFS: 14.9 m • ORR: 66%, p<0.001	
TOURMALINE-MM1[21] **Double-blind RCT** **Phase III** **Ixazomib (IX)**	• Median age: 66 • ECOG=2: 6% • ISS Stage III: 12% • Previous SCT: 57% • High risk: 19% • Prior regimens (median): 1 • Prior BOR: 69% • Prior LEN: 12%	**IX+LEN+DEX** (n=360)	**Placebo+LEN+DEX** (n=362)	• D/C due to AEs: 17% • SAEs: 47% • Tx-related deaths: NR
		• Median f/u (PFS): 23 m		
		• Deaths: 22.5%	Deaths: 24.8%	
		• PFS HR: 0.74 (95% CI: 0.59-0.94; p=0.01)		
		• Median PFS: 20.6 m • ORR: 78%	• Median PFS: 14.7 m • ORR: 72%, p=0.04	
PANORAMA-1[18] **Double-blind RCT** **Phase III** **Panobinostat (PAN)**	• Median age: 63 • ECOG=2: 5% • ISS Stage III: 22% • Previous SCT: 58% • 1 prior regimen: 51% • Prior BOR+DEX: 38% • Prior LEN: 21%	**PAN+BOR+DEX** (n=387) • Median f/u: 6.4 m	**Placebo+BOR+DEX** (n=381) • Median f/u: 5.9 m	• D/C due to AEs: 36% • SAEs: 60% • Tx-related deaths: 3%
		• OS HR: 0.94 (95% CI: 0.78-1.14; p=0.5435) • PFS HR: 0.63 (95% CI: 0.52-0.76; p<0.0001)		
		• Median PFS: 11.99 m • ORR: 60.7%	• Median PFS: 8.08 m • ORR: 54.6%, p=0.09	
MM-003[22] **Open-label RCT** **Phase III** **Pomalidomide (POM)**	• Median age 65 • ECOG 2-3: 18% • ISS Stage III: 32% • Previous SCT: 70% • Prior regimens (median): 5 • Prior LEN & BOR: 100% • Refractory to LEN & BOR: 75%	**POM+LoDEX** (n=302)	**HiDEX** (n=153)	• D/C due to AEs: 9% • SAEs: 61% • Tx-related deaths: 4%
		• Median f/u (PFS): 10.0 m • OS HR: 0.74 (95% CI: 0.56-0.97; p=0.285) • PFS HR: 0.48 (0.39-0.60; p<0.0001)		
		• Median PFS: 4.0 m • ORR: 31%	• Median PFS: 1.9 m • ORR: 10%, p<0.0001	

ECOG PS=Eastern Cooperative Oncology Group Performance Status score; ISS=International Staging System; SCT= stem cell transplant; f/u=follow-up; OS=overall survival; PFS=Progression-free survival; HR=hazard ratio; ORR=overall response rate; D/C=discontinuation; SAEs=serious adverse events; Tx=treatment

In contrast, the MM-003 and SIRIUS trials of POM+LoDEX and DARA, respectively, included patients with more advanced levels of disease. For example, in the POM+LoDEX trial, patients must have been refractory to their previous treatment, tried at least two previous consecutive cycles of BOR and LEN (alone or in combination), and failed treatment with either BOR or LEN.[22] Whereas the majority of patients in the trials of CFZ, ELO, and IX in combination with LEN+DEX and the trial of PAN+BOR+DEX had received 1-2 previous regimens and 6-21% had prior treatment with LEN, patients in the POM+LoDEX trial had a median of five prior therapies and 94% were refractory to LEN.[22] Patients in the DARA trial also had a median of five previous treatments, and 88% were refractory to LEN.[20]

Results

Clinical Benefits

Whether data are available on overall survival or on surrogate outcomes, interpretation of clinical trial results requires judgment about what gains represent "clinically significant" improvements. To address this question, the American Society of Clinical Oncology (ASCO) has convened working groups and published recommendations in four cancer types (see Table ES2). For both overall survival and progression-free survival (PFS), an additional 3-5 months was generally recommended as the range for minimum clinically meaningful improvements. There are currently no recommendations specific to MM, but given the consistency of these recommendations across different types of cancer it may be reasonable to consider them when interpreting findings from trials of new agents for MM.

Table ES2. Clinically-significant levels of improvement in surrogate and longer-term outcomes in four cancer types

			Primary Endpoint		Secondary Endpoint	
Cancer Type	**Patient Population**	**Current Baseline Median OS (m)**	Clinically Meaningful Improvement over Current OS (m)	Target HRs	Improvement in 1-yr Survival Rate (%)*	Improvement in PFS (m)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel-eligible patients	8 to 9	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18	4.5 to 6	0.76 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard 2nd- or 3rd-line options)	4 to 6	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; m, months; PFS, progression-free survival; *Current → target; Source: Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 201412:1277.[23]

Overall Survival (OS)

Improving overall survival (OS) with tolerable side effects is the ultimate goal of an investigational cancer therapy. In cancers with longer survival trends such as MM, demonstrating improved OS may take up to five years, and will be confounded by crossover from the control to the treatment arm of the trial as well as by sequential use of additional treatment regimens. All six of the key studies included data on overall survival, but only two reported final results (POM+LoDEX and PAN+BOR+DEX). POM+LoDEX was associated with a median of 4.6 months of improved survival compared to HiDEX therapy (12.7 vs. 8.1 months; HR 0.74; 95% CI 0.56-0.97; p=0.03) in this population with more advance disease.[22] While a similar absolute difference was noted in the PAN+BOR+DEX trial (median 40.3 vs. 35.8 months for BOR+DEX), the hazard ratio was not statistically significant (HR 0.94; 95% CI 0.78-1.14; p=0.54).[24] Data for PAN+BOR+DEX are currently available only from a conference abstract, so there is no clear explanation for the lack of a statistically significant benefit.

In an interim analysis of overall survival, ELO+LEN+DEX improved survival by a median of 4.1 months compared to LEN+DEX (43.7 vs. 39.6 months; HR 0.77; 95% CI 0.61-0.97; p=0.03), although these data are currently only available from conference proceedings (American Society of Hematology [ASH], December 5-8, 2015).[25] Interim overall survival also favored CFZ+LEN+DEX, although median duration of survival was not yet able to be calculated (HR 0.79 vs. LEN+DEX; 95% CI 0.63-0.99; p=0.04).[16] While no comparative data on overall survival are currently available for DARA, the SIRIUS trial showed a median OS of 17.5 months (95% CI 13.7-not estimable). Although a planned interim analysis of IX+LEN+DEX did not demonstrate an OS benefit, the median overall survival has not yet been reached in either treatment arm of the IX+LEN+DEX trial, so follow-up for the final analysis is ongoing.[19,21]

Progression-Free Survival (PFS)

As is standard for regulatory submissions to the FDA, all of the key trials other than the SIRIUS study of DARA (which employed overall response rate) used progression-free survival (PFS) as the primary endpoint of the study. PFS is calculated from the time of the start of treatment to disease progression or death. It has been used as a surrogate marker for duration of overall survival, but evidence on its predictive power in relapsed and/or refractory disease is mixed (see "Controversies and Uncertainties"). All of the MM regimens evaluated with RCTs showed statistically significant improvement in PFS relative to control treatment.[16-20,22] Improvements in median PFS ranged between 5-9 months in the studies of ELO, CFZ, and IX, all in combination with LEN+DEX. Risk reductions for progression (as documented by hazard ratios) were very comparable across these trials, ranging from 0.69 to 0.74.

The gain in median PFS was somewhat lower for PAN+BOR+DEX (3.9 months), but median duration of follow-up for PFS was also shorter in this study (6.4 months vs. 23-32 months in the other trials) due to a higher-than-expected number of study or treatment discontinuations. As described further in the "Controversies and Uncertainties" section, the FDA Oncologic Drugs Advisory

Committee (ODAC) questioned the validity of the PFS finding for the overall sample, due to censoring, drug discontinuation, and other concerns.[26] Data on PFS for PAN+BOR+DEX were also generated for the subgroup of patients who received ≥2 lines of treatment incuding BOR and an IMiD, the population that ultimately received the FDA indication. Gain in median PFS in this group of patients was approximately double that in the overall population (12.5 vs. 4.7 months for BOR+DEX; HR 0.47; 95% CI: 0.31-0.72).

Not surprisingly, because of their more advanced disease, patients in the POM+LoDEX versus HiDEX trial had a substantially shorter duration of PFS; results did favor POM+LoDEX, however (3.6 vs. 1.8 months; HR 0.45; p<0.001). Also, while no comparative data are yet available, median PFS in the single-arm study of DARA, in a population with comparably advanced disease, was of similar magnitude to that of POM+LoDEX (3.7 months).

Additional Analyses

Detailed information on OS and PFS results stratified by number of lines of prior treatment, cytogenetic risk, and the presence of prior refractory disease can be found in the full report and appendices. Subgroup data for OS were sparse across all of the strata of interest. In general, relative improvements in PFS were similar when stratified by the number of prior lines of treatment. Stratification by cytogenetic risk and prior refractory disease was variably defined across regimens and not available in several studies.

We also conducted indirect comparisons of the regimens of interest on OS and PFS using techniques of Bayesian network meta-analysis; detailed information on methods and results can be found in the Appendices. Findings generally supported improvements in PFS and OS for each regimen in relation to its comparator but no clinically meaningful differences between the newer regimens were identified.

Data on other clinical outcomes of interest, including overall response rate and health-related quality of life, can be found in the full report.

Harms

Across the key studies, the incidence of treatment-related death ranged from 2-4% across regimens,[2] although this was not reported for IX. Discontinuation of study therapy due to adverse events (AEs) ranged between 5% and 17% for all regimens except for PAN+BOR+DEX, which had a much higher rate (36%).[18] Diarrhea was among the AEs of most concern: whereas 1-6% of patients experienced Grade 3-4 diarrhea with the other regimens, a substantially greater proportion of patients (25%) treated with PAN+BOR+DEX reported Grade 3-4 diarrhea, and 4% discontinued treatment because of treatment-related diarrhea.[18] The label for PAN includes a black box warning

[2] The ELOQUENT-2 trial reported the proportion of patients who died from an adverse event; the other key trials reported treatment-related death.

that specifically mentions severe diarrhea.[27] Peripheral neuropathy, fatigue, and thrombocytopenia were additional AEs that disproportionately affected patients treated with PAN+BOR+DEX relative to patients treated with other regimens (peripheral neuropathy: 18% vs. 1-4% with other regimens; fatigue: 24% vs. 3-8%; thrombocytopenia: 67% vs. 12-22%).[18]

The prescribing information for POM also includes a black box warning. The POM label advises that patients take antithrombotic prophylaxis while treated with POM, as deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke may occur.[28] Differences in the incidence of Grade 3-4 thromboembolism (1% vs. 0% for POM+LoDEX vs. HiDEX) were slightly less than those seen with other regimens (3.0-5.7% of patients treated with ELO, IX, or CFZ in combination with LEN+DEX, compared to 2.2-4.1% for LEN+DEX);[16,17,22] use of thromboprophylaxis is not an explanatory factor, as this was a required element of treatment in all of the trials described above. The black-box warning may instead be a class decision, as the label for LEN carries a similar warning.

Cardiac toxicity has been associated with CFZ.[29] In the ASPIRE trial, 3.8% of patients in the CFZ+LEN+DEX group experienced Grade 3 or higher cardiac failure versus 1.8% in the LEN+DEX group; Grade 3 or higher ischemic heart disease occurred in 3.3% of the CFZ+LEN+DEX group compared to 2.1% in the LEN+DEX group.[16]

Hematological AEs were relatively common in the regimens of focus. Abnormalities included anemia, neutropenia, thrombocytopenia, lymphopenia, and leukopenia. Relative to LEN+DEX, BOR+DEX, or HiDEX, Grade 3 or higher thrombocytopenia occurred with at least 5% greater frequency with PAN-, CFZ-, and IX-based regimens, while Grade 3 neutropenia occurred in 5% or more of patients treated with POM-, PAN-, and ELO-based treatment.[16-19,22]

Controversies and Uncertainties

Multiple limitations in the body of evidence reduce our ability to make judgments regarding the comparative net health benefits of these treatments. First, with the exception of POM+LoDEX, final overall survival data demonstrating statistically significant improvement with newer regimens are not yet available. Debates in the oncology literature have raged for many years about the relative credibility of surrogate outcomes such as PFS and whether studies can even be designed in the current era to measure overall survival when patients receive multiple rounds of chemotherapy before and after the use of any one particular treatment.[8,30] In addition, PFS benefit as a justification for early aggressive treatment remains a hotly debated issue. Some clinicians advocate for early aggressive treatment with multiple drugs in pursuit of complete response, arguing that this approach gives patients the best chance for a prolonged treatment-free interval. As noted earlier, other clinicians prefer a more graduated approach to MM therapy, the "marathon, not a sprint." For these clinicians, the lack of definitive data demonstrating an OS advantage for newer drugs

supports their view that OS may, in the end, be the same for average-risk patients, whether aggressive treatment is started early or not.

There are also important uncertainties regarding the evidence on specific regimens. As noted earlier, the efficacy of PAN was questioned by FDA reviewers because of an unusually large amount of missing and censored data in the full sample of the PANORAMA-1 study. Furthermore, a larger proportion of deaths not attributed to progressive disease occurred with PAN (7% vs. 3% for control therapy) that may have been related to the drug's toxicity. There was discussion regarding the contribution of intravenous versus subcutaneous BOR toxicity levels seen with PAN+BOR+DEX, but limited data are currently available to address this issue (see full report).[31-34] Based on these concerns the FDA ODAC voted 5-2 that PAN's benefit did not outweigh its risk. This led the manufacturer to propose limiting the indication for PAN to patients who had received at least two prior regimens, including BOR and an IMiD. The FDA approved PAN in this subgroup with the condition that the manufacturer carry out additional Phase II and Phase III trials of PAN in combination with subcutaneous BOR and DEX in relapsed/refractory patients who were previously treated with an IMiD.[3,26,35,36]

The evidence base for DARA is less robust than that for other regimens given that it is currently limited to a Phase I/II dose-escalation/dose-expansion study and a Phase II study. Nonetheless, among patients who are experiencing disease progression, a trial without significant drop-out demonstrating relatively high response rates and a median PFS of at least 3-5 months can provide some information regarding improvement in the surrogate outcome. However, no comparator data are as yet available, so the incremental gain in PFS compared to another salvage therapy is unknown, and our certainty in DARA's effects is therefore low.

Our certainty in the efficacy of POM+LoDEX is also hampered somewhat by the lack of peer-reviewed data of the regimen against newer doublet or triplet therapy options. The comparison of POM+LoDEX to HiDEX was justified as the standard salvage treatment for heavily pretreated patients at the time of trial design. However, with the emergence of newer agents since the completion of the MM-003 trial, use of HiDEX alone may no longer serve as a relevant selection of a control salvage treatment.

But perhaps the greatest amount of uncertainty in comparative net health benefit lies in the lack of truly comparative data across trials. Given that many of these drugs were approved very recently, we do not expect there to be published head-to-head data available. However, the limited number of available studies as well as the absence of data for certain key subgroups precluded robust indirect comparisons of the regimens in our review.

[3] The Phase II and Phase III trials will be completed in 2018 and 2021, respectively.

Comparative Clinical Effectiveness: *Summary and Comment*

ICER evidence ratings for the comparisons of interest are provided in Table ES3. We judge there to be moderate certainty that CFZ, ELO, and IX, in combination with LEN+DEX, provide an incremental or better net health benefit for both second-line and third-line or subsequent therapy in adult patients with relapsed/refractory multiple myeloma relative to LEN+DEX alone. There is moderate certainty because while only one Phase III study was available for each regimen, the studies of focus had large patient populations and were of higher quality. Furthermore, the PFS benefit observed in each drug's key trial was consistent across subgroup analyses by number of prior lines of therapy. Side effect rates are high for all of these treatments, but these side effects are now well known and patients have already indicated by the common use of these treatments that the balance of benefits and harms is viewed positively by many. Data on side effects do not demonstrate a systematic overall advantage for any of these regimens. We therefore assign the current body of evidence on the comparative clinical effectiveness of CFZ, ELO, and IX a "B+" rating using the ICER Evidence Rating Matrix.

Table ES3. ICER evidence ratings, by regimen and line of therapy

Regimen	Comparator	Evidence Rating	
		Second-Line Therapy	Third-Line Therapy
CFZ+LEN+DEX	LEN+DEX	B+	B+
ELO+LEN+DEX	LEN+DEX	B+	B+
IX+LEN+DEX	LEN+DEX	B+	B+
PAN+BOR+DEX	BOR+DEX	I	P/I
POM+LoDEX	HiDEX	I	P/I
DARA	None	I	I

As a third-line or subsequent therapy, we judge the evidence for PAN+BOR+DEX to be "promising but inconclusive." We arrived at this rating because the results of a subset analysis in patients who had received prior BOR and IMiD therapy revealed a more favorable risk/benefit profile for the drug. However, concerns over toxicity and the limitations of the overall evidence base remain. Our judgment is that there is insufficient evidence to determine the net health benefit of PAN+BOR+DEX as second-line therapy. The evidence is insufficient because of concerns first raised by FDA reviewers with which we agree: a high level of missing data and censoring in the PANORAMA-1 trial introduced potential bias into estimates of PFS for all patients as well as those stratified by number of prior lines of treatment.

Evidence was also insufficient ("I") to determine a net health benefit for patients receiving POM+LoDEX for second-line treatment, as the key Phase III trial only evaluated patients receiving the regimen for third-line or later use. As a third-line or subsequent therapy, we find that the

evidence for POM+LoDEX provides moderate certainty of a net health benefit that is likely at least comparable to other salvage options, but the true level of net health benefit is unclear. Although POM+LoDEX is the only regimen to have demonstrated a statistically and clinically-significant overall survival benefit in a final analysis, this benefit is unknown relative to any salvage therapy other than high-dose dexamethasone. Because of this concern and because there is a small chance that POM+LoDEX could be net harmful relative to other available salvage options, we judge the comparative clinical effectiveness of POM+LoDEX to be "P/I" for third-line or subsequent treatment using the ICER Evidence Rating Matrix.

Finally, we find that the evidence is insufficient ("I") to determine the comparative net health benefit for DARA monotherapy as either second-line or third-line or subsequent therapy because at the time of this review there were no available randomized or comparative studies of the drug for this indication. Without any comparator data with which to judge incremental benefit, we could not estimate net health benefit with any degree of certainty. In addition, the intended use of the drug is for fourth-line or later use in patients who have previously been treated with a PI and an IMiD, or who are double refractory to both a PI and IMiD, and there are currently little to no data on the use of DARA relative to the timing of therapy of interest for this review.

Other Benefits or Disadvantages

All but two of the regimens of interest (IX and POM) in this assessment have at least one component that is administered via subcutaneous injection or intravenous infusion, which requires frequent office visits. Travel to a physician's office or clinic and the requirement for sometimes extensive infusions poses a burden to MM patients and caregivers at various stages of disease, so the convenience and potential quality-of-life benefits of all-oral treatments possible with IX and POM will be highly valued by some patients. Conversely, the monitoring and opportunity for patient education and counseling at office visits may offer additional benefits for some patients.

The availability of multiple classes of medication for this increasingly chronic condition may increase the likelihood that patients will respond to a specific combination of treatments and may also reduce the chance of poor response or resistance to multiple regimens. This is of significant clinical importance given that data are not yet sufficient to predict the type of patient who will respond to (or become resistant to) a particular regimen.

Comparative Value

The primary aim of our analysis of incremental costs per outcomes achieved was to estimate the long-term cost-effectiveness of various treatments for patients with MM who have received one or two previous therapies (i.e., second- or third-line treatment) relative to LEN+DEX treatment. The model analyzed second- and third-line treatments separately. Note that we were unable to include

DARA or POM+LoDEX in our analyses, as patients in these trials had more advanced disease than those receiving the other regimens of interest.

Outcomes were modeled using three health states: progression-free, progression, and death. Information on the relative effects of each regimen on PFS were combined with data from a pooled analysis of LEN+DEX survival data and a published meta-analysis on the relationship between PFS and OS in MM to estimate life expectancy.[37-40] Both unadjusted and quality-adjusted time spent in each health state as well as associated costs were summed to provide estimates of life expectancy, quality adjusted life expectancy and total costs. We utilized a health system perspective (i.e., we focused on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death. We used a 3% discount rate for all future outcomes and costs.

We also used outputs from this model to inform a population-based analysis of the one- and five-year potential budget impact of different treatment regimens. Potential budget impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug costs as well as potential cost savings from treatment. Based on long-term incremental cost-effectiveness ratios, we define a "value-based price benchmark" for the regimens of interest. As part of our price benchmark we also highlight whether the potential budget impact for any new drug at list price would surpass a threshold related to growth targets for net health care cost growth at the national level. Details on methods and inputs for all analyses can be found in the full report and appendices.

Incremental Costs per Outcomes Achieved: *Results*

The results of the pairwise comparisons are provided in Table ES4 for the second-line setting and Table ES5 for the third-line setting. These tables report detailed results for each regimen in each line as well as the incremental results versus LEN+DEX. Only deterministic results are shown (i.e., the model results that use only the point estimate for every input). Note that PFS results in the tables will not match those seen in clinical trials because of our anchoring of hazard ratios to the baseline survival curves for LEN+DEX (rather than use of observed survival curves in each trial) in order to have a common baseline across regimens.

Incremental cost-effectiveness ratios differed for each second-line regimen versus LEN+DEX; the ratio was approximately $200,000 per quality-adjusted life year (QALY) gained for CFZ+LEN+DEX versus >$400,000 per QALY for IX or ELO in combination with LEN+DEX. Use of each of the second-line regimens resulted in a gain of approximately one year of survival (range: 0.93 for IX+LEN+DEX to 1.17 for CFZ+LEN+DEX) relative to LEN+DEX, which represented relatively equivalent gains in survival prior to progression and after progression. On a quality-adjusted basis, QALYs gained versus LEN+DEX ranged from 0.69 for IX+LEN+DEX to 0.86 for CFZ+LEN+DEX. Incremental costs ranged from a low of approximately $173,000 for CFZ+LEN+DEX to approximately $354,000 for ELO+LEN+DEX versus LEN+DEX, nearly all of which were driven by increased drug costs rather than

costs from progression, supportive care, or adverse event costs. Lower incremental drug costs for CFZ+LEN+DEX versus the other triplet regimens of interest are due primarily to treatment with CFZ+LEN+DEX for a fixed number of cycles (18), while IX+LEN+DEX and ELO+LEN+DEX are given continuously until progression or unacceptable toxicity. In addition, incremental drug costs for all triplet regimens included both additional costs of the new drug for each regimen as well as extended use of LEN+DEX due to improved PFS. For example, when given as part of the CFZ+LEN+DEX regimen, the treatment cost of LEN prior to progression is $260,392, whereas the cost of LEN is $239,745 when given as part of the LEN+DEX regimen. The higher total cost for LEN in the CFZ+LEN+DEX treatment arm is due to the longer time in treatment prior to progression.

Use of CFZ+LEN+DEX, ELO+LEN+DEX, and IX+LEN+DEX as third-line regimens resulted in gains of 1.12, 1.07, and 0.89 years of survival, respectively, relative to LEN+DEX. On a quality-adjusted basis, QALYs gained versus LEN+DEX ranged from 0.56 for IX+LEN+DEX to 0.71 for CFZ+LEN+DEX. Incremental costs ranged from a low of approximately $168,000 for CFZ+LEN+DEX to approximately $325,000 for ELO+LEN+DEX versus LEN+DEX, nearly all of which were again driven by increased drug costs. Incremental cost effectiveness ratios were estimated to be approximately $239,000 per QALY for CFZ+LEN+DEX, $481,000 per QALY for ELO+LEN+DEX, and $485,000 per QALY for IX+LEN+DEX.

PAN+BOR+DEX was estimated to provide more QALYs than LEN+DEX as a third-line therapy, at a lower total cost; therefore, PAN+BOR+DEX would be the preferred treatment (i.e., was dominant) versus LEN+DEX. However, results for PAN+BOR+DEX should be interpreted with great caution. As noted previously, serious concerns were raised regarding the viability of results in the overall population and even in the full third-line subgroup (versus the subset of third-line patients with prior BOR and IMiD use that ultimately received FDA approval), based on issues of censoring and high rates of discontinuation due to toxicity. This is also the only regimen without direct comparative evidence versus LEN+DEX. While censoring is factored into our analytic approach, the relative treatment effect of PAN+BOR+DEX versus LEN+DEX therefore has much greater uncertainty than the other comparisons.

We addressed this concern in part by conducting a scenario analysis in which each third-line regimen was compared to BOR+DEX rather than LEN+DEX. Cost-effectiveness ratios increased for all regimens, primarily because of the lower drug costs for BOR versus LEN (Appendix E). However, PAN+BOR+DEX was no longer cost-saving when the comparator was changed to BOR+DEX, with a cost-effectiveness ratio of $10,230 per QALY gained.

Table ES4. Clinical and economic outcomes in the second-line

Results by Regimen

2nd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX
Total Costs	**$284,400**	**$457,350**	**$638,144**	**$582,428**
Drug Costs	$240,913	$398,767	$569,796	$532,873
Supportive Care Costs	$528	$1,882	$2,607	$2,491
Administration Costs		$8,377	$14,698	
Progression Costs	$38,901	$44,103	$43,886	$43,062
Adverse Event Costs	$4,057	$4,221	$7,156	$4,001
Total QALYs	**2.59**	**3.45**	**3.41**	**3.27**
PFS QALYs	1.41	1.91	1.89	1.81
Progression QALYs	1.17	1.54	1.52	1.46
Total Life Years (OS)	**3.53**	**4.71**	**4.66**	**4.46**
PFS LYs	1.73	2.34	2.31	2.21
Progression LYs	1.80	2.37	2.34	2.25

Incremental Results vs. LEN-DEX

2nd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX
ICER (vs. L+Dex)	**--**	**$199,982**	**$427,607**	**$433,794**
Total Costs	**--**	**$172,951**	**$353,744**	**$298,028**
Drug Costs	--	$157,854	$328,883	$291,960
Supportive Care Costs	--	$1,354	$2,079	$1,963
Administration Costs	--	$8,377	$14,698	
Progression Costs	--	$5,202	$4,985	$4,161
Adverse Event Costs	--	$164	$3,099	-$56
Total QALYs	**--**	**0.86**	**0.83**	**0.69**
PFS QALYs	--	0.50	0.48	0.39
Progression QALYs	--	0.37	0.35	0.29
Total Life Years (OS)	**--**	**1.17**	**1.12**	**0.93**
PFS LYs	--	0.61	0.58	0.48
Progression LYs	--	0.56	0.54	0.45

Table ES5. Clinical and economic outcomes in the third-line

Results by Regimen

3rd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX	PAN-BOR-DEX
Total Costs	**$258,609**	**$427,027**	**$583,531**	**$530,228**	**$196,021**
Drug Costs	$216,151	$369,865	$517,785	$481,956	$136,366
Supportive Care Costs	$473	$1,779	$2,364	$2,255	$415
Administration Costs		$8,113	$13,394		$3,128
Progression Costs	$37,928	$43,049	$42,833	$42,016	$46,984
Adverse Event Costs	$4,057	$4,221	$7,156	$4,001	$9,128
Total QALYs	**2.04**	**2.74**	**2.71**	**2.60**	**3.46**
PFS QALYs	1.00	1.37	1.36	1.30	1.82
Progression QALYs	1.03	1.37	1.36	1.30	1.63
Total Life Years (OS)	**3.25**	**4.37**	**4.32**	**4.14**	**5.27**
PFS LYs	1.55	2.12	2.09	2.00	2.59
Progression LYs	1.70	2.25	2.23	2.14	2.68

Incremental Results vs. LEN-DEX

3rd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX	PAN-BOR-DEX
ICER (vs. L+Dex)	**--**	**$238,560**	**$481,244**	**$484,582**	**-$44,084**
Total Costs	**--**	**$168,418**	**$324,922**	**$271,619**	**-$62,588**
Drug Costs	--	$153,714	$301,634	$265,805	-$79,784
Supportive Care Costs	--	$1,307	$1,891	$1,783	-$58
Administration Costs	--	$8,113	$13,394		$3,128
Progression Costs	--	$5,121	$4,905	$4,087	$9,055
Adverse Event Costs	--	$164	$3,099	-$56	$5,071
Total QALYs	**--**	**0.71**	**0.68**	**0.56**	**1.42**
PFS QALYs	--	0.37	0.35	0.29	0.82
Progression QALYs	--	0.34	0.32	0.27	0.60
Total Life Years (OS)	**--**	**1.12**	**1.07**	**0.89**	**2.02**
PFS LYs	--	0.57	0.54	0.45	1.04
Progression LYs	--	0.55	0.53	0.44	0.98

Sensitivity Analyses

Findings from sensitivity analyses are described in detail in the full report. Results were by far most sensitive to the PFS hazard ratios for each intervention versus LEN+DEX, followed by the estimated link between PFS and OS (2.45 months of OS for each month of PFS), drug costs, dosage intensity,

and health state utilities.[6] However, even at the low end of each varied range, cost-effectiveness estimates still exceeded commonly-accepted thresholds for nearly all variables.

In addition to the BOR+DEX comparison described above, we also conducted a number of scenario analyses in which we (a) increased the number of months of OS achieved for each additional month of PFS; (b) adjusted LEN+DEX progression-free survival based on data from the comparator arms of the newest trials; and (c) estimated improved quality of life with triplet vs. doublet therapy based on recent trial data. Full results are available in Appendix E. Findings were similar to those of primary analyses for all of these scenarios.

Threshold Analyses

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table ES6 for second-line treatments and Table ES7 for third-line treatments. For IX, there was no positive price that could be charged and achieve a level of cost-effectiveness-threshold of $50,000/QALY. This occurs primarily for two reasons, both related to the fact that these newer agents are administered as part of a triplet regimen. First, each drug is given in combination with LEN+DEX, which is relatively costly on its own. Second, the additional progression-free survival obtained by using these triplet regimens leads to higher costs for LEN+DEX, as each regimen calls for LEN+DEX to be administered on a treat-to-progression basis. This phenomenon of requiring discounts approaching or exceeding 100% to reach standard cost-effectiveness levels is well known and relates to situations when current treatment is already near or beyond the cost-effectiveness threshold.[41] Adding even more expense with a new treatment on top of existing treatment, as is the case for multiple myeloma drugs, means that to reach standard cost-effectiveness levels the entire regimen, including the older, existing drugs that are part of the regimen, would need to be deeply discounted, or certain treatment costs must be considered "unrelated" and excluded from the economic evaluation.[42,43]

Table ES6. Threshold analysis for unit price per drug for second-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

Table ES7. Threshold analysis for unit price per drug for third-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

Note that PAN is removed from this table due to concerns with its comparison to LEN+DEX. The wholesale acquisition cost of PAN is $1,222 per capsule. In comparsion to BOR+DEX, cost-effectiveness at this price is approximately $10,000 per QALY gained. The price per capsule for PAN could increase to $1,980 (a 62% premium), $2,933 (140%), and $3,886 (218%), and still achieve cost-effectiveness ratios of $50,000, $100,000, and $150,000 per QALY gained. As described previously, however, all results for PAN should be interpreted with caution given concerns with the available clinical evidence.

As one method of addressing concerns about the policy relevance of "negative" pricing, we also considered a scenario in which we allowed for equal discounts on both the new drug and LEN in these triplet regimens. The results of this analysis are shown in Tables ES8 and ES9. While significant discounts would be required to achieve cost-effectiveness thresholds of $50,000 - $150,000 per QALY (from ~30%-97% depending on regimen and threshold), the negative pricing situation is avoided.

Table ES8. Threshold analysis for second-line treatment: Percentage discount and price for both drugs

Willingness-to-pay	Discount from WAC					
	CFZ/LEN		ELO/LEN		IX/LEN	
$50,000	83.5%	$307/$83	95.1%	$116/$25	90.5%	$275/$48
$100,000	55.6%	$827/$223	82.5%	$414/$88	78.7%	$616/$107
$150,000	27.8%	$1,344/$363	69.9%	$713/$151	66.9%	$957/$166
WAC price per vial/capsule		**$1,862/$503**		**$2,368/$503**		**$2,890/$503**

Table ES9. Threshold analysis for third-line treatment: Percentage discount and price for both drugs

Willingness-to-pay	Discount from WAC					
	CFZ/LEN		ELO/LEN		IX/LEN	
$50,000	87.9%	$225/$61	96.7%	$78/$17	91.9%	$234/$41
$100,000	64.6%	$659/$178	85.5%	$343/$73	81.3%	$540/$94
$150,000	41.3%	$1,093/$295	74.3%	$609/$129	70.7%	$847/$147
WAC price per vial/capsule		**$1,862/$503**		**$2,368/$503**		**$2,890/$503**

Note that we did not formally explore changes in the price of both PAN and BOR that would yield cost-effectiveness ratios ranging from $50,000 to $150,000 per QALY vs. BOR+DEX, as the resulting premiums would be even greater than those that would result from changing the price of PAN alone.

Potential Budgetary Impact Model: *Results*

We used available prevalence data to estimate the number of individuals with MM in the U.S. (approximately 92,000).[44] Data from a claims-based analysis suggested proportions of patients receiving second- and third-line therapy (approximately 37% and 13% respectively). This resulted in candidate population sizes of 33,941 and 11,930 patients.

Based on several criteria, we estimated that the theoretical "unmanaged" uptake of these newest regimens would be very high, with 75% of candidate patients receiving at least one of the regimens of interest by year five following their introduction. Uptake was assumed to be very high because of the gains in progression-free survival that have been demonstrated in available clinical trials as well as acceptable levels of toxicity in most circumstances. Uptake was apportioned equally to the three second-line regimens of interest (i.e., 25% each by year 5) and the four third-line regimens (18.75% each by year 5). Note that this analysis is performed from an *ex ante* perspective; that is, it treats all of the drugs being evaluated as though they will be new to market, whether or not they have already been launched. We estimated the net costs of adding each drug to LEN+DEX (or BOR+DEX for PAN+BOR+DEX), assuming no current use of the drug.

Table ES10 presents the potential budgetary impact of the three second-line regimens in the candidate population, assuming the uptake pattern previously described. Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 8,485 persons receiving each regimen for one or more years, or 25,455 patients across all three regimens. The average potential budget impact per year is approximately $226 million for CFZ+LEN+DEX, or 25% of the budget impact threshold of $904 million for a new drug. Average potential budget impact per year is estimated to be approximately $395 million per year for ELO+LEN+DEX (44% of the threshold), and approximately $330 million for IX+LEN+DEX (35% of threshold).

Table ES10. Potential budget impact (BI) of second-line regimens based on assumed patterns of uptake (25% per regimen by Year 5)

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Regimen	Eligible Population	Number Treated	Annual BI per Patient	Total BI (millions)	Number Treated	Weighted BI per Patient*	Avg. BI/Year (millions)
CFZ+LEN+DEX	33,941	1,697	$107,422	$182.3	8,485	$133,097	$225.9
ELO+LEN+DEX	33,941	1,697	$122,566	$208.0	8,485	$232,848	$395.1
IX+LEN+DEX	33,941	1,697	$94,463	$160.3	8,485	$194,388	$329.9
Total	33,941	5,091	$108,150	$550.6	25,455	$186,777	$950.9

*For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year.

Potential budget impact was lower for third-line regimens due to the smaller size of the candidate population and the division of uptake by four regimens rather than three. The third-line budget impact comparator for PAN+BOR+DEX was calculated relative to BOR+DEX, as this is the more realistic comparator for budget impact considerations. Average potential budget impact per year is approximately $59 million for CFZ+LEN+DEX, approximately $99 million per year for ELO+LEN+DEX, approximately $83 million for IX+LEN+DEX, and approximately $12 million for PAN+BOR+DEX. No regimen approached the potential budget impact threshold of $904 million for a new drug.

Table ES11. Potential budget impact (BI) of third-line regimens based on assumed patterns of uptake (18.75% per regimen by Year 5)

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Regimen	Eligible Population	Number Treated	Annual BI per Patient	Total BI (millions)	Number Treated	Weighted BI per Patient*	Avg. BI/Year (millions)
CFZ+LEN+DEX	11,930	447	$106,239	$47.5	2,235	$132,358	$59.2
ELO+LEN+DEX	11,930	447	$121,295	$54.2	2,235	$222,438	$99.4
IX+LEN+DEX	11,930	447	$92,890	$41.5	2,235	$185,379	$82.9
PAN+BOR+DEX**	11,930	447	$65,926	$29.5	2,235	$26,414	$11.8
Total	11,930	1,788	$96,588	$172.7	8,940	$141,648	$253.3

*For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year.
**vs. BOR+DEX

Value-Based Price Benchmark

The draft value-based price benchmark results are shown in Table ES12 for second-line treatments. These price benchmarks are taken from the analysis of long-term cost-effectiveness shown in Tables ES6 and ES7. They represent the prices for the individual new drug, i.e., CFZ, ELO, IX and PAN that would be required to align with established cost-effectiveness thresholds. As noted above, we also performed analyses to determine the prices at which discounts to both the new drugs and to LEN or BOR would be able to meet cost-effectiveness thresholds, but we are not using

those figures as the primary source for our value-based price benchmarks because we do not believe there is currently a mechanism through which it is likely that "regimen" discounts can be negotiated or administered in the U.S. health care system. If this could be achieved, value-based price benchmarks for newer drugs would be higher, as shown in Tables ES8 and ES9.

Therefore, the ICER value-based price benchmark for second-line CFZ is $673 to $1,267 per vial. This price represents a 32%-64% discount from the estimated cost of CFZ. The draft ICER value-based price benchmark for second-line ELO is $267 to $588 per 400 mg vial, representing a 75%-89% discount from the cost per vial. The draft ICER value-based price benchmark for second-line IX is $181 to $587 per capsule, representing an 80%-94% discount from the WAC price. Greater discounts are required for those regimens with "treat to progression" dosing schedules.

Table ES12. Draft value-based price benchmarks for second-line regimens

Regimen	WAC Price per Vial/Capsule	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Draft Value-Based Price Benchmark
CFZ+LEN+DEX	$1,862	$673	$1,267	$673 to $1,267
ELO+LEN+DEX	$2,368	$267	$588	$267 to $588
IX+LEN+DEX	$2,890	$181	$587	$181 to $587

Our draft value-based benchmark prices for each third-line regimen are shown in Table ES13. The draft ICER value-based price benchmark for CFZ as a third-line MM treatment, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $432 to $974 per vial. This price represents a 48%-77% discount from the WAC price. The draft ICER value-based price benchmark for third-line ELO is $178 to $466 per vial, representing an 80%-93% discount from the per-vial cost. The draft ICER value-based price benchmark for third-line IX would be $74 to $440 per capsule, or an 85%-97% discount. The price benchmarks for PAN ($2,933-$3,886 per vial) are listed in relation to use of this agent with BOR+DEX versus BOR+DEX alone, based on the results of our scenario analyses, as this would be the more realistic comparator for pricing considerations.

Table ES13. Draft value-based price benchmarks for third-line regimens

Regimen	WAC Price per Vial/Capsule	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Draft Value-Based Price Benchmark
CFZ+LEN+DEX	$1,862	$432	$974	$432 to $974
ELO+LEN+DEX	$2,368	$178	$466	$178 to $466
IX+LEN+DEX	$2,890	$74	$440	$74 to $440
PAN+BOR+DEX*	$1,222	$2,933	$3,886	$2,933 to $3,886

*Compared to BOR+DEX

Comparative Value: *Summary and Comment*

Our model results are consistent with clinical trial results demonstrating that newer regimens for second- and third-line use in multiple myeloma appear to confer clinical benefits in terms of lengthening progression-free and overall survival as well as improved quality of life. However, at current wholesale acquisition costs, the estimated long-term incremental cost-effectiveness of these regimens exceeds commonly-cited thresholds, meaning that at list price they do not achieve levels considered to represent high value. Achieving levels of value more closely aligned with patient benefit would require substantial discounts from the list price in many cases, and in some cases, there is no price for the newest agents that would achieve these thresholds.

We note again here that health economists and technology assessment organizations have struggled with situations in which a new intervention that improves health outcomes does not appear to be cost-effective even when the price is close to or approaches zero.[41] In many cases, as has been illustrated in our results, adding very expensive new treatments on to existing treatments that are already marginally cost-effective at best can, by extending the amount of time that the entire package of treatments is taken, lead to overall care costs that cannot reach cost-effectiveness thresholds unless the price for the entire package of treatments is deeply discounted. One solution that has been proposed in the literature is to treat any additional costs brought about by prolonged use of the existing standard of care as "unrelated," and so exclude them from the evaluation of the cost-effectiveness of the new intervention.[45] However, this approach is not without controversy, [46,47] and so we did not attempt its calculation for this review. It is likely that in areas like multiple myeloma, mechanisms to seek discounts on the costs for all components of a multi-drug regimen will need to be developed in order for the addition of new drugs on top of existing drugs to meet reasonable cost-effectiveness thresholds.

1. Background

1.1 Introduction

Background

Normally, plasma cells make up less than one percent of cells in the bone marrow. Multiple myeloma (MM) is a hematological cancer in which the bone marrow produces an overabundance of malignant plasma cells. Ultimately, the proliferation of plasma cells can cause bone and skeletal damage, anemia, hypercalcemia, neutropenia, and renal failure.[1] Like all cancers, MM is also a heterogeneous condition; prognosis varies depending on a number of variables, including the profile of the underlying genetic abnormalities, comorbid conditions, and the degree of response to initial treatment.

MM is the second most common hematological malignancy after non-Hodgkin's lymphoma; approximately 25,000 cases of MM are diagnosed in the U.S. annually, with three-quarters of affected individuals over 70 years of age.[2] There is no cure for MM, but its progression can be relatively slow in many individuals, often involving multiple rounds of remission after treatment, followed by subsequent relapse. Recent advances in therapy have greatly improved disease prognosis. Nearly half of all patients will survive at least five years after diagnosis, and nearly 100,000 individuals are currently living with the disease in the U.S.[2]

Over the past decade the treatment of MM in the U.S. has been anchored by the use of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), often given in combination with the steroid dexamethasone as well as other cytotoxic agents. Drugs that have become mainstays of treatment include the PI bortezomib (Velcade®, Takeda Millennium) as well as the second-generation IMiD lenalidomide (Revlimid®, Celgene), which has largely supplanted earlier use of thalidomide. Depending on a patient's cytogenetic risk (a marker of the aggressiveness of disease), these agents may be used as induction therapy prior to autologous stem cell transplant (or as first-line treatment in those ineligible for transplant due to age, frailty, and/or organ dysfunction), and as maintenance therapy following transplant.[4] More recently, newer agents have been approved for treatment in patients who are refractory to first-line treatment or who relapse following such treatment, including newer-generation IMiDs and PIs as well as monoclonal antibodies, immunostimulatory antibodies, and histone deacetylase inhibitors (see Section 2 for detailed descriptions of classes and agents). There is uncertainty, however, regarding the comparative tradeoffs between effectiveness and toxicity of these therapies, their various combinations, and options for their sequencing in the care of individual patients.

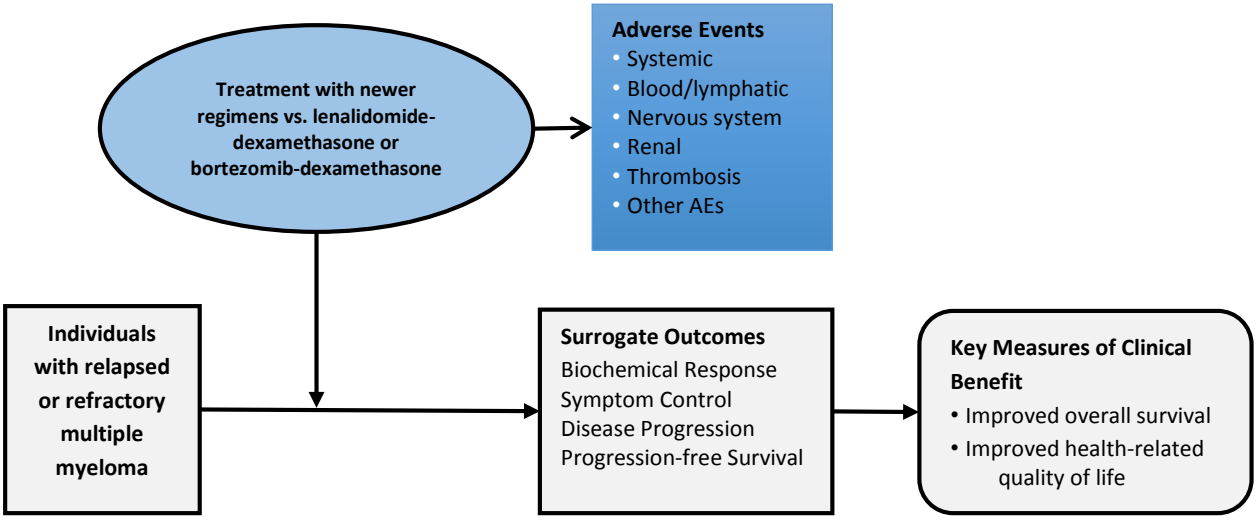
Scope of the Assessment

This assessment evaluates the health and economic outcomes of multiple treatment regimens for relapsed or refractory MM. The scope is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.[48]

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.

Figure 1. Analytic framework



Populations

The population of focus for the review included adults with MM whose disease has not responded to at least one previous line of treatment (i.e., refractory) or has relapsed following such treatment, are not currently on maintenance treatment, and are not being considered for hematopoietic stem cell transplant.

Interventions

The interventions of interest are listed below. Regimens listed are based on FDA-labeled indications for treatment of relapsed/refractory disease as well as expert input regarding common treatment approaches for the populations of interest.

- Carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- Daratumumab monotherapy (DARA)

- Elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- Ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)
- Panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)
- Pomalidomide with low-dose dexamethasone (POM+LoDEX)

Comparators

The primary comparators of interest included the historical standard treatments for this population, either lenalidomide or bortezomib in combination with dexamethasone; these also represented the most common comparators in available clinical trials. We recognize, however, that several recent trials have involved comparisons to dexamethasone alone and/or placebo, or have only been studied using single-arm designs. To account for these differences, we present results across all comparators as well as stratified by type of comparator for agents whose effects have been compared to multiple regimens.

Outcomes

This review examined key clinical outcomes associated with MM, including surrogate outcomes common to cancer trials. In order to inform considerations regarding possible treatment sequencing, we summarize results on an overall basis as well as stratified by number of prior treatments where such data were available. Outcomes of interest included the following:

- Overall survival
- Disease progression-related measures (progression-free survival, time to progression)
- Biochemical response (overall response rate)
- Health-related quality of life
- Treatment-related adverse events:
    - Rates of Grade 3 or 4 key adverse events
    - Rates of serious adverse events
    - Discontinuation due to adverse events
    - Treatment-related deaths

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration and time period.

Settings

We considered all relevant settings, including inpatient, clinic, and outpatient settings.

2. The Topic in Context

As noted previously, survival in MM has greatly improved since the introduction of PI and IMiD therapy. Data from one institutional study indicates median survival of nearly four years among newly-diagnosed patients using these agents versus 2.5 years in an historical cohort;[49] among relapsed patients, survival has more than doubled (median of 2.5 versus 1.2 years). However, survival among patients with inadequate response or relapse while receiving treatment with PI and/or IMiD therapy remains poor, averaging approximately six months.[3] In the setting of relapsed and/or refractory disease, treatment is guided largely by four major factors: (1) the presence of "aggressive" or "high-risk" disease characteristics; (2) the level and duration of response as well as toxicity experienced with prior treatment; (3) patient overall functional status and comorbidities that raise risks of treatment; and (4) patient values regarding the trade-offs between the potential benefits and side effects of additional treatment options.[4,5] Aggressive, "high-risk" disease less likely to respond well to treatment is characterized by cytogenetic abnormalities (e.g., t[14:16], del17p13), extensive skeletal disease, the presence of plasma cell leukemia in addition to MM, and other factors. With the availability of PI and IMiD therapy, median survival is now 8-10 years among patients with standard-risk disease, but is typically only 2-3 years in those whose disease has high-risk features.[6,7]

There remains a debate among oncologists about the appropriate intensity of treatment in relation to risk, however, with some preferring to employ all available active agents as early in the disease course as possible, and others reserving aggressive therapy for high-risk patients and using a "disease control" approach that maximizes quality of life and minimizes toxicity in others. This distinction in approach to practice has been termed the "sprint" approach to treatment versus the "marathon" approach.[8] Other factors that influence the balance of benefits and risks from treatment include older age, impaired functioning and/or Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of certain comorbidities (e.g., pulmonary disease, renal impairment).[50]

Biochemical response to treatment is measured based on the level of monoclonal (M) protein in serum and urine as a marker of clonal plasma cell activity. Survival has been shown to be more than twice as long in newly-diagnosed patients with complete versus partial response to their first course of treatment. However, following disease progression, the relative impact of the level of response is less certain, as complete response (CR) is not consistently predictive of overall or even progression-free survival in these patients.[51] In addition, reliance on CR as a surrogate for prolonged remission or survival may be problematic on its face, as data used to determine CR are not yet fully standardized across laboratories; toxicity tradeoffs for certain regimens make attainment of CR unrealistic; and observational data suggest that patients with standard-risk disease attain similar survival regardless of response status.[52]

Introduction of these new agents has greatly expanded treatment options for patients and clinicians, leading to substantial variation in the care pathways for individual patients. In addition to differences in treatment philosophy around the use of aggressive treatment in the early stages of MM, guidelines from multiple clinical societies suggest many potentially appropriate treatment regimens and combinations for any given type of patient and sequence of treatment.[9,10]

The newest agents have also become available in an era in which the costs of managing the condition and the financial burden borne by patients are substantial. The cost of a single course of drug therapy for MM in the United States has been estimated to range from $75,000 - $250,000 for patients with relapsed or refractory disease; these estimates are likely conservative, given the increasing use of triplet therapy and "treat to progression" labeling for the newest agents.[11] Out-of-pocket expenses for a single new cancer drug are estimated to total $20,000-$30,000 annually, approximately half of the average annual household income in the U.S.[12,13] Recent surveys indicate that one-third of working-age cancer patients have had to borrow money or go into debt to pay for treatment, and bankruptcy rates for cancer patients are 2-3 times higher than individuals of comparable age, sex, and location.[14,15]

Definitions[4,33]

Risk stratification definitions are evolving. Current definitions are below:

- *High risk*: t(14;16), t(14;20), or del17p13 mutations, lactate dehydrogenase (LDH) levels ≥2 times of normal, features of plasma cell leukemia, high risk signature on gene expression profiling
- *Intermediate risk*: t(4;14) or gain (1q) mutations
- *Standard risk*: all patients whose disease lacks intermediate- or high-risk features

Response criteria:

- *Complete response*: negative for M protein in serum/urine by immunofixation electrophoresis (IFE); disappearance of soft tissue plasmacytomas; and <5% plasma cells in bone marrow (normal free light chain [FLC] ratio in patients whose only measurable disease is by serum FLC testing)
- *Very good partial response*: ≥90% reduction in serum M protein plus urine M component <100 mg/24h; or >90% decrease in difference between involved and uninvolved FLC levels in patients without measurable disease by other means
- *Partial response*: ≥50% reduction in serum M protein and reduction in 24-hour urine M protein by ≥90% or to <200 mg/24h; or ≥50% decrease in difference between involved and uninvolved FLC levels in patients without measurable disease by other means
- *Minimal response*: ≥25% but ≤49% reduction in serum M protein and reduction in 24-hour urine M protein 50-89%

- *Progressive disease*: increase of 25% from lowest response value in serum M, urine M, and/or differences in FLC levels; development of new bone lesions or soft tissue plasmacytomas or definite increase in size; development of disease-attributable hypercalcemia

NOTE: *patients without any objective evidence of at least a partial response to treatment have a relatively poor prognosis, so regulatory agencies are generally interested in the proportion of patients who achieve a partial response or better*.[4]

Refractory disease: No response to current treatment (refractory) or evidence of progressive disease within 60 days of last treatment (relapsed and refractory).

Double refractory disease: MM which has been refractory to both IMiD and PI therapy.

Relapsed disease: Initial response to treatment followed by evidence of progressive disease more than 60 days after completion of last treatment.

Maintenance treatment: use of chemotherapy and/or biologic agents to suppress residual MM cells during periods of remission. Discontinued when progressive disease is observed.

ECOG performance status: a measure of functional status and ability to perform activities of daily living on a 6-point scale: 0 (fully active); 1 (restricted only in strenuous activity); 2 (ambulatory and capable of self-care but unable to work); 3 (capable of only limited self-care, confined to bed or chair >50% of waking hours); 4 (completely disabled); 5 (dead).

Disease staging: Two systems have been used. Durie-Salmon staging is based on hemoglobin, serum calcium, bone radiography, and M protein levels. The newer International Staging System (ISS) relies on β2 microglobulin and albumin levels, and is generally preferred for clinical use. Both systems have three stages, with higher-number stages indicating poorer prognosis and need for more aggressive treatment.

Major Therapeutic Alternatives

The major classes of drugs to treat MM that are the focus for this review are described below. Most of the agents listed are used in combination with dexamethasone, a synthetic corticosteroid that has been shown to be cytotoxic to MM cell lines at high doses and has additional anti-inflammatory properties that may be beneficial to patients with MM.[53] Key attributes of the drugs considered for this review can be found in Table 1.

Newer agents received FDA approval primarily based on improvements in progression-free survival (PFS), which is defined as the length of time during or after treatment that a patient lives with cancer without evidence of worsening disease. PFS is an important surrogate endpoint for measuring the benefits of new cancer therapies in clinical trials, and both PFS and time to

progression (TTP) have become the standard for regulatory approval of treatments for MM. However, PFS and TTP may be problematic as surrogates for overall survival in clinical practice, as they have not been shown to be universally predictive of a survival benefit. Clinicians and methodologists differ about how meaningful outcomes other than overall survival and health-related quality of life are in guiding the selection and timing of the use of different drugs.

Table 1. Drugs of interest for the evidence review

Drug (Brand Name)	Class	Administration & Dosage Form	Dosage	Treatment Duration	Unit Price (USD)‡
Carfilzomib (CFZ) (Kyprolis®; Onyx/Amgen)	Proteasome inhibitor	Intravenous *Powder for solution*	Starting dose 20 mg/m^2, escalated to 27 mg/m^2	18 cycles	$1,861.95 for 60 mg vial
Daratumumab (DARA) (Darzalex™; Janssen Biotech)	CD38-directed monoclonal antibody	Intravenous *Solution*	16 mg/kg	Until progression	$450.00 for 5 ml vial; $1,800.00 for 20 ml vial
Elotuzumab (ELO) (Empliciti™; Bristol Myers-Squibb)	SLAMF7-directed immunostimulatory antibody	Intravenous *Powder for solution*	10 mg/kg	Until progression	$1,776.00 for 300 mg vial; $2,368.00 for 400 mg vial
Ixazomib (IX) (Ninlaro®; Takeda Millennium)	Proteasome inhibitor	Oral *Capsule*	4 mg	Until progression	$2,890.00/cap
Panobinostat (PAN) (Farydak®; Novartis)	Histone deacetylase inhibitor	Oral *Capsule*	20 mg	8 - 16 cycles$^{\mu}$	$1,222.22/cap
Pomalidomide (POM) (Pomalyst®; Celgene)	Immunomodulatory agent	Oral *Capsule*	4 mg	Until progression	$621.81/cap
Lenalidomide (LEN) (Revlimid®; Celgene)	Immunomodulatory agent	Oral *Capsule*	25 mg	Until progression	$502.69/cap
Bortezomib (BOR) (Velcade®; Takeda Millennium)	Proteasome inhibitor	Intravenous or subcutaneous *Powder for solution*	1.3 mg/m^2	8 cycles$^{\alpha}$	$1,612.00 for 3.5 mg vial
Dexamethasone (DEX)	Corticosteroid	Intravenous or oral	20-40 mg	Varies	$1.29/ tab$^{\beta}$

Cap=capsule; tab=tablet; α patients not previously treated with bortezomib may continue on maintenance therapy after Cycle 8; β average per capsule; μ 8 cycles + 8 additional cycles for patients with clinical benefit (unless unresolved severe or medically significant toxicity) ‡ Unit price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed March 22, 2016).

Whether data are available on overall survival or on surrogate outcomes, interpretation of clinical trial results requires judgment about what gains represent "clinically significant" improvements. To address this question, the American Society of Clinical Oncology (ASCO) has convened working groups and published recommendations in four cancer types (see Table 2).[23] For both overall survival and PFS, an additional 3-5 months was generally recommended as the range for minimum clinically meaningful improvements. There are currently no recommendations specific to MM, but given the consistency of these recommendations across different types of cancer, it may be reasonable to consider them when interpreting findings from trials of new agents for MM.

Table 2. Clinically-significant levels of improvement in surrogate and longer-term outcomes in four cancer types

Cancer Type	Patient Population	Primary Endpoint			Secondary Endpoint	
		Current Baseline Median OS (m)	Clinically Meaningful Improvement over Current OS (m)	Target HRs	Improvement in 1-yr Survival Rate (%)*	Improvement in PFS (m)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel-eligible patients	8 to 9	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18	4.5 to 6	0.76 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard 2nd- or 3rd-line options)	4 to 6	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; m, months; PFS, progression-free survival; *Current → target; Source: Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32(12):1277-1280.[23]

Proteasome Inhibitors

Proteasomes are multi-enzyme complexes that help clear abnormal, mutant, or cytotoxic proteins; several studies have shown that cancer cells are more reliant on proteasomes for protein clearance than normal cells.[54-56] Pre-clinical studies of bortezomib (Velcade®, Takeda Millennium) showed a direct inhibition of MM cell lines that had shown resistance to other therapies; it was approved for use in relapsed MM patients in 2003. Carfilzomib (Kyprolis®, Onyx/Amgen) is a newer-generation PI that was approved in 2015 for use with lenalidomide and dexamethasone in patients with 1-3 prior lines of treatment. Unlike bortezomib, carfilzomib irreversibly binds to the proteasome, which may provide more sustained inhibition.[57] The most recent entrant to the class is ixazomib (Ninlaro®, Takeda Millennium), a reversible inhibitor of the β_5 subunit of the proteasome that was approved in 2015 for use with lenalidomide and dexamethasone in patients with at least one prior line of treatment. While bortezomib and carfilzomib require parenteral administration, ixazomib is an oral agent, which allows for all-oral triplet combination therapy.

Immunomodulatory Drugs

Clinical studies have shown that IMiDs bind preferentially to the protein cereblon, which facilitates the degradation of critical transcription factors for multiple myeloma cells and inhibits further cell growth.[58-60] Thalidomide (Thalomid®, Celgene) and its analogue lenalidomide (Revlimid®, Celgene) were both FDA-approved in 2006 in combination with dexamethasone; thalidomide was approved for newly-diagnosed patients and lenalidomide was indicated for those who had received at least one prior line of treatment. A second thalidomide analogue, pomalidomide (Pomalyst®, Celgene), was approved for use with low-dose dexamethasone in 2013 for patients who had received two prior therapies including lenalidomide and a PI. All IMiDs are available as oral agents, but the IMiDs differ in both their effects on MM cell proliferation and toxicity. For example, thalidomide does not materially affect MM cell proliferation or survival, but lenalidomide and pomalidomide do.[61] Also, clinical benefits are seen at successively lower daily doses (800, 25, and 4 mg for thalidomide, lenalidomide, and pomalidomide, respectively), which may correlate with reduced rates of myelosuppression, neuropathy, and asthenia for newer-generation IMiDs versus thalidomide.[62] There have been no head-to-head clinical trials of the IMiDs, however.

Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) are enzymes that are key mediators of DNA regulation and expression. Clinical studies have shown that inhibition of these enzymes interferes with cell-cycle progression and replication of DNA in cancer cell lines as well as synergistic effects when used with a PI.[63] Panobinostat (Farydak®, Novartis), an oral agent, was FDA-approved in 2015 as the first HDAC inhibitor for treatment of MM. It is indicated for use with bortezomib and dexamethasone in patients who have received at least two prior lines of treatment, including bortezomib and an IMiD.

Targeted Antibody Therapies

There has long been interest in developing targeted antibodies in MM due to the range of antigens expressed on MM cells.[64] Daratumumab (Darzalex™, Janssen Biotech) is a monoclonal antibody to the CD38 protein, which is highly expressed in more than three-quarters of cases of MM.[65] Efficacy in early studies was observed when daratumumab was given as monotherapy in heavily pre-treated patients; initial FDA approval in 2015 was aligned with these data, with an indication for monotherapy in patients who have received at least three prior lines of treatment, including a PI and an IMiD, or who are double refractory to a PI or IMiD. Combination studies with PI and IMiD therapy are ongoing. Elotuzumab (Empliciti™, Bristol Myers-Squibb) is an immunostimulatory, SLAMF7-directed antibody to CS1, a signaling lymphocyte activating-molecule that is highly expressed on both normal and MM plasma cells.[66] Early studies of elotuzumab showed little to no clinical response when used as monotherapy,[67] but clinical benefit was observed in combination with lenalidomide and dexamethasone. The FDA approved elotuzumab in 2015 in combination with

these two agents for MM patients with 1-3 prior lines of treatment. Both daratumumab and elotuzumab are administered intravenously.

3. Summary of Coverage Policies & Clinical Guidelines

Drugs administered intravenously are usually covered under the medical benefit portion of insurance, whereas oral drugs are usually covered separately under the drug benefit. A drug benefit's formulary allows a payer to tier drugs in order to use differential patient cost-sharing as a mechanism to manage utilization of both generic and brand name drugs. Because the general structure of a medical benefit does not allow for this same tiering structure, some payers are beginning to move IV drugs from the medical benefit to the drug benefit to better manage the usage of the drug and control costs.

All of the drugs under review in this report are covered by private insurers for use within their FDA labeled indications. Some payers, such as Anthem, have developed treatment "pathways" or recommended regimens for which providers can qualify for enhanced reimbursement[68].

We have also summarized here the clinical guidelines available for the treatment of relapsed or refractory MM. We reviewed the National Comprehensive Cancer Network's (NCCN) guidelines for Multiple Myeloma, version 3.2016,[9] for each regimen within the scope, as well as guidelines from the National Institute for Health and Care Excellence (NICE)[69] and the International Myeloma Working Group (IMWG).[10] Specifically, NICE has published a myeloma pathway that recommends bortezomib monotherapy after a patient's first relapse, and subsequent treatment with lenalidomide and dexamethasone or panobinostat with bortezomib and dexamethasone.

Carfilzomib

NCCN Guidelines

NCCN includes carfilzomib with lenalidomide and dexamethasone as a preferred regimen for patients with relapsed/refractory myeloma. NCCN designated this regimen as category 1, which is defined as having uniform NCCN consensus that the intervention is appropriate, based upon high-level evidence.

NICE Guidelines

A NICE appraisal of both carfilzomib with lenalidomide with dexamethasone and carfilzomib with dexamethasone alone is currently underway, with scheduled publication in April 2017.[70]

Daratumumab

NCCN Guidelines

The NCCN guideline update in January 2016, reflected in version 3.2016, added daratumumab to the list of preferred regimens for patients with relapsed/refractory myeloma on the basis of category 2A evidence and with a footnote specifying that this drug is indicated for patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMID), or patients who are refractory to both a PI and an IMID.

NICE Guidelines

NICE guidelines regarding daratumumab are currently in development.[71]

Elotuzumab

NCCN Guidelines

The NCCN guideline update in January 2016, reflected in version 3.2016, added elotuzumab with lenalidomide and dexamethasone to the list of preferred regimens for patients with relapsed/refractory myeloma. The update cites evidence categorized as category 1, and specifies that the drug is indicated for patients who have received one to three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent.

NICE Guidelines

NICE guidelines regarding elotuzumab are currently in development.[72]

Ixazomib

NCCN Guidelines

The NCCN guideline update in January 2016, reflected in version 3.2016, added ixazomib plus lenalidomide and dexamethasone to its list of preferred regimens for patients with relapsed/refractory myeloma and designated the regimen as category 1. NCCN included a footnote specifying an indication for the treatment of patients who have received at least one prior therapy.

NICE Guidelines

NICE guidelines regarding ixazomib are currently in development.[73]

Panobinostat

NCCN Guidelines

The NCCN guidelines include on its list of preferred regimens panobinostat plus bortezomib and dexamethasone for patients with relapsed/refractory myeloma and designate the regimen as a category 1 option for patients who have received at least two prior therapies, including an immunomodulatory drug and bortezomib.

NICE Guidelines

NICE guidelines suggest panobinostat plus bortezomib and dexamethasone as a possible treatment option for people with relapsed or refractory multiple myeloma, specifically those patients who have been treated with at least two other treatments, including bortezomib and an immunomodulatory drug.[69]

Pomalidomide

NCCN Guidelines

The NCCN guidelines include pomalidomide combined with dexamethasone as a preferred regimen. The guidelines indicate this treatment for patients that have been treated with at least two prior therapies, including an immunomodulatory agent and bortezomib, and patients whose disease has progressed within 60 days of completion of prior therapy. NCCN designates this regimen as category 1.

NICE Guidelines

For patients with relapsed/refractory multiple myeloma who have been treated with at least two prior regimens, including lenalidomide and bortezomib, NICE specifically does *not* recommend pomalidomide plus dexamethasone.[69]

IMWG Recommendations[10]

The International Myeloma Working Group (IMWG) guidelines recommend the following for the management of relapsed myeloma:

For first relapse:

- Patients, after six to nine months treatment-free, can be retreated with initial treatment or can save initial treatment for re-treatment during a second relapse.
- Patients with a negative experience with initial treatment (poor response or toxicity) should be treated with an agent not previously used.
- For regimens with lenalidomide, bortezomib, or both, the choice of treatment is based on response and tolerability, as well as other factors including prior treatment, co-morbidities and access to other agents.
- Patients with more aggressive disease should consider three- or four-drug regimens; patients with less aggressive disease should consider one- or two-drug regimens.
- Patients with more aggressive disease should be treated to progression. Patients with less aggressive disease can consider incorporating treatment-free intervals with consideration from their physician.
- In patients refractory to bortezomib and lenalidomide, use carfilzomib and pomalidomide.

For second relapse and beyond:

- When appropriate, patients should participate in a clinical trial.
- Patients who experience a second relapse (or beyond) should be treated with at least one agent not previously used.
- Patients with more aggressive disease should consider three- or four-drug regimens; patients with less aggressive disease should consider one- or two-drug regimens.
- Patients should receive treatment until no longer tolerated or until the disease progresses.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of newer treatment regimens for relapsed and/or refractory multiple myeloma, we abstracted evidence from available clinical studies of these agents, whether in published, unpublished, or in abstract form. Regimens of interest included:

- Carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- Daratumumab monotherapy (DARA)
- Elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- Ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)
- Panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)
- Pomalidomide with low-dose dexamethasone (POM+LoDEX)

As described previously in the Background section, comparators of interest included lenalidomide plus dexamethasone, bortezomib with dexamethasone, and dexamethasone alone. Our review focused on clinical benefits (i.e., progression-free and overall survival, biochemical response, quality of life) as well as potential harms (drug-related adverse events). We focused attention on both descriptive and quantitative analyses of these outcomes, including direct comparisons available from the individual trials as well as indirect comparisons between the newer regimens.

To inform clinical and coverage policy decisions regarding the potential sequence of treatment (e.g., second- versus third-line or later use), where data were available, results for key outcomes were stratified by the number of prior lines of therapy patients had received. Other subgroups of interest included patients with high cytogenetic risk and patients who were refractory to one or more prior treatments.

4.2 Methods

We included evidence from randomized controlled trials (RCTs) as well as high-quality systematic reviews where available. Single-arm studies were included if these represented the only form of evidence available for a particular agent. We did not restrict studies according to clinical development phase, comparators, or study setting; however, we limited our review to those studies that matched FDA-approved indications for use and dosing for the regimens of interest, as well as those that captured the key outcomes of interest. We excluded studies comparing one of the listed regimens for this assessment to an investigational regimen that does not have a current FDA

indication in MM. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on these MM regimens followed established best methods used in systematic review research.[74] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

The timeframe for our search spanned the period from January 1996 to January 20, 2016 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm are available in Appendix Tables A2 and A3.

Additional searches were performed to identify relevant grey literature based on an organization and source checklist developed by the Canadian Agency for Drugs and Technologies in Health (https://www.cadth.ca/resources/finding-evidence/grey-matters). Other grey literature sources included sites deemed relevant specifically for MM, such as clinical societies, research foundations, and advocacy organizations.

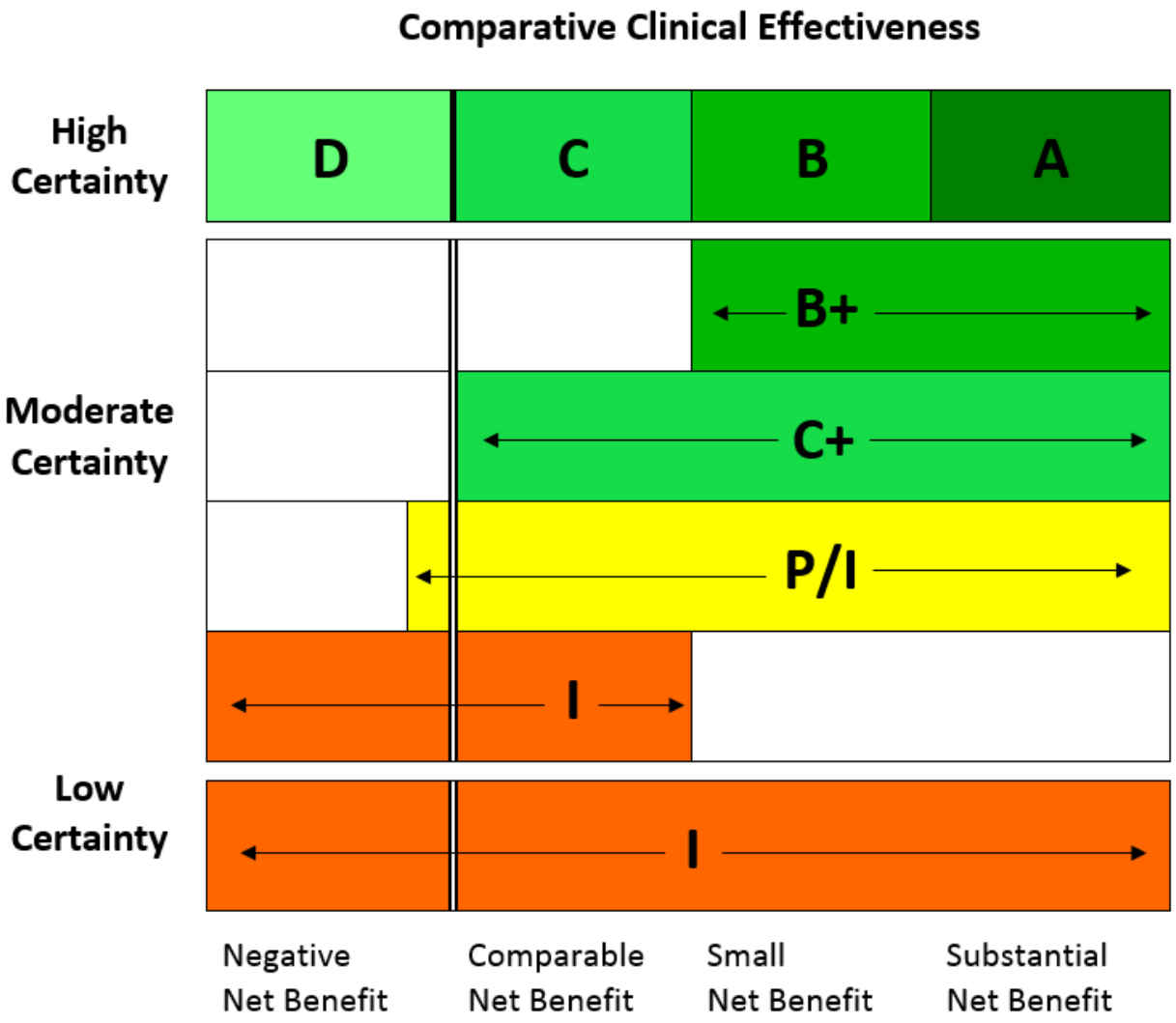
Further information on methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data can be found in the appendices.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[75]

Figure 2. ICER evidence rating matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D="Negative"**-** High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.3 Results

Study Selection

Our literature search identified 1,254 potentially relevant references (see Appendix B, Figure B1), of which 38 references met our inclusion criteria; these citations related to nine individual studies. Primary reasons for study exclusion included use of a dose or administration schedule not approved by the FDA, comparison to an experimental treatment regimen, and no information on the outcomes of interest. Details of the included studies are described in Appendix B Table B1 and key trials are summarized in Table 3.

There have been no published studies of head-to-head comparisons of the treatment regimens of interest in this review. Our search identified one published Phase III study each of CFZ+LEN+DEX and ELO+LEN+DEX compared to LEN+DEX alone.[16,17] Published Phase III studies were also identified comparing PAN+BOR+DEX to BOR+DEX alone and POM+low-dose DEX (LoDEX) to high-dose DEX (HiDEX) alone.[18,22] Finally, results of the Phase III trial of IX+LEN+DEX versus LEN+DEX were published in the interim following posting of our draft report; our summary of findings has been updated accordingly.[d,21]

We found no Phase III trials (published or unpublished) comparing DARA monotherapy to an alternative regimen of interest for this review. Available evidence was limited to the Phase II single-arm SIRIUS trial as well as a Phase I-II dose-escalation/dose-expansion study.[20,76]

Finally, we identified two Phase II randomized trials that compared different doses and/or dosing schedules of POM+DEX as well as a single Phase Ib-II RCT dose-escalation trial of two different doses of ELO+LEN+DEX.[77-79] These two studies (as well as the Phase I-II DARA study) are summarized in evidence tables but are not a focus of our review given the lack of alternative comparator treatments.

Key Studies

We identified six key studies of interest for this review. These are summarized in Table 3, including five Phase III studies and the Phase II study of DARA. Key outcomes from each trial are also provided in Table B1, and described in further detail in the sections that follow.

The trials evaluating CFZ, ELO, IX, and PAN in combination with LEN or BOR plus DEX[e] specified similar inclusion criteria. Each trial included adult patients (≥18 years of age) with measurable relapsed and/or refractory multiple myeloma. All patients had received 1-3 prior therapies and had

[d] Results of this trial were summarized in the draft evidence report using unpublished sources. The current version of this report has been updated to reflect information presented in the peer-reviewed publication of the trial.
[e] Patients in the comparator arms of the double-blind trials that evaluated IX and PAN were given a placebo in addition to LEN+DEX or BOR+DEX

adequate renal, hepatic, and hematologic function. Trial populations were similar with respect to age, ECOG performance status, ISS stage, receipt of prior stem cell transplant (SCT), and number and distribution of prior regimens. Definitions of disease risk varied (see Appendix C, Table C6), but the percentage of patients with high-risk disease ranged from 13-32% across studies reporting this element.[16-18,21]

In contrast, the MM-003 and SIRIUS trials of POM+LoDEX and DARA, respectively, included patients with more advanced levels of disease. For example, in the POM+LoDEX trial, patients must have been refractory to their previous treatment, tried at least two previous consecutive cycles of BOR and LEN (alone or in combination), and failed treatment with either BOR or LEN.[22] Whereas the majority of patients in the trials of CFZ, ELO, and IX in combination with LEN+DEX and the trial of PAN+BOR+DEX had received 1-2 previous regimens and 6-21% had prior treatment with LEN, patients in the POM+LoDEX trial had a median of five prior therapies and 94% were refractory to LEN.[22] Patients in the DARA trial also had a median of five previous treatments, and 88% were refractory to LEN.[20]

Quality of Individual Studies

Using criteria from U.S. Preventive Services Task Force (USPSTF), we rated three publications of two double-blind, placebo-controlled trials (of IX+LEN+DEX and PAN+BOR+DEX, respectively) to be of good quality.[18,21,80] We judged these reports to be of good quality because study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. We rated ten publications of six trials to be of fair quality because of the open-label design of these studies.[16,17,22,77-79,81-84] While it is the case that most of the measures of interest were based on objective reporting, there is also no clear reason for the lack of placebo control in these studies. Single-arm trials were rated as poor quality (n=2) because of the lack of comparator.[20,76] We did not assign a quality rating to the remaining 24 documents, which were obtained from conference proceedings and regulatory packages.

Table 3. Key trials

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Treatment Arm)
ASPIRE[16] **Open-label RCT** **Phase III** **Carfilzomib (CFZ)**	• Median age: 64 • ECOG=2: 9.5% • ISS Stage III: 20% • Previous SCT: 57% • High risk: 12.6% • Prior regimens (median): 2 • Prior BOR: 65.8% • Prior LEN: 19.8%	**CFZ+LEN+DEX** (n=396) • Median f/u: 32.3 m	**LEN+DEX** (n=396) • Median f/u: 31.5 m	• D/C due to AEs: 15% • SAEs: 60% • Tx-related deaths: 2%
		• OS HR: 0.79 (95% CI: 0.63-0.99; p=0.04) • PFS HR: 0.69 (95% CI: 0.57-0.83)		
		• Median PFS: 26.3 m • ORR: 87.1%	• Median PFS: 17.6 m • ORR: 66.7%, p<0.001	
SIRIUS[20] **Open-label single-arm study** **Phase II** **Daratumumab (DARA)**	• Median age: 63.5 • ECOG=2: 8% • ISS Stage III: 38% • Previous SCT: 80% • del(17p): 17% • Prior regimens (median): 5 • Refractory to LEN & BOR: 82%	**DARA** (n=106)	**None**	• D/C due to AEs: 5% • SAEs: 30% • Tx-related deaths: 0
		• Median f/u: 9.3 m • Median OS: 17.5 m (95% CI: 13.7-NE) • Median PFS: 3.7 m • ORR: 29.2%		
ELOQUENT-2[17] **Open-label RCT** **Phase III** **Elotuzumab (ELO)**	• Median age: 66 • ECOG=2: 9% • ISS Stage III: 21% • Previous SCT: 54% • del(17p): 32% • Prior regimens (median): 2 • Prior BOR: 70% • Prior LEN: 6%	**ELO+LEN+DEX** (n=321)	**LEN+DEX** (n=325)	• D/C due to AEs: 13% • SAEs: 65% • Tx-related deaths: 2%
		• Median f/u: 24.5 m • OS HR: 0.77 (95% CI: 0.61-0.97) • PFS HR: 0.70 (95% CI: 0.57-0.85; p<0.001)		
		• Median PFS: 19.4 m • ORR: 79%	• Median PFS: 14.9 m • ORR: 66%, p<0.001	
TOURMALINE-MM1[21] **Double-blind RCT** **Phase III** **Ixazomib (IX)**	• Median age: 66 • ECOG=2: 6% • ISS Stage III: 12% • Previous SCT: 57% • High risk: 19% • Prior regimens (median): 1 • Prior BOR: 69% • Prior LEN: 12%	**IX+LEN+DEX** (n=360)	**Placebo+LEN+DEX** (n=362)	• D/C due to AEs: 17% • SAEs: 47% • Tx-related deaths: NR
		• Median f/u (PFS): 23 m		
		• Deaths: 22.5%	Deaths: 24.8%	
		• PFS HR: 0.74 (95% CI: 0.59-0.94; p=0.01)		
		• Median PFS: 20.6 m • ORR: 78%	• Median PFS: 14.7 m • ORR: 72%, p=0.04	
PANORAMA-1[18] **Double-blind RCT** **Phase III** **Panobinostat (PAN)**	• Median age: 63 • ECOG=2: 5% • ISS Stage III: 22% • Previous SCT: 58% • 1 prior regimen: 51% • Prior BOR+DEX: 38% • Prior LEN: 21%	**PAN+BOR+DEX** (n=387) • Median f/u: 6.4 m	**Placebo+BOR+DEX** (n=381) • Median f/u: 5.9 m	• D/C due to AEs: 36% • SAEs: 60% • Tx-related deaths: 3%
		• OS HR: 0.94 (95% CI: 0.78-1.14; p=0.5435) • PFS HR: 0.63 (95% CI: 0.52-0.76; p<0.0001)		
		• Median PFS: 11.99 m • ORR: 60.7%	• Median PFS: 8.08 m • ORR: 54.6%, p=0.09	
MM-003[22] **Open-label RCT** **Phase III** **Pomalidomide (POM)**	• Median age 65 • ECOG 2-3: 18% • ISS Stage III: 32% • Previous SCT: 70% • Prior regimens (median): 5 • Prior LEN & BOR: 100% • Refractory to LEN & BOR: 75%	**POM+LoDEX** (n=302)	**HiDEX** (n=153)	• D/C due to AEs: 9% • SAEs: 61% • Tx-related deaths: 4%
		• Median f/u (PFS): 10.0 m • OS HR: 0.74 (95% CI: 0.56-0.97; p=0.285) • PFS HR: 0.48 (0.39-0.60; p<0.0001)		
		• Median PFS: 4.0 m • ORR: 31%	• Median PFS: 1.9 m • ORR: 10%, p<0.0001	

ECOG PS=Eastern Cooperative Oncology Group Performance Status score; ISS=International Staging System; SCT= stem cell transplant; f/u=follow-up; OS=overall survival; PFS=Progression-free survival; HR=hazard ratio; ORR=overall response rate; D/C=discontinuation; SAEs=serious adverse events; Tx=treatment

Some elements of the design and conduct of these trials limit our confidence in the comparability and generalizability across studies. Elements of concern included a lack of standardized definitions of study elements (e.g., renal impairment, risk stratification) as well as lack of consistent stratification for important subgroups (e.g., disease risk, prior refractory disease). These uncertainties do not pertain specifically to USPSTF's study quality criteria. However, we further address uncertainties in the evidence in the "Controversies and Uncertainties" section.

Clinical Benefits

A detailed review of each clinical outcome of interest is presented in the sections that follow. All key studies were designed primarily to measure improvement in PFS, with the exception of the DARA study, which used overall response rate as its primary endpoint.

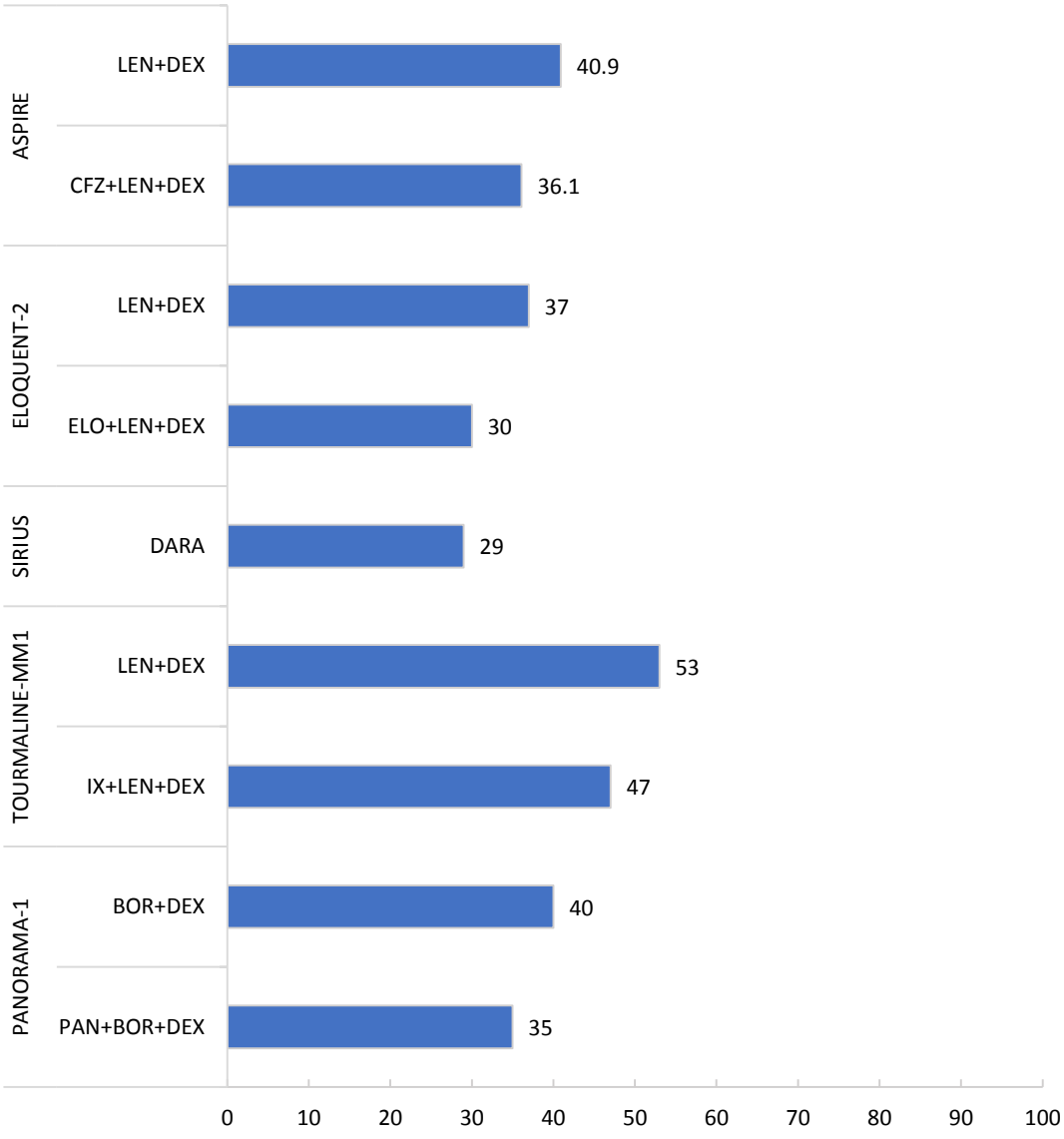
Overall Survival (OS)

Improving overall survival (OS) is the ultimate goal of an investigational cancer therapy. In cancers with longer survival trends such as MM, demonstrating improved OS may take up to five years, and will be confounded by crossover from the control to the treatment arm of the trial as well as by sequential use of additional treatment regimens. As noted previously, FDA supports the use of surrogate markers to estimate OS for the purposes of regulatory approval.[85] The current data for OS among the regimens of interest are relatively limited. All six of the key studies included data on overall survival, but only two reported final results (POM+LoDEX and PAN+BOR+DEX). POM+LoDEX was associated with a median of 4.6 months of improved survival compared to HiDEX therapy (12.7 vs. 8.1 months; HR 0.74; 95% CI 0.56-0.97; p=0.03).[22] While a similar absolute difference was noted in the PAN+BOR+DEX trial (median 40.3 vs. 35.8 months for BOR+DEX), the hazard ratio was not statistically significant (HR 0.94; 95% CI 0.78-1.14; p=0.54).[24] Data for PAN+BOR+DEX are currently available only from a conference abstract, so there is no clear explanation for the lack of a statistically-significant benefit.

In an interim analysis of overall survival, ELO+LEN+DEX improved survival by a median of 4.1 months compared to LEN+DEX (43.7 vs. 39.6 months; HR 0.77; 95% CI 0.61-0.97; p=0.03), although these data are currently only available from conference proceedings (American Society of Hematology [ASH], December 5-8, 2015).[25] Interim overall survival also favored CFZ+LEN+DEX, although median duration of survival was not yet able to be calculated (HR 0.79 vs. LEN+DEX; 95% CI 0.63-0.99; p=0.04).[16] While no comparative data on overall survival are currently available for DARA, the SIRIUS trial showed a median OS of 17.5 months (95% CI 13.7-not estimable). Although a planned interim analysis of IX+LEN+DEX did not demonstrate an OS benefit, the median overall survival has not yet been reached in either treatment arm of the IX+LEN+DEX trial, so follow-up for the final analysis is ongoing.[19,21]

As an additional comparative analysis, Figure 3 shows the percentage of reported deaths in each treatment arm of the trials of CFZ+LEN+DEX, ELO+LEN+DEX, IX+LEN+DEX, PAN+BOR+DEX, and DARA. Similar absolute reductions in reported deaths (~5-7%) were noted in the trials of CFZ, ELO, IX, and PAN, although differences were not tested statistically. The absolute rate of death (29%) was similar in the single-arm SIRIUS trial of DARA relative to these other trials (30-40%).[16-18,20,21]

Figure 3. Percent deaths reported in each treatment arm of the key MM trials



Overall survival data are presented for particular subgroups of interest below, including number of prior lines of treatment, cytogenetic or other markers of disease risk, and results in patients refractory to prior therapy. Comparisons across regimens were problematic in general, as

subgroups were not consistently defined and some analyses were missing entirely for certain regimens.

Subgroup Analyses to Inform Second- versus Third- or Later-Line Use

Stratified analyses of overall survival by prior lines of treatment were limited. In the trial of ELO+LEN+DEX, survival was improved among patients with at least two prior lines of treatment (HR 0.67, 95% CI 0.49-0.92), while the hazard ratio for patients with one prior line of treatment was 0.92 and not statistically significant.[25] Data from an ASH abstract of the trial of PAN+BOR+DEX focus only on the subset of 147 patients with two or more prior lines of treatment including BOR and an IMiD (i.e., the population in the FDA label), and reported only the median duration of overall survival (25.5 vs. 19.5 months, significance not reported).[24]

Patients in the trial of POM+LoDEX had more advanced disease, and this subgroup analysis is presented for patients with up to three versus more than three prior lines of treatment. A statistically-significant improvement in OS was observed among patients with three or fewer prior lines of treatment (median 11.1 vs. 6.9 months; HR 0.56, 95% CI 0.33-0.96; p=0.02).[82,86] In contrast, the hazard ratio for patients with more than three prior lines of treatment (0.76) was not statistically significant. No subgroup data on OS by number of prior lines of treatment are available for CFZ+LEN+DEX, IX+LEN+DEX, or DARA.

Other Subgroups

Additional subgroup analyses for OS were extremely sparse. Cytogenetic risk was determined based on the presence of genetic mutations associated with higher MM mortality. These mutations include translocations (t[4;14] and t[14;16]) and deletions (del[17p]), but somewhat different stratifications were used across trials (see Appendix Table C3). In the ELO+LEN+DEX trial, interim analyses did not indicate statistical improvements in OS for patients with either the del(17p) or t(14;16) high-risk mutations.[25] In the trial of POM+LoDEX, no statistical differences were noted for the hazard ratio among patients at "moderate-high" cytogenetic risk versus the overall sample.[22] Subgroup OS results based on disease risk were not available for CFZ+LEN+DEX, IX+LEN+DEX, PAN+BOR+DEX, or DARA.

We were able to examine the OS subgroup results for prior-refractory patients from only the trial of POM+LoDEX. This analysis was not very illustrative since non-responsiveness to BOR and/or IMiD therapy was a condition of enrollment in the trial. As a result, hazard ratios for the overall sample and the proportion refractory to both BOR and LEN (which represented 75% of the patients studied) were very similar (0.74 vs. 0.77 respectively).[22]

Progression-free Survival (PFS)

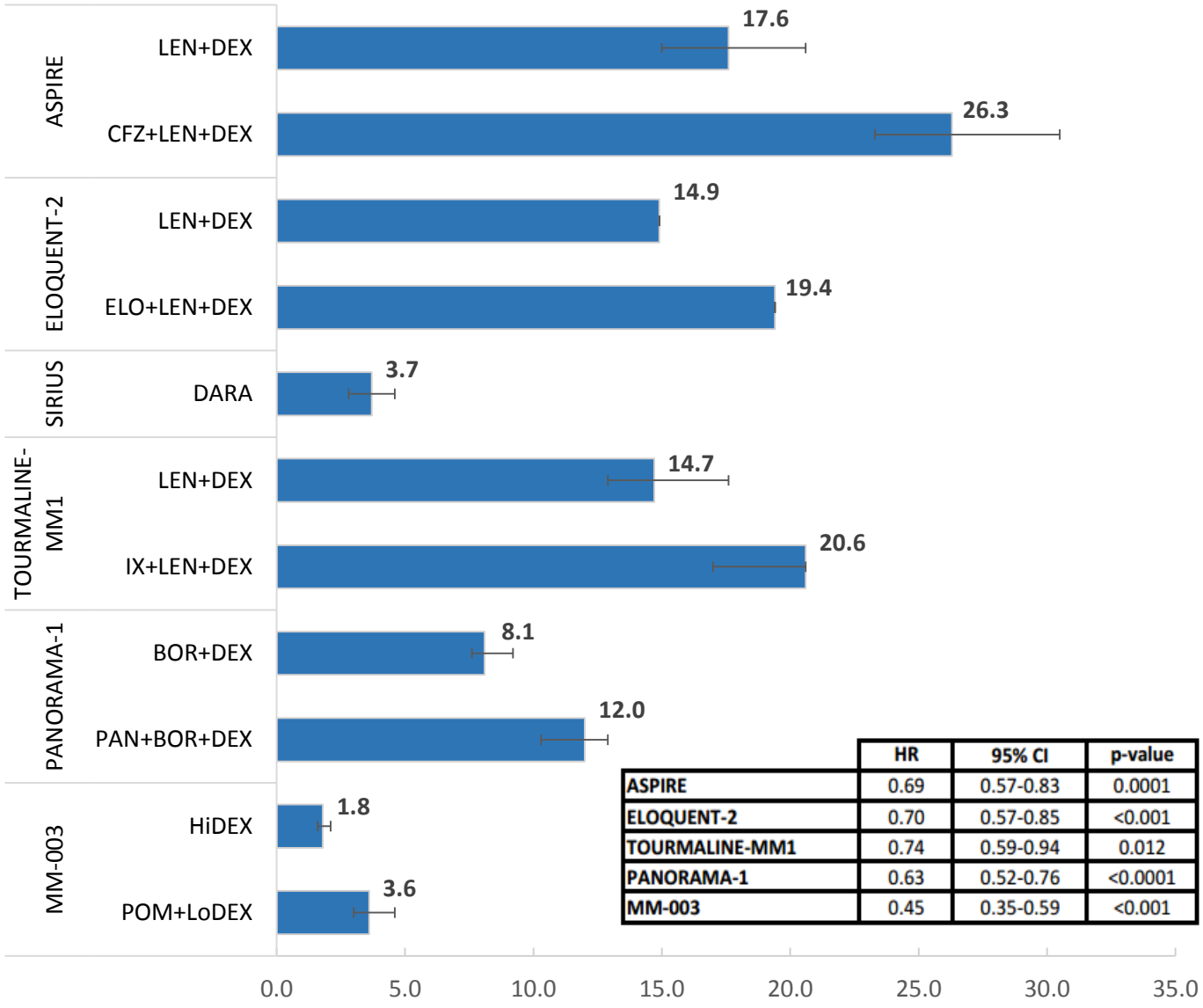
As is standard for regulatory submissions, all of the key trials other than the SIRIUS study of DARA used progression-free survival (PFS) as the primary endpoint of the study. PFS is calculated from

the time of the start of treatment to disease progression or death. It has been used as a surrogate marker for duration of overall survival, but evidence on its predictive power in relapsed and/or refractory disease is mixed (see "Controversies and Uncertainties"). As is shown in Figure 4, all of the MM regimens evaluated with RCTs showed statistically-significant improvement in PFS relative to control treatment.[16-18,20-22] Improvements in median PFS ranged between 5-9 months in the studies of ELO, CFZ, and IX, all in combination with LEN+DEX. As a point of reference, ASCO's guidance on clinically-important improvements in median PFS for other cancers ranges from 3-5 months.[23] Risk reductions for progression (as documented by hazard ratios) were very comparable across these trials, ranging from 0.69 to 0.74.

The gain in median PFS was somewhat lower for PAN+BOR+DEX (3.9 months), but median duration of follow-up was also shorter in this study (6.4 months vs. 23-32 months in the other trials) due to a higher-than-expected number of study or treatment discontinuations. As described further in the "Controversies and Uncertainties" section, the FDA Oncologic Drugs Advisory Committee (ODAC) questioned the validity of the PFS finding for the overall sample, due to censoring, drug discontinuation, and other concerns.[26] Data on PFS were also generated for the subgroup of patients who received at least two lines of treatment including BOR and an IMiD (i.e., the population in the FDA label), and are presented in further detail in the subgroup section below.

Not surprisingly, because of their more advanced disease, patients in the POM+LoDEX versus HiDEX trial had a substantially shorter duration of PFS; results did favor POM+LoDEX, however (3.6 vs. 1.8 months; HR 0.45; $p<0.001$). Also, while no comparative data are yet available, median PFS in the single-arm study of DARA, in a population with comparably advanced disease, was of similar magnitude to that of POM+LoDEX (3.7 months).

Figure 4. Median months of progression-free survival presented in the key multiple myeloma trials for the regimens of interest



	HR	95% CI	p-value
ASPIRE	0.69	0.57-0.83	0.0001
ELOQUENT-2	0.70	0.57-0.85	<0.001
TOURMALINE-MM1	0.74	0.59-0.94	0.012
PANORAMA-1	0.63	0.52-0.76	<0.0001
MM-003	0.45	0.35-0.59	<0.001

Subgroup Analyses to Inform Second- versus Third- or Later-Line Use

Unlike with OS, subgroup data on PFS by number of prior lines of treatment were more readily available. Median PFS and hazard ratios stratified by the number of prior lines of treatment can be found in Table 4. In general, differences in PFS (where available) and hazard ratios were similar across treatments for patients with one versus two or more prior lines of therapy (CFZ+LEN+DEX: 0.69 vs. 0.69; ELO+LEN+DEX: 0.75 vs. 0.65; PAN+BOR+DEX: 0.66 vs. 0.64).[16-18] The one exception was the pivotal trial of IX+LEN+DEX, which showed a somewhat better HR versus LEN+DEX alone (0.58) in patients with two or more prior treatments compared with those treated with one prior

line (0.88).[87] We have no explanation for why this regimen would have better performance in more heavily-pretreated patients.

It should be noted that the subgroup data for PAN+BOR+DEX are based on stratification of the full study sample. As mentioned previously and discussed in further detail in the "Controversies and Uncertainties" section, the FDA ODAC was concerned about the impact of high rates of censoring and drug discontinuation in the overall sample, and the FDA found more persuasive evidence of benefit in the subgroup of patients who had received two or more prior lines of treatment, including BOR and an IMiD (median PFS: 12.5 vs. 4.7 months; HR: 0.47; 95% CI: 0.31-0.72).[80] The labeled indication for PAN+BOR+DEX is restricted to this population.

As with OS, subgroup analyses in the trial of POM+LoDEX are presented for patients with three or fewer versus more than three prior lines of treatment. In contrast to the results from the OS subgroup analysis, the hazard ratio for PFS is somewhat better among more heavily pretreated patients (0.45 vs. 0.63 for ≤3 prior lines), although both represents statistically-significant effects versus HiDEX treatment.[82,86] No subgroup data on PFS by prior lines of treatment are available for DARA.

Other Subgroups

Similar to findings stratified by number of prior lines of therapy, hazard ratios among patients with higher-risk versus standard-risk cytogenetics were generally comparable (CFZ+LEN+DEX: HR 0.64 vs. 0.66; ELO+LEN+DEX: 0.64 vs. 0.77; POM+LoDEX: 0.46 vs. 0.50; see Table C3 in Appendix C).[22,88,89] Risk reduction in the trial of IX+LEN+DEX versus LEN+DEX was somewhat better for the high-risk subgroup in comparison to findings for the overall sample (0.54 vs. 0.74 respectively).[19,21,90]

We were able to compare the PFS subgroup results for prior-refractory patients from only the trials of CFZ+LEN+DEX and POM+LoDEX (see Appendix C).[16,22,86] As with OS, this analysis was not very informative for POM+LoDEX, given that lack of response to BOR and/or IMiD therapy was an entry criterion in the trial. In the trial of CFZ+LEN+DEX, the hazard ratio relative to LEN+DEX was less favorable in the refractory subgroup (0.89 vs. 0.69 for the overall population). This relationship is consistent with the understanding that double refractory patients tend to have more aggressive disease subtypes. However, the analysis was conducted in a small subset (n=51) of double-refractory patients, so findings should be interpreted with caution.

Additional subgroup results are presented in the evidence tables in Appendix B.

Table 4. PFS results: overall and stratified by number of prior lines of therapy

	ASPIRE					
	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX
	All patients[16]	All patients[16]	Patients with 1 prior line[91]	Patients with 1 prior line[91]	Patients with ≥2 prior lines[91]	Patients with ≥2 prior lines[91]
Median months	26.3	17.6	29.6	17.6	25.8	16.7
(95% CI)	(23.3-30.5)	(15.0-20.6)	(23.3-33.5)	(15.0-22.2)	(22.2-31.0)	(13.0-22.0)
HR	0.69		0.69		0.69	
(95% CI)	(0.57-0.83); p=0.0001		(NR); p=0.0083		(NR); p=0.0017	
	ELOQUENT-2					
	ELO+LEN+DEX	LEN+DEX	ELO+LEN+DEX	LEN+DEX	ELO+LEN+DEX	LEN+DEX
	All patients[17]	All patients[17]	Patients with 1 prior line[17]	Patients with 1 prior line[17]	Patients with 2 or 3 prior lines[17]	Patients with 2 or 3 prior lines[17]
Median months	19.4	14.9	NR	NR	NR	NR
(95% CI)	(16.6-22.2)	(12.1-17.2)	NR	NR	NR	NR
HR	0.70		0.75		0.65	
(95% CI)	(0.57-0.85); p<0.001		(0.56-1.00)		(0.49-0.87)	
	TOURMALINE-MM1					
	IX+LEN+DEX	LEN+DEX	IX+LEN+DEX	LEN+DEX	IX+LEN+DEX	LEN+DEX
	All patients[19]	All patients[19]	Patients with 1 prior line[87]	Patients with 1 prior line[87]	Patients with 2 or 3 prior lines[87]	Patients with 2 or 3 prior lines[87]
Median months	20.6	14.7	20.6	16.6	not estim.	12.9
(95% CI)	(17.0-not estim.)	(12.9-17.6)	NR	NR	NR	NR
HR	0.74		0.88		0.58	
(95% CI)	(0.59-0.94); p=0.012		(0.65-1.20)		(0.4-0.84)	
	PANORAMA-1					
	PAN+BOR+DEX	BOR+DEX	PAN+BOR+DEX	BOR+DEX	PAN+BOR+DEX	BOR+DEX
	All patients[92]	All patients[92]	Patients with 1 prior line[92]	Patients with 1 prior line[92]	Patients with 2 or 3 prior lines[92]	Patients with 2 or 3 prior lines[92]
Median months	12.0	8.1	12.3	8.5	12.0	7.6
(95% CI)	(10.3-12.9)	(7.6-9.2)	(9.5-14.6)	(7.7-10.4)	(9.5-13.7)	(6.0-8.7)
HR	0.63		0.66		0.64	
(95% CI)	(0.52-0.76); p<0.0001		(0.50-0.86)		(0.50-0.83)	
	MM-003					
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
	All patients[22]	All patients[22]	Patients with ≤3 prior lines[82,86]	Patients with ≤3 prior lines[82,86]	Patients with >3 prior lines[82,86]	Patients with >3 prior lines[82,86]
Median months	4.0	1.9	3.7	1.9	4.4	2.0
(95% CI)	(3.6-4.7)	(1.9-2.2)	(NR); p=0.02		p<0.001	
HR	0.48		0.63		0.45	
(95% CI)	(0.39-0.60); p<0.0001		(0.40-1.0)		(0.35-0.57)	

Network Meta-Analyses of Overall and Progression-Free Survival

In addition to the descriptive analyses of key measures of clinical benefit, we conducted Bayesian network meta-analyses in order to perform indirect comparisons across the treatment regimens of interest. We focused attention on OS and PFS for these analyses. Detailed descriptions of methods and results can be found in Appendix D.

Because the network was made of primarily single-study connections, random-effects models could not be employed. We instead used a fixed-effects model, with the intention of conducting sensitivity analyses for key subgroups to address between-study heterogeneity. Data on these subgroups were limited, however. Subgroup data were not sufficient to conduct sensitivity analyses for OS, and we were only able to conduct analyses of PFS stratified by number of prior lines of therapy (1 versus 2-3). We also could not include DARA or POM+LoDEX in the network because both trial populations had more advanced disease than patients in the trials of the other regimens of interest, and because methods to incorporate single-arm data of DARA in a network meta-analysis are immature and unvalidated.[93-95]

Consistent with the data previously presented, OS was improved for both ELO+LEN+DEX and CFZ+LEN+DEX versus LEN+DEX, while the comparison of PAN+BOR+DEX to BOR+DEX produced a 95% "credible interval" (the Bayesian analog to the confidence interval) that included 1.0. IX+LEN+DEX could not be included in this analysis because hazard ratios for OS are not yet available. When the newer regimens were compared to each other, HR estimates were much closer to 1.0. In addition, all credible intervals were wide and included 1.0, precluding any definitive conclusions regarding differences in performance.

Results were similar in our analyses of PFS (see Appendix D). HR values for each newer regimen versus the regimen to which it was compared in clinical trials (i.e., LEN+DEX for CFZ, ELO, and IX, BOR+DEX for PAN) indicated substantial risk reductions with 95% credible intervals that did not include 1.0. However, when the newer regimens were compared to each other, resulting HRs were much closer to 1.0 and all credible intervals included 1.0, again preventing any clear ranking of performance. Sensitivity analyses stratifying by number of prior lines of treatment showed similar findings (Appendix D).

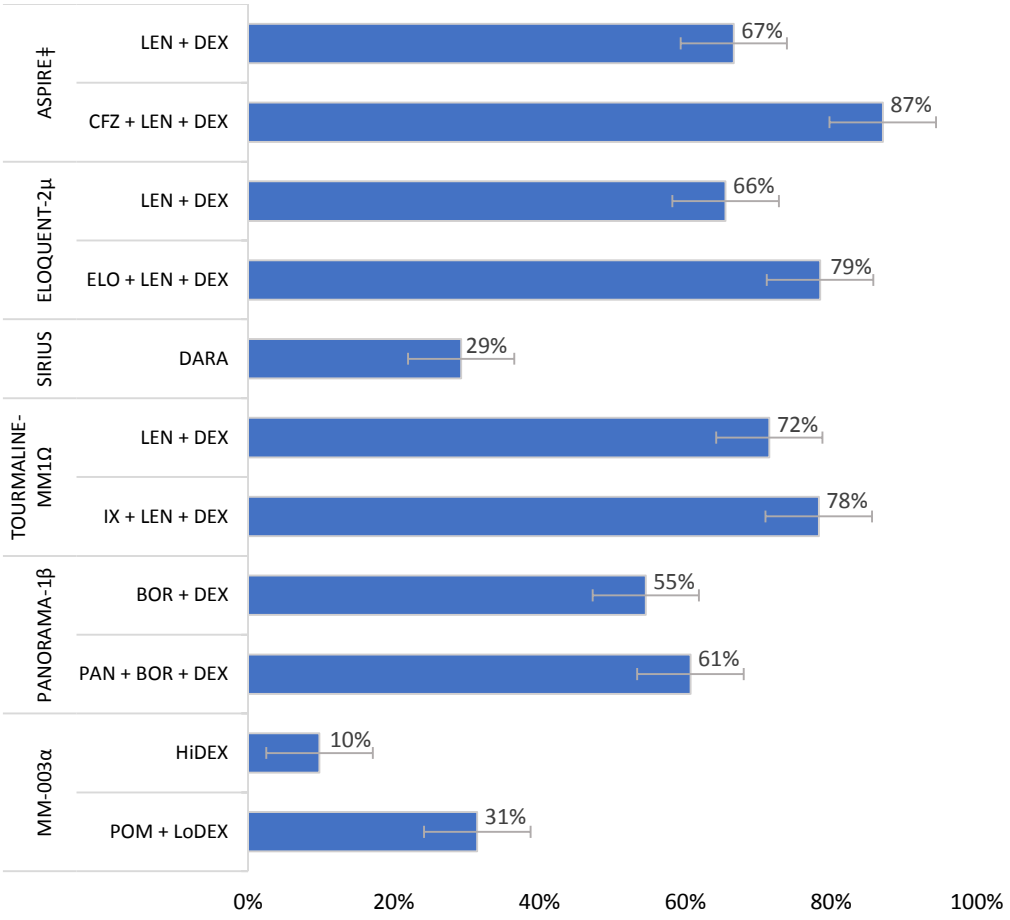
We also conducted sensitivity analyses based on the use of digitized progression-free survival curve data and creation of time-dependent hazard ratios at 1, 2, and 5 years respectively, using established methods (see Appendix D for further details).[96] All comparisons, whether to LEN+DEX or between regimens, included wide credible intervals that crossed 1.0 at all timepoints. In addition, HR estimates did not remain consistent across timepoints and crossed 1.0 in some circumstances, indicating violation of the proportional hazards assumption. Findings were similar for both the full network and the subset based on LEN+DEX comparator data from the CFZ, ELO, and IX trials.

Overall Response Rate (ORR)

Treatment response was evaluated in each of the key studies of interest for this review, albeit as a secondary endpoint in the trials of interest (except for the ELO+LEN+DEX trial and the single-arm DARA study). Overall response rate (ORR) was universally-defined as a partial response or better (see the "Topic in Context" section for detailed descriptions of response criteria from the International Myeloma Working Group). With the exception of PAN+BOR+DEX, overall response rate was statistically-significantly higher with newer regimens versus their comparators (Figure 5).[16-18,22] The lack of a significant effect of PAN+BOR+DEX on response represented another question of efficacy for the FDA Advisory Committee. A subgroup analysis conducted by Richardson and colleagues based on prior treatments received found that overall response was statistically-significantly improved among patients receiving PAN+BOR+DEX who had been treated with prior BOR and IMiD therapy (59% vs. 39% for control therapy, p=0.017).[80] As discussed in the "Controversies and Uncertainties" section, this subgroup analysis informed the FDA's decision to approve PAN in this specific subpopulation.

Findings for other regimens stratified by second- versus third-line or later use as well as cytogenetic risk largely followed those of the overall analyses of ORR. Further details are presented in Appendix C.

Figure 5. Overall response rate



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

Quality of Life

Given the current length of the disease course for MM, requirements for most therapies to be used until evidence of disease progression, and consequent tradeoffs between prolongation of survival and management of drug toxicity, health-related quality of life (HrQoL) is a critically important outcome in MM. However, we found HrQoL data in studies of only four of our six regimens, three of which used open-label designs and therefore may overstate quality of life gains by patients who knew that they were receiving a newer regimen rather than historical standard treatment. All four studies used the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30). The EORTC QLQ-C30 questionnaire is comprised of five functional scales, three symptom scales, and a global quality of life scale. Each scale's score ranges from 0 to 100; higher scores indicate better HrQoL for functional domains and lower scores indicate better HrQoL for the symptoms.

In the trial of CFZ+LEN+DEX, patients in the treatment group had statistically-greater improvements in global HrQoL compared with LEN+DEX over 18 cycles of treatment ($p<0.001$); the minimum clinically-important difference (MID) cited by the authors (5 points) was met at Cycle 12 and approached at Cycle 18.[16] Of note, the study cited by the authors of the trial publication actually determined a non-trivial mean difference in the EORTC QLQ-C30 global score to be 4 or more points;[97] using this standard, the MID was met at both Cycle 12 and Cycle 18.

Whereas no differences in favor of high-dose DEX were observed in the MM-003 trial of POM, significant differences ($p<0.05$) or trends ($p<0.10$) favoring POM+LoDEX were observed at specific timepoints in six of the EORTC QLQ-C30's eight domains. These improvements were reported in the physical functioning, emotional functioning, health utility, pain, fatigue, disease symptoms, and side effects of treatment domains.[81] The authors of the POM+LoDEX study defined a MID based on the standard error of the mean baseline score of each domain of the EORTC QLQ-C30.[f]

Over 23 months of follow-up, patients in both the IX+LEN+DEX and LEN+DEX groups of the TOURMALINE-MM1 study reported comparable levels of HrQoL.[21] Similarly, no differences in HrQoL were reported in the ELOQUENT-2 trial of ELO+LEN+DEX versus LEN+DEX.[17]

Data on HrQoL have not yet been presented or published for PAN+BOR+DEX or DARA.

Harms

Adverse event frequencies and rates of Grade 3/4 events are reported by regimen in Table 5. Across the key studies, the incidence of treatment-related death ranged from 2-4% across regimens,[g] although this was not reported for IX. Discontinuation of study therapy due to adverse events (AEs) ranged between 5% and 17% for all regimens except for PAN+BOR+DEX (36%).[18] As discussed in the "Controversies and Uncertainties" section, concern regarding high toxicity levels with PAN+BOR+DEX led the FDA Oncologic Drugs Advisory Committee (ODAC) to conclude that the drug's benefits did not outweigh its risks for the entire study population.[26]

Diarrhea was among the AEs of most concern: whereas 1-6% of patients experienced Grade 3/4 diarrhea with the other regimens, a substantially greater proportion of patients (25%) treated with PAN+BOR+DEX reported Grade 3/4 diarrhea and 4% discontinued treatment because of treatment-emergent diarrhea.[18] The label for PAN includes a black box warning that specifically mentions severe diarrhea.[27] Peripheral neuropathy, fatigue, and thrombocytopenia were additional AEs that disproportionately affected patients treated with PAN+BOR+DEX relative to patients treated with

[f] Improvement was defined as a score change from baseline that was ≥1 standard error of the mean for symptom domains and ≤-1 for symptom domains.
[g] The ELOQUENT-2 trial reported the proportion of patients who died from an adverse event; the other key trials reported treatment-related death.

other regimens (peripheral neuropathy: 18% vs. 1-4% with other regimens; fatigue: 24% vs. 3-8%; thrombocytopenia: 67% vs. 12-22%).[18]

The prescribing information for POM also includes a black box warning. The pomalidomide label advises that patients take antithrombotic prophylaxis while treated with POM, as deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke may occur.[28] However, differences in the incidence of Grade 3/4 thromboembolism (1% vs. 0% for POM+LoDEX vs. HiDEX) were slightly less than those seen with other regimens (3.0-5.7% of patients treated with ELO, IX, or CFZ in combination with LEN+DEX, compared to 2.2-4.1% for LEN+DEX).[16,17,22] Use of thromboprophylaxis is not an explanatory factor, as this was a required element of treatment for all of the trials described above. The black-box warning may instead be a class decision, as the label for LEN carries a similar warning.

Cardiac toxicity has been associated with CFZ.[29] In the ASPIRE trial, 3.8% of patients in the CFZ+LEN+DEX group experienced Grade 3 or higher cardiac failure versus 1.8% in the LEN+DEX group; Grade 3 or higher ischemic heart disease occurred in 3.3% of the CFZ+LEN+DEX group compared to 2.1% in the LEN+DEX group.[16]

Hematological AEs were relatively common in the regimens of focus. Abnormalities included anemia, neutropenia, thrombocytopenia, lymphopenia, and leukopenia. Relative to LEN+DEX, BOR+DEX, or HiDEX, Grade 3 or higher thrombocytopenia occurred with at least 5% greater frequency with PAN-, CFZ-, and IX-based regimens, while Grade 3 neutropenia occurred in 5% or more of patients treated with POM-, PAN-, and ELO-based treatment.[16-19,22]

Table 5. Measures of safety, including commonly reported Grade 3/4 adverse events

	CFZ+LEN+DEX[16,98]	DARA[20]	ELO+LEN+DEX[17,89,99]	IX+LEN+DEX[19,21,90]	PAN+BOR+DEX[18,27]	POM+LoDEX[22,28]
Discontinuation due to AEs	15%	5%	13%	17%	36%	9%
All serious AEs	60%	30%α	65%	47%β	60%	61%
Treatment-related Death	2%	0	2%ǂ	NR	3%	4%
Grade ≥3 AEs						
Fatigue	8%	3%	8%	4%	24%	5%
Diarrhea	4%	1%*	5%	6%	25%	1%
Peripheral neuropathy	3%	NR	4%	2%	18%	1%
Anemia	18%	24%	19%	9%	18%	33%
Thromboembolism	4.1%	NR	5.7%	3.0%	NR	1%
Thrombocytopenia	17%	19%	19%	12%	67%	22%
Neutropenia	30%	12%	34%	18%	34%	48%
Leukopenia	25%	40%*	32%	NR	23%	9%

*Data were pooled from 3 trials reported in FDA Prescribing Information; α treatment-emergent serious AE; β 68% experienced AE ≥ Grade 3; ǂ Death from an adverse event; AE=adverse event; NR=not reported

Controversies and Uncertainties

Multiple limitations in the body of evidence reduce our ability to make judgments regarding the comparative net health benefits of these treatments. First, with the exception of POM+LoDEX, final overall survival data demonstrating statistically-significant improvement with newer regimens are not yet available. As discussed previously, statistical improvements in PFS do not guarantee an overall survival benefit. Debates in the oncology literature have raged for many years about the relative credibility of surrogate outcomes such as PFS and whether studies can even be designed in the current era to measure overall survival when patients receive multiple rounds of chemotherapy before and after the use of any one particular treatment.[8,30] As noted earlier, PFS and other surrogate outcomes have been adopted by FDA as the primary criteria for regulatory approval of new MM regimens, and even skeptics of PFS acknowledge that this may be a reasonable standard for deciding when to make new treatments available for use. Nevertheless, PFS as a justification for early aggressive treatment remains a hotly debated issue. Some clinicians advocate for early aggressive treatment with multiple drugs in pursuit of complete response, arguing that this approach gives patients the best chance for a prolonged treatment-free interval. Others consider MM therapy to require the more chronic therapeutic strategy of a "marathon, not a sprint." These clinicians reserve additional new drugs for later in the disease course in order to avoid the increased risk of toxicity from earlier use and to have options for subsequent relapses. For this group of clinicians, the lack of data demonstrating an OS advantage for newer drugs supports their view that OS may, in the end, be the same for average-risk patients, whether aggressive treatment is started early or not.

There are also important uncertainties regarding the evidence on specific regimens. The efficacy of PAN was questioned by FDA reviewers because of an unusually large amount of missing and censored data in the PANORAMA-1 study (47% of patients in the PAN group and 32% in the control group were censored), which led to significant variation in the observed PFS during sensitivity analyses. Furthermore, a larger proportion of deaths not attributed to progressive disease occurred with PAN (7% vs. 3% for control therapy) that may have been related to the drug's toxicity. The high toxicity witnessed in the trial may have partially been the result of intravenous administration of BOR, which produces more frequent side effects than subcutaneous administration.[31-33] Data from a recent conference presentation do in fact suggest lower rates of Grade 3 or higher diarrhea with PAN in combination with subcutaneous BOR (11.8% vs. 25% in the PANORAMA-1 trial), but this information comes from a small (n=39) single-arm study in a population with a median treatment duration of only 9.4 weeks.[34]

Based on these concerns the FDA ODAC voted 5-2 that PAN's benefit did not outweigh its risk. This, in turn, led Novartis to propose limiting the indication for PAN to patients who had received prior treatment with BOR and an IMiD. The FDA approved PAN in this subgroup with the condition that Novartis carry out additional Phase II and Phase III trials of PAN in combination with subcutaneous BOR and DEX in relapsed/refractory patients who were previously exposed to an IMiD.[h,26,35,36]

The evidence base for DARA is less robust than that for other regimens given that it is currently limited to a Phase I/II dose-escalation/dose-expansion study and a Phase II study. Nonetheless, among patients who are experiencing disease progression, a trial without significant drop-out demonstrating relatively high response rates and a median PFS of at least 3-5 months can provide some information regarding improvement in the surrogate outcome. However, no comparator data are as yet available, so the incremental gain in PFS compared to another salvage therapy is unknown, and our certainty in DARA's effects is therefore low. In addition, questions about the relationship of PFS on DARA to overall survival remain.

Our certainty in the efficacy of POM+LoDEX is also hampered somewhat by the lack of peer-reviewed data of the regimen against newer doublet or triplet therapy options. The comparison of POM+LoDEX to HiDEX was justified as the standard salvage treatment for heavily pretreated patients at the time of trial design. However, with the emergence of newer agents since the completion of the MM-003 trial, use of HiDEX alone may no longer serve as a relevant salvage treatment.

Perhaps the greatest amount of uncertainty in comparative net health benefit lies in the lack of truly comparative data across trials. Given that many of these drugs were approved very recently, we do not expect there to be published head-to-head data available. However, the limited number of available studies as well as the absence of data for certain key subgroups precluded robust

[h] The Phase II and Phase III trials will be completed in 2018 and 2021, respectively.

indirect comparisons of the regimens in our review. As noted in the "Topic in Context" section, some of this variability might be due to differences in laboratory standards across studies, but there is clearly room for improvement in availability of subgroup data as well as standardization of patient-centered outcomes.

In addition, while subgroup analyses generally suggested comparable performance between earlier- and later-line use for most regimens, the survival trajectory for MM suggests that many patients will eventually use all available drugs. Therefore, further study should elucidate each regimen's performance at different points during the disease course, ideally in head-to-head comparative studies of treatment pathways.

Finally, evidence from the key trials may have limited validity for patients in the U.S. Of note, the median age of participants in the key trials was younger than the median age at diagnosis in the U.S. (age 69).[2,26] In addition, twice as many black patients as patients of other races are diagnosed with MM in the U.S., yet these patients were underrepresented in trials available at the time of this review (2-4% of all trial participants), with the exception of the single-arm SIRIUS trial of DARA (14%).[2,16-20,22]

Summary

ICER evidence ratings for the comparisons of interest are provided in Table 6. As noted previously, the lack of head-to-head data and challenges in making indirect comparisons among the newer regimens indicate "insufficient" evidence to assess comparative net health benefit when these newer regimens are compared to each other. We can, however, determine comparative net health benefit between the newer regimens and the control therapies to which they were directly compared. We judge there to be moderate certainty that CFZ, ELO, and IX, in combination with LEN+DEX, provide an incremental or better net health benefit for both second-line and third-line or subsequent therapy in adult patients with relapsed/refractory multiple myeloma relative to LEN+DEX alone. There is moderate certainty because while only one Phase III study was available for each regimen, the studies of focus had large patient populations and were of higher quality. Furthermore, the PFS benefit observed in each drug's key trial was consistent across subgroup analyses by number of prior lines of therapy. Side effect rates are high for all of these treatments, but these side effects are now well known and patients have already indicated by the common use of these treatments that the balance of benefits and harms is viewed positively by most. Data on side effects do not demonstrate a systematic overall advantage for any of these regimens. We therefore assign the current body of evidence on the comparative clinical effectiveness of CFZ, ELO, and IX a "B+" rating using the ICER Evidence Rating Matrix.

Table 6. ICER evidence ratings, by regimen and line of therapy

Regimen	Comparator	Evidence Rating	
		Second-Line Therapy	Third-Line & Subsequent Therapy
CFZ+LEN+DEX	LEN+DEX	B+	B+
ELO+LEN+DEX	LEN+DEX	B+	B+
IX+LEN+DEX	LEN+DEX	B+	B+
PAN+BOR+DEX	BOR+DEX	I	P/I
POM+LoDEX	HiDEX	I	P/I
DARA	None	I	I

As a third-line or subsequent therapy, we judge the evidence for PAN+BOR+DEX to be "promising but inconclusive." We arrived at this rating because the results of a subset analysis in patients who had received prior BOR and IMiD therapy revealed a more favorable risk/benefit profile for the drug. However, concerns over toxicity and the limitations of the overall evidence base remain. Our judgment is that there is insufficient evidence to determine the net health benefit of PAN+BOR+DEX as second-line therapy. The evidence is insufficient because concerns regarding a high level of missing data and censoring in the PANORAMA-1 trial introduced potential bias into estimates of PFS for all patients as well as those stratified by number of prior lines of treatment. In addition, given concerns over high rates of certain toxicities, the net health benefit among all second-line patients remains unclear. We therefore assign the evidence for PAN+BOR+DEX an ICER Evidence Rating of "P/I" for third-line and subsequent therapy and "I" for second-line therapy.

Evidence was also insufficient ("I") to determine a net health benefit for patients receiving POM+LoDEX for second-line treatment, as the key Phase III trial only evaluated patients receiving the regimen for third-line or later use. As a third-line or subsequent therapy, we find that the evidence for POM+LoDEX provides moderate certainty of a net health benefit that is likely at least comparable to other salvage options, but the true level of net health benefit is unclear. While POM+LoDEX is the only regimen to have demonstrated a statistically- and clinically-significant overall survival benefit in a final analysis, this benefit is unknown relative to any salvage therapy other than high-dose dexamethasone. Because of this concern, and because there is a small chance that POM+LoDEX could be net harmful relative to other available salvage options, we judge the comparative clinical effectiveness of POM+LoDEX to be "P/I" for third-line or subsequent treatment using the ICER Evidence Rating Matrix.

Finally, we find that the evidence is insufficient ("I") to determine the comparative net health benefit for DARA monotherapy as either second-line or third-line or subsequent therapy because at the time of this review, there were no available randomized or comparative studies of the drug.

Without any comparator data with which to judge incremental benefit, we could not estimate net health benefit with any degree of certainty. In addition, the intended use of the drug is for fourth-line or later use in patients who have previously been treated with a PI and an IMiD, or who are double refractory to both a PI and IMiD, and there are currently little to no data on the use of DARA relative to the timing of therapy of interest for this review.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

All but two of the regimens of interest (IX and POM) in this assessment have at least one component that is administered via subcutaneous injection or intravenous infusion, which requires frequent office visits. Travel to a physician's office or clinic and the requirement for sometimes extensive infusions poses a burden to MM patients and caregivers at various stages of disease, so the convenience and potential quality-of-life benefits of all-oral treatments possible with IX and POM will be highly valued by some patients. Conversely, the monitoring and opportunity for patient education and counseling at office visits may offer additional benefits for some patients.

The availability of multiple classes of medication for this increasingly chronic condition may increase the likelihood that patients will respond to a specific combination of treatments and may also reduce the chance of poor response or resistance to multiple regimens. This is of significant clinical importance given that data are not yet sufficient to predict the type of patient who will respond to (or become resistant to) a particular regimen.

6. Comparative Value

6.1 Overview

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis (CEA) using a simulation model of second- and third-line treatment outcomes and costs in representative cohorts of patients with multiple myeloma. We estimated the incremental cost-effectiveness of multiple myeloma drugs relative to lenalidomide plus dexamethasone using drug cost estimates derived from current prices and estimates of adverse events and other clinical parameters from relevant trial data.

We also used outputs from this model to inform a population-based analysis of the one- and five-year potential budget impact of different treatment regimens. Potential budget impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug costs as well as potential cost savings from treatment. Based on long-term incremental cost-effectiveness ratios, we define a "value-based price benchmark" for the regimens of interest. As part of our price benchmark, we also highlight whether the potential budget impact for any new drug at list price would surpass a threshold related to growth targets for net health care cost growth at the national level.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Novel Multiple Myeloma Treatments

A recently published cost-effectiveness analysis sponsored by Amgen, the manufacturers of carfilzomib, examined CFZ+LEN+DEX versus LEN+DEX in relapsed multiple myeloma from a U.S. perspective.[100] Although the total incremental cost estimated by the Amgen model was similar to that of the ICER model ($179,400 versus $173,000, respectively), the estimate of QALYs gained with CFZ+LEN+DEX was notably different (1.67 versus 0.86). This appears to be due to three key differences between models: (1) the use of independent parametric model functions fit to trial data versus ICER's modeling of treatment effect derived from network meta-analysis; (2) the choice of the log-logistic parametric function for modeling PFS curves versus ICER's use of the Weibull function; and (3) the use of SEER data to establish survival after progression versus ICER's extrapolation of observed PFS curves beyond available follow-up time and use of a large retrospective analysis of multiple myeloma trials to establish a relationship between PFS and OS. We note some concerns with these methodologic choices. In the Amgen analysis, the independently modeled PFS and OS curves yielded much more favorable estimates of treatment effect for CFZ+LEN+DEX than those actually reported in the ASPIRE trial versus LEN+DEX (PFS: 0.51 [model] versus 0.69 [published hazard ratio]; OS: 0.70 [model] versus 0.79 [published hazard ratio]); these differences appear to explain a modeled increase in progression-free survival that was over five months longer than the median PFS observed in the ASPIRE trial. Second, the log-logistic parametric function is prone to long tails in the

distribution, which may overestimate time spent in the pre-progression state. Third, while the SEER survival data was adjusted for decade of diagnosis, data collected beyond five years is unlikely to account for the survival impacts of recent treatment advances. Finally, we also note that one of the findings of the Amgen analysis appears to be counter intuitive: CFZ+LEN+DEX patients spend approximately four years in the post-progression state in the model versus approximately three years for LEN+DEX, but the post-progression costs for LEN+DEX are higher.

We did not identify any additional published articles or public presentations pertaining to the costs and/or cost-effectiveness of these regimens in a U.S. context. Previous technology assessments for PAN+BOR+DEX and POM+LoDEX have been conducted in the UK and Canada, and are summarized in Appendix F. Briefly, guidance from the National Institute for Health and Care Excellence (NICE) recommended use of PAN+BOR+DEX only in the subgroup of patients with prior use of BOR and an IMiD, citing concerns with data on the overall population that were similar to those expressed by the FDA. NICE did not recommend POM+LoDEX based primarily on comparison to a treatment (HiDEX) not reflective of UK clinical practice, as well as suggestions that patients in the POM+LoDEX Phase III trial were healthier than other double-refractory populations, which may have overstated benefits. In contrast, the Pan-Canadian Oncology Drug Review (pCODR) recommended use of POM+LoDEX, provided steps were taken to improve its cost-effectiveness (approximately CAN $132,000 to $173,000 depending on time horizon at its current price).

6.3 Incremental Costs per Outcome Achieved

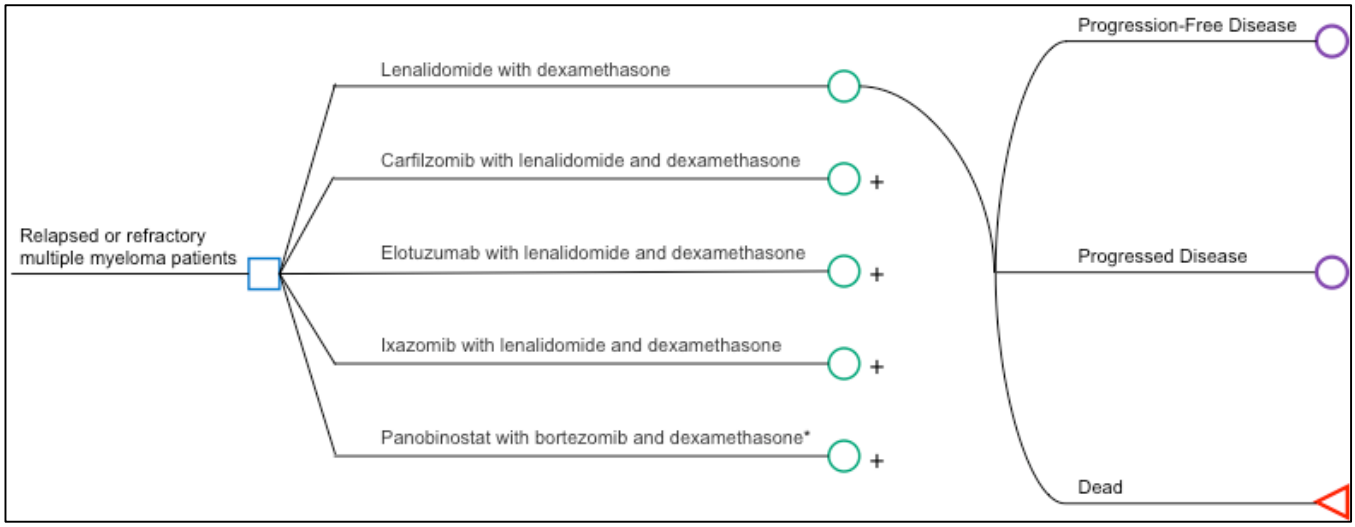
Cost-Effectiveness Model: Methods

Model Structure

The primary aim of this analysis was to estimate the cost-effectiveness of various treatments for patients with MM who have received one or two previous therapies (i.e., second- or third-line treatment). The model analyzed second- and third-line treatments separately. The model framework is depicted in Figure 6. The model was developed in Microsoft Excel.

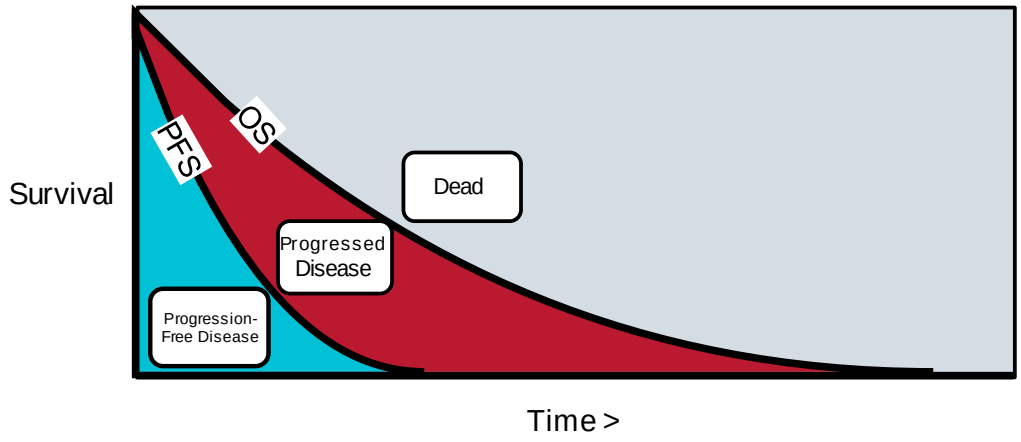
Outcomes were modeled using a partition survival approach and three health states: progression-free (PF), progression (PRO), and death (see Figure 7). Advantages of partition survival models are that they are less data intensive than other more complex modeling approaches, and that they leverage commonly available data reported in clinical trial publications. For each treatment regimen, a hypothetical patient population comparable to the baseline comparator will spend time in the progression-free health state and the progressed health state. Mean time, quality adjusted time, and costs in each health state are summed to provide estimates of life expectancy, quality adjusted life expectancy and total costs. We used a cycle length of one week to reflect the dosing schedules for included drug regimens. We utilized a health system perspective (i.e., we focused on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death. We used a 3% discount rate for all future outcomes and costs and employed a half-cycle correction.

Figure 6. Model framework: Management of relapsed/refractory multiple myeloma



*Only evaluated in the third-line

Figure 7. Partition survival model approach



We made a number of key assumptions to inform our model, as described below.

Table 7. Key assumptions

Assumption	Rationale
Treatment effect as represented by the PFS hazard ratio is consistent for the second- and third-line settings	Hazard ratios were similar for most regimens when stratified by prior lines of treatment Face validity concerns with the limited available data for some of the stratified hazard ratios Studies were not powered to detect subgroup differences
Trial populations were sufficiently homogeneous to allow for comparisons via network meta-analysis	Review of patient characteristics that were universally reported across clinical trials
Hazard of progression assumed to be proportional across all relevant comparisons	Proportional hazards modeling used in each clinical trial serving as input to network meta-analysis
No vial sharing between patients occurs	Vial sharing illegal for Medicare beneficiaries receiving drugs on outpatient basis (majority of MM patients)
Treatment received after progression is uniform across all comparators	Detailed information on post-progression therapy not available or not provided for all regimens of interest

Target Population

The population for the review included adults with MM whose disease has not responded to at least one previous line of treatment (i.e., refractory) or has relapsed following such treatment, are not currently on maintenance treatment, and are not being considered for stem cell transplant. An average patient height and weight was assumed based on data from a retrospective study of 318 multiple myeloma patients treated at the Penn State Hershey Cancer Institute (see Table 8). This was necessary for accurately

calculating drug dosage in each regimen. Patient height and weight were fixed among regimens to enable direct comparisons.

Table 8. Model cohort characteristics

	Value	Primary Source
Mean age	60	Assumption
Mean weight (kg)	80	Talamo et al.[101]
Mean height (m)	1.7	Talamo et al.[101]

Note: Model is agnostic to age; provided to aid in communication of the model and its findings.

Treatment Strategies

The interventions of interest are listed below. Regimens listed are based on FDA-labeled indications for treatment of relapsed/refractory disease as well as expert input regarding common treatment approaches for the populations of interest. Note that two regimens from the evidence review (DARA and POM+LoDEX) were not included in the model. DARA was not included because only single-arm data are available and therefore no incremental treatment effect versus LEN+DEX could be estimated. Additionally, DARA and POM+LoDEX were studied in populations with more advanced disease (i.e., refractory to BOR and/or LEN) and so their effects could not be considered comparable to those of the other regimens.

Second-line (i.e., after one previous line of treatment):

- Carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- Elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- Ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Third-line (i.e., after two previous therapies):

- Carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
- Elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
- Ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)
- Panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX)

The primary baseline comparator was lenalidomide in combination with dexamethasone (LEN+DEX), as this represented the most common comparator for the regimens of interest. We recognize, however, that several recent trials have involved comparisons to BOR+DEX, DEX alone, and/or placebo. To account for the various trials and trial comparisons, a network meta-analysis was conducted (see Section 4 and Appendix D for further details and results).

Model Inputs: Clinical

We fit parametric survival curves to progression-free survival (PFS) Kaplan-Meier data for the universal comparator (LEN+DEX) in both the second- and third-line settings, utilizing the approach described by Hoyle

and Henley. [102] First, we extracted data points from digitized copies of available survival curves, then used the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data. We assumed that the rate of censoring was the same between the second- and third-line settings, which allowed us to estimate the number at risk at set timepoints for the second- and third-line curves from the pooled number at risk data. The candidate model curves included the distributional forms Weibull, exponential, log-normal, log-logistic. We selected the Weibull parametric function in the base case.

Base case PFS curves for LEN+DEX were derived from parametric fits to pooled Kaplan-Meier data from the MM-009 and MM-010 trials of LEN+DEX as described above; a Celgene slide presentation of pooled results stratified by second- and third-line therapy, available online, was used to fit parametric curves by line of treatment.[37-39] We then used PFS hazard ratios acquired from the network meta-analysis, applied to the universal comparator curves, to derive survival curves for the other interventions (see Table 2). We assumed that the treatment effect was consistent for the second- and third-line settings. This approach allowed us to model the relative efficacy of the interventions and survival beyond available follow-up time.

The data on overall survival for these regimens were not uniformly available and were prone to bias due to crossover to the active comparator, as well as the availability of different drugs after progression over the timeframe for the trials considered in the model. Therefore, we applied an estimate of the relationship between the PFS and OS curves derived from a systematic review of this relationship in studies of nearly 23,000 MM patients to estimate regimen-specific OS curves for the regimens.[40] This analysis has been used widely, including for support of previous model submissions to HTA agencies. [103] Specifically, we estimated a 2.45-month (95% confidence interval, 1.7–3.2) increase in median OS for each additional month of median PFS. We operationalized this estimate by deriving an OS to PFS hazard ratio that we applied to each regimen's PFS curve. We varied this parameter in a sensitivity analysis, and ran a scenario analysis using a weighted average estimate of the relationship of PFS to OS from the available clinical trials in our assessment (3.27-month increase in OS for each additional month of median PFS).

Table 9. Progression-free survival hazard ratios in patients with 1-3 prior treatments*

Regimen	vs. BOR+DEX			vs. LEN+DEX		
	HR	Range: Low	Range: High	HR	Range: Low	Range: High
PAN+BOR+DEX	0.58	0.48	0.71	0.54	0.29	1.02
CFZ+LEN+DEX	0.74	0.39	1.39	0.69	0.57	0.83
ELO+LEN+DEX	0.75	0.40	1.41	0.70	0.57	0.86
IX+LEN+DEX	0.80	0.42	1.52	0.74	0.59	0.93
LEN+DEX	1.07	0.49	1.71	---	---	---

*Based on intention-to-treat analysis

Model Inputs: Adverse Events

The model included Grade 3/4 adverse events derived from key clinical trials and/or each drug's prescribing information. The model included any reported Grade 3/4 adverse events that occurred in at least 5% of patients for *any* of the treatment comparators (see Appendix E).

Model Inputs: Drug Utilization

The estimation of drug utilization was derived from several factors, including the relative dose intensity reported in trials or directly provided by manufacturers, and the dosing schedule (see Appendix Table E3), where the dose may be fixed by weight or by body surface area (BSA), assuming patient characteristics as shown in Table 8. If a regimen is based on treat-to-progression, the treatment utilization and cost were applied to all patients who remain in the PF health state over time. If a finite number of cycles is used, patients may remain in the PF state without active treatment. The model could account for whether or not vial sharing among patients is utilized, but no vial sharing was assumed in the base case (see "Key Assumptions" above). Drug unit costs (see Table 10) were applied to the utilization estimates to calculate total estimated treatment costs.

Model Inputs: Costs

We used the wholesale acquisition cost (WAC) for each drug and noted each available formulation (Table 10). Based on the regimen-specific dosage specified above, the model utilized the lowest cost combination of tablets and/or vials for each regimen.

Table 10. 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).

Costs per adverse event were based on a prior published analysis, supplemented by data from the Centers for Medicare and Medicaid Services (CMS) list of Medicare Severity-Diagnosis Related Groups (MS-DRGs) for the fiscal year 2015 (see Appendix E).

To estimate costs in the progression health state, we used a treatment landscape analysis to estimate the proportion of patients who receive different available treatments upon progression. The specific treatment distribution is derived from Farr et al. (see Table 11).[104] The model assumes that patients will receive one further line of treatment lasting 124 days (95% confidence interval: 100-194) followed by best supportive care. We then calculated a mean cost per month weighted by the proportion of patients receiving each treatment.

Table 11. Treatment distribution after progression

Bortezomib	Carfilzomib	Lenalidomide	Cyclophosphamide	Dexamethasone	Best Supportive Care
19%	16%	30%	7%	8%	20%

Model Inputs: Health State Utilities

Health state utilities were derived from publicly available literature and/or manufacturer-submitted data and applied to the disease states of progression-free and progressed disease (Table 12). We used consistent health state utility values across treatments evaluated in the model. For the progression-free health state, different utilities were applied depending on whether the patient was on or off treatment, to represent decreased quality of life due to treatment. We applied a regimen-weighted disutility for experiencing any Grade 3/4 adverse event; the total percentage of patients who experienced any Grade 3-4 adverse events for each regimen was multiplied by the AE disutility and then subtracted from the total QALYs gained during PFS for each regimen. We assumed that the total time with a Grade 3-4 adverse event for patients experiencing any Grade 3-4 adverse event was one month.

Table 12. Health state utilities

Second-Line	Base Case	Distribution	Source
Progression-free disease, on treatment	0.82	Beta	AMGEN/ASPIRE[105]
Progression-free disease, off treatment	0.84	Beta	AMGEN/ASPIRE[105]
Progressed disease	0.65	Beta	AMGEN/ASPIRE[105]
Third-Line			
Progression-free disease, on treatment	0.65	Beta	MM-003/NICE[103]
Progression-free disease, off treatment	0.72	Beta	Acaster et al.[106]
Progressed disease	0.61	Beta	MM-003/NICE[103]
Disutility for any Grade 3-4 adverse event	-0.076	Beta	MM-003/NICE[103]

Model Outcomes

The model estimated the amount of time, on average, patients spend progression-free and in progression. Unadjusted and utility-adjusted time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy.

Model outcomes of interest for each intervention included:

- Quality adjusted life expectancy (undiscounted and discounted)
- Life expectancy (undiscounted and discounted)
- Mean time in the progression-free and post-progression health states (undiscounted and discounted)
- Pre-progression, post-progression, and total costs (undiscounted and discounted)

In pairwise comparisons, incremental cost-effectiveness ratios for each intervention versus the standard comparator (LEN+DEX) were also calculated.

Sensitivity Analyses

The model programming allows for flexible and comprehensive sensitivity analyses. One-way sensitivity analyses used 95% confidence intervals from clinical evidence where available. When 95% confidence intervals were not available, uncertainty ranges were based on plausible values from the published literature.

We also conducted a probabilistic sensitivity analysis (PSA) by jointly varying all model parameters over 4,000 simulations, then calculating 95% credible range estimates for each model outcome.

Finally, we ran four scenario analyses: 1) using an unadjusted estimate of the relationship of median PFS to median OS based on a weighted average from the trials in our analysis that report both outcomes (3.27-month increase in OS for each additional month of median PFS); 2) using BOR+DEX as the baseline comparator; 3) adjusting the second- and third-line baseline curves to reflect more recent LEN+DEX regimen curves using the relationship between the ASPIRE trial LEN+DEX data and the MM-009/MM-010 pooled LEN+DEX data; and 4) using different second-line utility estimates for triplet (0.83, 0.85, and 0.66 for PFS on treatment, PFS off treatment, and progression, respectively) versus doublet regimens (0.81, 0.83, 0.64, respectively) derived from the ASPIRE trial data.

Cost-Effectiveness Model: Results

Base Case Results

The results of the pairwise comparisons are provided in Table 13 for the second-line setting and Table 14 for the third-line setting. These tables report detailed results for each regimen in each line as well as the incremental results versus LEN+DEX. Only deterministic results are shown (i.e., the model results that use only the point estimate for every input).

Use of each of the second-line regimens resulted in a gain of approximately one year of survival (range: 0.93 for IX+LEN+DEX to 1.17 for CFZ+LEN+DEX) relative to LEN+DEX, which was split relatively evenly between the pre-progression and progressed health states. On a quality-adjusted basis, QALYs gained versus LEN+DEX ranged from 0.69 for IX+LEN+DEX to 0.86 for CFZ+LEN+DEX. Incremental costs ranged from a low of approximately $173,000 for CFZ+LEN+DEX to approximately $354,000 for ELO+LEN+DEX versus LEN+DEX, nearly all of which were driven by increased drug costs rather than progression, supportive care, or adverse event costs. Lower incremental drug costs for CFZ+LEN+DEX versus the other triplet regimens of interest are due primarily to treatment with CFZ+LEN+DEX for a fixed number of cycles (up to 18), while IX+LEN+DEX and ELO+LEN+DEX are given continuously until progression or unacceptable toxicity.

Importantly, incremental drug costs included both additional costs of the new drug for each regimen as well as extended use of LEN+DEX due to improved PFS. For example, the total treatment cost of LEN in the pre-progression state when given as part of the CFZ+LEN+DEX regimen is $260,392, versus $239,745 when

given as part of the LEN+DEX regimen, because of the longer time in the progression-free state and therefore longer time on treatment. Incremental cost-effectiveness ratios for second-line regimens versus LEN+DEX were estimated to be slightly below $200,000 per QALY for CFZ+LEN+DEX and greater than $400,000 per QALY for ELO+LEN+DEX and IX+LEN+DEX.

Note that PFS results in the table will not match those seen in clinical trials because of our anchoring of hazard ratios to the baseline survival curves for LEN+DEX (rather than use of observed survival curves in each trial). However, due to the fixed-effects nature of the network meta-analyses, relative effects from each trial are essentially preserved. Our drug cost estimates also had good face validity when compared against an analysis performed by Potluri et al. using the MarketScan claims database (total LEN+DEX cost in the model: $280,000 versus Potluri: approximately $310,000).[107]

Use of CFZ+LEN+DEX, ELO+LEN+DEX, and IX+LEN+DEX as third-line regimens resulted in gains of 1.12, 1.07, and 0.89 years of survival, respectively, relative to LEN+DEX. On a quality-adjusted basis, QALYs gained versus LEN+DEX ranged from 0.56 for IX+LEN+DEX to 0.71 for CFZ+LEN+DEX. Incremental costs ranged from a low of approximately $168,000 for CFZ+LEN+DEX to approximately $325,000 for ELO+LEN+DEX versus LEN+DEX, nearly all of which were again driven by increased drug costs. Incremental cost effectiveness ratios were estimated as approximately $239,000 per QALY for CFZ+LEN+DEX, $481,000 per QALY for ELO+LEN+DEX, and $485,000 per QALY for IX+LEN+DEX. PAN+BOR+DEX was estimated to provide more QALYs than LEN+DEX as a third-line therapy, at a lower total cost; therefore, PAN+BOR+DEX would be the preferred treatment (i.e., was dominant) versus LEN+DEX.

Results for PAN+BOR+DEX should be interpreted with great caution. As we note in Section 4, serious concerns were raised regarding the viability of results in the overall population and even in the full third-line subgroup (versus the subset of third-line patients with prior BOR and IMiD use that ultimately received FDA approval), based on issues of censoring and high rates of discontinuation due to toxicity. This is also the only regimen without direct comparative evidence versus LEN+DEX, and therefore greater reliance on the study network and its assumptions regarding minimal heterogeneity across study populations and constant hazards over time was required. While censoring is factored into our analytic approach, the relative treatment effect of PAN+BOR+DEX versus LEN+DEX therefore has much greater uncertainty than the other comparisons.

As described above, we also conducted a scenario analysis in which each regimen of interest was compared to BOR+DEX instead of LEN+DEX. Cost-effectiveness ratios increased for all regimens, primarily because of the lower drug costs for BOR versus LEN (Appendix E). However, PAN+BOR+DEX was no longer cost-saving when the comparator was changed to BOR+DEX, with a cost-effectiveness ratio of $10,230 per QALY gained.

Table 13. Clinical and economic outcomes in the second-line

Results by Regimen

2nd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX
Total Costs	**$284,400**	**$457,350**	**$638,144**	**$582,428**
Drug Costs	$240,913	$398,767	$569,796	$532,873
Supportive Care Costs	$528	$1,882	$2,607	$2,491
Administration Costs		$8,377	$14,698	
Progression Costs	$38,901	$44,103	$43,886	$43,062
Adverse Event Costs	$4,057	$4,221	$7,156	$4,001
Total QALYs	**2.59**	**3.45**	**3.41**	**3.27**
PFS QALYs	1.41	1.91	1.89	1.81
Progression QALYs	1.17	1.54	1.52	1.46
Total Life Years (OS)	**3.53**	**4.71**	**4.66**	**4.46**
PFS LYs	1.73	2.34	2.31	2.21
Progression LYs	1.80	2.37	2.34	2.25

Incremental Results vs. LEN-DEX

2nd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX
ICER (vs. L+Dex)	**--**	**$199,982**	**$427,607**	**$433,794**
Total Costs	**--**	**$172,951**	**$353,744**	**$298,028**
Drug Costs	--	$157,854	$328,883	$291,960
Supportive Care Costs	--	$1,354	$2,079	$1,963
Administration Costs	--	$8,377	$14,698	
Progression Costs	--	$5,202	$4,985	$4,161
Adverse Event Costs	--	$164	$3,099	-$56
Total QALYs	**--**	**0.86**	**0.83**	**0.69**
PFS QALYs	--	0.50	0.48	0.39
Progression QALYs	--	0.37	0.35	0.29
Total Life Years (OS)	**--**	**1.17**	**1.12**	**0.93**
PFS LYs	--	0.61	0.58	0.48
Progression LYs	--	0.56	0.54	0.45

Table 14. Clinical and economic outcomes in the third-line

Results by Regimen

3rd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX	PAN-BOR-DEX
Total Costs	**$258,609**	**$427,027**	**$583,531**	**$530,228**	**$196,021**
Drug Costs	$216,151	$369,865	$517,785	$481,956	$136,366
Supportive Care Costs	$473	$1,779	$2,364	$2,255	$415
Administration Costs		$8,113	$13,394		$3,128
Progression Costs	$37,928	$43,049	$42,833	$42,016	$46,984
Adverse Event Costs	$4,057	$4,221	$7,156	$4,001	$9,128
Total QALYs	**2.04**	**2.74**	**2.71**	**2.60**	**3.46**
PFS QALYs	1.00	1.37	1.36	1.30	1.82
Progression QALYs	1.03	1.37	1.36	1.30	1.63
Total Life Years (OS)	**3.25**	**4.37**	**4.32**	**4.14**	**5.27**
PFS LYs	1.55	2.12	2.09	2.00	2.59
Progression LYs	1.70	2.25	2.23	2.14	2.68

Incremental Results vs. LEN-DEX

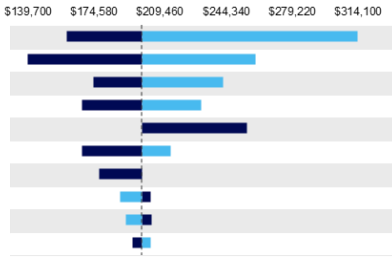
3rd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX	PAN-BOR-DEX
ICER (vs. L+Dex)	**--**	**$238,560**	**$481,244**	**$484,582**	**-$44,084**
Total Costs	**--**	**$168,418**	**$324,922**	**$271,619**	**-$62,588**
Drug Costs	--	$153,714	$301,634	$265,805	-$79,784
Supportive Care Costs	--	$1,307	$1,891	$1,783	-$58
Administration Costs	--	$8,113	$13,394		$3,128
Progression Costs	--	$5,121	$4,905	$4,087	$9,055
Adverse Event Costs	--	$164	$3,099	-$56	$5,071
Total QALYs	**--**	**0.71**	**0.68**	**0.56**	**1.42**
PFS QALYs	--	0.37	0.35	0.29	0.82
Progression QALYs	--	0.34	0.32	0.27	0.60
Total Life Years (OS)	**--**	**1.12**	**1.07**	**0.89**	**2.02**
PFS LYs	--	0.57	0.54	0.45	1.04
Progression LYs	--	0.55	0.53	0.44	0.98

Sensitivity Analyses

Detailed findings from the one-way sensitivity analyses can be found in Figure 8. In each one-way analysis, results were by far most sensitive to the PFS hazard ratios for each intervention versus LEN+DEX, followed by the estimated link between PFS and OS (2.45 months of OS for each month of PFS, per Felix et al.), drug costs, dosage intensity, and health state utilities.[6] Also of note, the PFS hazard ratio for PAN+BOR+DEX versus LEN+DEX is the only one with a 95% credible interval that crossed 1.0 (0.29, 1.02). Therefore, at the low end of this range, PAN+BOR+DEX was more effective and less expensive than LEN+DEX; at the high end of the range, PAN+BOR+DEX was both less effective and less expensive.

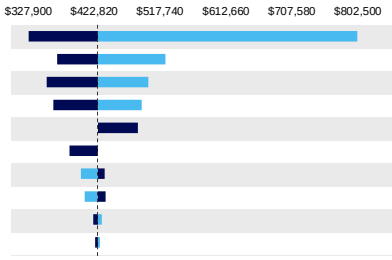
Figure 8. One-way sensitivity analysis results: Tornado diagrams

2nd-line CFZ + LEN + DEX



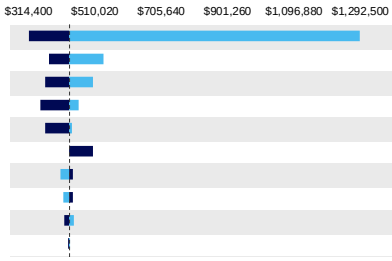
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, CL+Dex	0.57	0.83	$160,285	$314,075	$153,789
Dose Intensity: CL+Dex Lenalidomide	64.4%	96.6%	$139,764	$260,200	$120,436
Felix Hazard Ratio	0.31	0.58	$174,454	$243,041	$68,588
Cost: Carfilzomib 60 mg vial	$1,489.56	$2,234.34	$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

2nd-line ELO + LEN + DEX



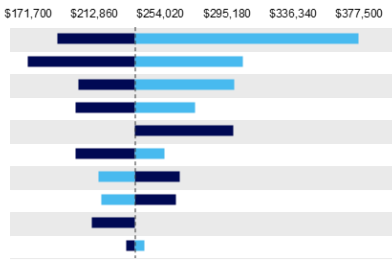
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, EL+Dex	0.57	0.86	$327,978	$802,456	$474,478
Felix Hazard Ratio	0.31	0.58	$369,081	$526,168	$157,087
Cost: Elotuzumab 400 mg vial	$1,894.40	$2,841.60	$353,752	$501,462	$147,709
Dose Intensity: EL+Dex Lenalidomide	65.8%	98.8%	$363,984	$491,230	$127,245
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$485,705	$427,607	$58,098
Dose Intensity: EL+Dex Elotuzumab	76.8%	100.0%	$387,075	$427,607	$40,532
2nd Line Utility, Progressed Disease	0.62	0.74	$437,306	$403,148	$34,159
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$439,016	$409,486	$29,530
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$422,082	$433,132	$11,050
Cost: Elotuzumab administration	$182.30	$273.44	$424,053	$431,160	$7,107

2nd-line IX + LEN + DEX



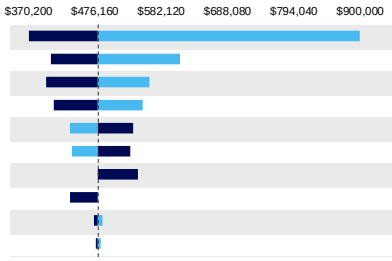
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, IL+Dex	0.59	0.93	$314,410	$1,292,442	$978,032
Felix Hazard Ratio	0.31	0.58	$374,118	$534,110	$159,991
Cost: Ixazomib 4 mg capsule	$2,312.00	$3,468.00	$362,578	$505,010	$142,433
Dose Intensity: IL+Dex Lenalidomide	75.0%	100.0%	$350,287	$461,392	$111,106
Dose Intensity: IL+Dex Ixazomib	77.9%	100.0%	$362,578	$443,299	$80,722
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$503,722	$433,794	$69,929
2nd Line Utility, Progressed Disease	0.62	0.74	$443,674	$408,889	$34,784
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$445,301	$415,511	$29,790
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$420,215	$447,373	$27,157
Dose Intensity: IL+Dex Dexamethasone	73.8%	100.0%	$433,393	$433,963	$570

3rd-line CFZ + LEN + DEX



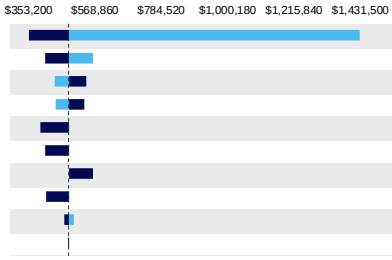
Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, CL+Dex	0.57	0.83	$190,168	$377,443	$187,274
Dose Intensity: CL+Dex Lenalidomide	64.4%	96.6%	$171,715	$305,404	$133,689
Felix Hazard Ratio	0.31	0.58	$203,649	$300,101	$96,452
Cost: Carfilzomib 60 mg vial	$1,489.56	$2,234.34	$201,418	$275,701	$74,283
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$299,660	$238,560	$61,101
Dose Intensity: CL+Dex Carfilzomib	72.8%	100.0%	$201,418	$256,926	$55,508
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$266,343	$216,025	$50,318
3rd Line Utility, Progressed Disease	0.49	0.73	$263,793	$217,732	$46,061
Cost: Carfilzomib vial sharing?	Yes	No	$211,845	$238,560	$26,715
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$232,816	$244,303	$11,488

3rd-line ELO + LEN + DEX



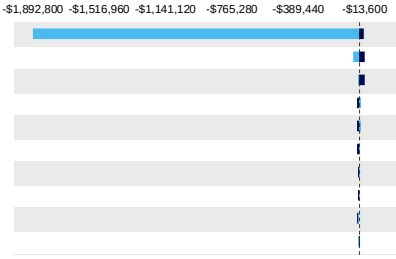
Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, EL+Dex	0.57	0.86	$370,259	$899,971	$529,712
Felix Hazard Ratio	0.31	0.58	$406,544	$612,762	$206,218
Cost: Elotuzumab 400 mg vial	$1,894.40	$2,841.60	$398,784	$563,705	$164,921
Dose Intensity: EL+Dex Lenalidomide	65.8%	98.8%	$410,633	$551,856	$141,223
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$537,236	$435,822	$101,414
3rd Line Utility, Progressed Disease	0.49	0.73	$532,222	$439,179	$93,043
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$545,125	$481,244	$63,881
Dose Intensity: EL+Dex Elotuzumab	76.8%	100.0%	$436,573	$481,244	$44,671
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$474,514	$487,974	$13,460
Cost: Elotuzumab administration	$182.30	$273.44	$477,277	$485,212	$7,935

3rd-line IX + LEN + DEX



Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, IL+Dex	0.59	0.93	$353,231	$1,431,422	$1,078,191
Cost: Ixazomib 4 mg capsule	$2,312.00	$3,468.00	$405,633	$563,531	$157,897
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$540,570	$439,103	$101,467
3rd Line Utility, Progressed Disease	0.49	0.73	$536,064	$442,122	$93,941
Dose Intensity: IL+Dex Lenalidomide	75.0%	100.0%	$392,008	$484,582	$92,574
Dose Intensity: IL+Dex Ixazomib	77.9%	100.0%	$405,633	$484,582	$78,949
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$561,495	$484,582	$76,914
Felix Hazard Ratio	0.31	0.58	$409,061	$484,582	$75,521
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$468,921	$500,242	$31,321
Dose Intensity: IL+Dex Dexamethasone	73.8%	100.0%	$484,138	$484,582	$444

3rd-line PAN + BOR + DEX



Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, PB+Dex (vs. B+Dex)	0.29	1.02	-$16,034	-$1,892,783	$1,876,749
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	-$13,636	-$74,533	$60,897
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	-$13,636	-$44,084	$30,449
Cost: Panobinostat 20 mg capsule	$977.78	$1,466.66	-$55,785	-$32,383	$23,402
Dose Intensity: PB+Dex Panobinostat	64.6%	96.8%	-$55,785	-$32,383	$23,402
3rd Line Utility, Progression-free, off treatment	0.58	0.86	-$55,702	-$36,476	$19,226
Cost: Bortezomib 3.5 mg vial	$1,289.60	$1,934.40	-$51,461	-$36,707	$14,754
Dose Intensity: PB+Dex Bortezomib	60.6%	90.8%	-$51,461	-$36,707	$14,754
Cost: Bortezomib vial sharing?	Yes	No	-$54,728	-$44,084	$10,644
3rd Line Utility, Progression-free, on treatment	0.52	0.78	-$40,337	-$48,599	$8,261

Results of our PSA analysis can be found in Appendix E. Our findings show substantial variability in model outcomes. However, the range of possible incremental cost-effectiveness ratios only approached commonly-cited thresholds (i.e., $50,000 - $150,000 per QALY gained) for CFZ+LEN+DEX and PAN+BOR+DEX.

In the first scenario analysis (see Appendix E, Table E7 and E8), we used an unadjusted estimate (3.27-month increase in OS for each additional month of median PFS) derived from a weighted average ratio of median OS to median PFS from trials included in this evaluation and for which median OS data was available. The pairwise incremental cost-effectiveness ratios were uniformly lower using this factor, but did not go below commonly accepted thresholds for any regimen other than PAN+BOR+BDEX.

As described previously, in the second scenario analysis with BOR+DEX as the universal comparator (see Appendix Table E5 and Table E6), the incremental cost-effectiveness ratios compared to BOR+DEX were uniformly higher for each regimen, owing primarily to the lower unit cost for BOR as compared to LEN.

In the third scenario analysis in which we adjusted the second- and third-line baseline curves to reflect more recent LEN+DEX regimen curves using the relationship between the ASPIRE trial

LEN+DEX data and the M009/M010 pooled LEN+DEX, PFS and OS increased for all regimens due to the improved survival observed in the ASPIRE trial's LEN+DEX arm compared to that observed in the MM-009 and MM-010 trials. This also increased treatment costs for all regimens due to additional time on treatment. The ICER for CFZ+LEN+DEX decreased slightly because of the increased survival while carfilzomib therapy remained limited to 18 cycles, limiting its cost compared to treat-to-progression regimens. The other regimens' ICERs were slightly increased.

In the fourth scenario analysis in which we used different second-line utility scores for triplet versus doublet regimens, the incremental QALYs increased for all triplet regimens compared to LEN+DEX, thereby decreasing the ICERs to some extent.

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Note that PAN is removed from Table 16 due to concerns with its comparison to LEN+DEX. The wholesale acquisition cost of PAN is $1,222 per vial. In comparison to BOR+DEX, cost-effectiveness at this price is approximately $10,000 per QALY gained. The capsule price for PAN could increase to $1,980 (a 62% premium), $2,933 (140%), and $3,886 (218%), and still achieve cost-effectiveness ratios of $50,000, $100,000, and $150,000 per QALY gained. As described previously, however, all results for PAN should be interpreted with caution given concerns with the available clinical evidence.

Table 15 for second-line treatments and Table 16 for third-line treatments. Note that PAN is removed from Table 16 due to concerns with its comparison to LEN+DEX. The wholesale acquisition cost of PAN is $1,222 per vial. In comparison to BOR+DEX, cost-effectiveness at this price is approximately $10,000 per QALY gained. The capsule price for PAN could increase to $1,980 (a 62% premium), $2,933 (140%), and $3,886 (218%), and still achieve cost-effectiveness ratios of $50,000, $100,000, and $150,000 per QALY gained. As described previously, however, all results for PAN should be interpreted with caution given concerns with the available clinical evidence.

For IX, there was no positive price that could be charged and achieve a cost-effectiveness threshold of $50,000/QALY. This occurs primarily for two reasons, both related to the fact that IX is administered as part of a triplet regimen. First, each drug is given in combination with LEN+DEX, which is relatively costly on its own. Second, the additional progression-free survival obtained by using these triplet regimens leads to higher costs for LEN+DEX, as each regimen calls for LEN+DEX to be administered on a treat-to-progression basis. This phenomenon of requiring discounts approaching or more than 100% to reach standard cost-effectiveness levels is well known and relates to situations when current treatment is already near or beyond the cost-effectiveness threshold.[41] Adding even more expense with a new treatment on top of existing treatment, as is the case for multiple myeloma drugs, means that to reach standard cost-effectiveness levels the entire regimen, including the older, existing drugs that are part of the regimen, would need to be deeply discounted, or certain treatment costs must be considered "unrelated" and excluded from the economic evaluation.[42,43]

Note that PAN is removed from Table 16 due to concerns with its comparison to LEN+DEX. The wholesale acquisition cost of PAN is $1,222 per vial. In comparison to BOR+DEX, cost-effectiveness at this price is approximately $10,000 per QALY gained. The capsule price for PAN could increase to $1,980 (a 62% premium), $2,933 (140%), and $3,886 (218%), and still achieve cost-effectiveness ratios of $50,000, $100,000, and $150,000 per QALY gained. As described previously, however, all results for PAN should be interpreted with caution given concerns with the available clinical evidence.

Table 15. Threshold analysis for price per drug for second-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**

Table 16. Threshold analysis for price per drug for third-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**

As one method of addressing concerns about the policy relevance of "negative" pricing, we also considered a scenario in which we allowed for equal discounts on both the new drug and LEN or BOR in these triplet regimens. The results of this analysis are shown in Tables 17 and 18. While significant discounts would be required to achieve cost-effectiveness thresholds of $50,000 - $150,000 per QALY (from ~30%-97% depending on regimen and threshold), the negative pricing situation is avoided.

Table 17. Threshold analysis for second-line treatment: percentage discount and price per vial/capsule for both drugs

Willingness-to-pay	Discount from WAC					
	CFZ/LEN		ELO/LEN		IX/LEN	
$50,000	83.5%	$307/$83	95.1%	$116/$25	90.5%	$275/$48
$100,000	55.6%	$827/$223	82.5%	$414/$88	78.7%	$616/$107
$150,000	27.8%	$1,344/$363	69.9%	$713/$151	66.9%	$957/$166
WAC price per vial/capsule		**$1,862/$503**		**$2,368/$503**		**$2,890/$503**

Table 18. Threshold analysis for third-line treatment: Percentage discount and price per vial/capsule for both drugs

Willingness-to-pay	Discount from WAC					
	CFZ/LEN		ELO/LEN		IX/LEN	
$50,000	87.9%	$225/$61	96.7%	$78/$17	91.9%	$234/$41
$100,000	64.6%	$659/$178	85.5%	$343/$73	81.3%	$540/$94
$150,000	41.3%	$1,093/$295	74.3%	$609/$129	70.7%	$847/$147
WAC price per vial/capsule		**$1,862/$503**		**$2,368/$503**		**$2,890/$503**

Note that we did not formally explore changes in the price of both PAN and BOR that would yield cost-effectiveness ratios ranging from $50,000 to $150,000 per QALY versus BOR+DEX, as the resulting premiums would be even greater than those that would result from changing the price of PAN alone.

6.4 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total potential budget impact of these multiple myeloma treatments, based on assumed patterns of product uptake. The potential budget impact analyses assumed a specific product uptake rate over the five-year period.

Potential Budget Impact Model: Methods

Potential budget impact was defined as the total incremental cost of the therapy for the treated population, calculated as incremental health care costs (including drug, administration, supportive care, and progression treatment costs) minus any offsets in these costs from averted health care events. Note that this analysis is performed from an *ex ante* perspective; that is, it treats all of the drugs being evaluated as though they will be new to market, whether or not they have already been launched. We estimated the net costs of adding each drug to LEN+DEX (or to BOR+DEX for PAN+BOR+DEX), assuming no current use of the drug. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

We calculated potential budget impact by including the entire candidate populations for treatment: adults with MM who have relapsed or not responded to at least one prior line of therapy, who are not currently on maintenance treatment, and who are not being considered for stem cell transplant. The National Cancer Institute reported the 2012 prevalence of MM cases in the U.S. as 89,658 patients,[44] which equates to 0.0285% of the 2012 U.S. population.[108] Applying that rate to the projected 2016 U. S. population[109] of 323,996,000 leads to an estimate of 92,482 prevalent MM cases in 2016.

To estimate the size of the potential candidate population for each line of therapy, we used the proportions from a claims analysis of treatment patterns in the U.S. from 2006-2014.[110] This analysis of MM treatment patterns found that 19.7% of MM patients received second-line therapy, while 7.9% received third-line treatment. However, the authors report that approximately 46% of the patients in this analysis were not treated for MM, and speculate that the ICD-9 code being used to identify patients may also include patients with smoldering/indolent MM or monoclonal gammopathy of undetermined significance (MGUS), a precursor condition to MM. SEER prevalence estimates "include invasive cases only unless otherwise noted."[44]

Given that "invasive cases" would generally exclude asymptomatic MM patients, we assumed that the untreated patients in the Song article were asymptomatic and therefore would not be included in the prevalence estimate. If we exclude those untreated patients, the proportion of patients receiving second-line treatment becomes 36.7%, with 12.9% of treated patients getting third-line treatment. Applying these proportions to the U.S. prevalence of 92,482, we estimated that 33,941 MM patients would be candidates for second-line treatment, and 11,930 MM patients would receive third-line treatment.

ICER's methods for estimating potential budget impact are described in detail elsewhere. Briefly, our calculations assume that the utilization of new drugs or devices occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug/device uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate unmanaged uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year five); 2) high (50% uptake by year five); 3) intermediate (25% uptake by year five); and 4) low (10% uptake by year five). In this analysis, we assumed a very high uptake pattern (75%) across all of the MM treatments of interest in each line. Uptake was assumed to be very high because of the gains in progression-free survival that have been demonstrated in available clinical trials as well as acceptable levels of toxicity in most circumstances. In the absence of reliable data on current or future market share, we assumed that 25% would receive each of the three regimens. Similarly, the four third-line regimens were assumed to equally divide 75% of that market, or achieve 18.75% each by year 5. We note the

absence of DARA and POM+LoDEX in these estimates; however, because DARA's labeled indication is for fourth-line or later use (in patients who have received prior treatment with a PI or an IMiD or who are double refractory to both a PI and IMiD), and POM+LoDEX is reserved for patients who are refractory to both LEN and a PI, second- or third-line use is currently expected to be limited.

The resulting population size after five years, assuming an estimated 25% uptake per second-line regimen and 18.75% per third-line regimen, was 8,485 for each second-line treatment, and 2,237 for each third-line treatment. For consistency, uptake was assumed to occur in equal proportions across the five-year timeframe, and we adjusted net costs to account for this. For example, in a population estimated to have a 25% five-year uptake, 5% of patients would be assumed to initiate therapy each year. Patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of the five-year costs.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/Slides-on-value-framework.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in U.S. gross domestic product (GDP) +1%, the average number of new drug (or device) approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs (or devices) to total health care spending. Calculations are performed as shown in Table 19.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 19. Calculation of potential budget impact threshold

Item	Parameter	Estimate	Source
1	Growth in U.S. GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS National Health Expenditures (NHE), 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS NHE, Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 20 presents the potential budget impact of five years of utilization of each second-line regimen rather than LEN+DEX in the candidate population, assuming the uptake patterns previously described. Results from the model showed that, with the uptake pattern assumptions mentioned above, each second-line regimen would be given to an estimated 1,697 individuals in the U.S. in the first year. Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 8,485 persons receiving each regimen for one or more years, or 25,455 patients across all three regimens.

Over this timeframe, the weighted potential budget impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $133,000 per patient receiving CFZ+LEN+DEX, $233,000 per patient receiving ELO+LEN+DEX, and $194,000 per patient receiving IX+LEN+DEX. In this particular case, weighted potential budget impact is driven by a number of factors, including dosing frequency and dose intensity, dosing strategy (i.e., treat to progression versus fixed-duration treatment), and the rate of progression for each regimen.

Over five years, the average potential budget impact per year is approximately $226 million for CFZ+LEN+DEX, or 25% of the budget impact threshold of $904 million for a new drug. Average potential budget impact per year is estimated to be approximately $395 million per year for ELO+LEN+DEX (44% of the threshold), and approximately $330 million for IX+LEN+DEX (35% of threshold).

Table 20. Potential budget impact (BI) of second-line regimens based on assumed patterns of uptake (25% per regimen by Year 5)

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Regimen	Eligible Population	Number Treated	Annual BI per Patient	Total BI (millions)	Number Treated	Weighted BI per Patient*	Avg. BI/Year (millions)
CFZ+LEN+DEX	33,941	1,697	$107,422	$182.3	8,485	$133,097	$225.9
ELO+LEN+DEX	33,941	1,697	$122,566	$208.0	8,485	$232,848	$395.1
IX+LEN+DEX	33,941	1,697	$94,463	$160.3	8,485	$194,388	$329.9
Total	33,941	5,091	$108,150	$550.6	25,455	$186,777	$950.9

*For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year.

Results for the four third-line regimens are shown in Table 21. The third-line budget impact comparator for PAN+BOR+DEX was calculated relative to BOR+DEX, as this is a more realistic comparator for budget impact considerations. We modeled the potential budget impact of five years of utilization of each regimen in the candidate population, assuming 75% uptake divided equally among the four regimens. Given that assumption, each third-line regimen would be given to an estimated 447 individuals in the U.S. in the first year. Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 2,235 persons receiving each regimen for one or more years, or 8,940 patients across all four regimens. Over this timeframe, the weighted potential budget impact is approximately $132,000 per patient receiving CFZ+LEN+DEX, $222,000 per patient receiving ELO+LEN+DEX, and $185,000 per patient receiving IX+LEN+DEX. Using PAN+BOR+DEX rather than BOR+DEX over the 5-year timeframe produces a potential budget impact of approximately $26,400 per patient.

Average potential budget impact per year is approximately $59 million for CFZ+LEN+DEX, approximately $99 million per year for ELO+LEN+DEX, approximately $83 million for IX+LEN+DEX, and $11.8 million for PAN+BOR+DEX. No regimen approached the potential budget impact threshold of $904 million for a new drug.

Table 21. Potential budget impact (BI) of third-line regimens based on assumed patterns of uptake (18.75% per regimen by Year 5)

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
Regimen	Eligible Population	Number Treated	Annual BI per Patient	Total BI (millions)	Number Treated	Weighted BI per Patient*	Avg. BI/Year (millions)
CFZ+LEN+DEX	11,930	447	$106,239	$47.5	2,235	$132,358	$59.2
ELO+LEN+DEX	11,930	447	$121,295	$54.2	2,235	$222,438	$99.4
IX+LEN+DEX	11,930	447	$92,890	$41.5	2,235	$185,379	$82.9
PAN+BOR+DEX**	11,930	447	$65,926	$29.5	2,235	$26,414	$11.8
Total	11,930	1,788	$96,588	$172.7	8,940	$141,648	$253.3

*For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year.
**vs. BOR+DEX

6.5 Value-Based Price Benchmarks

Our draft value-based benchmark prices for each second-line regimen are provided in Table 22, and for each third-line regimen in Table 23. As noted in the ICER methods document, the draft value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained, without exceeding the $904 million budget impact threshold for new drugs. In this case, none of the evaluated drugs are projected to exceed that budget impact threshold.

As noted above, we also performed analyses to determine the prices at which discounts to both the new drugs and to LEN or BOR would be able to meet cost-effectiveness thresholds, but we are not using those figures as the primary source for our value-based price benchmarks because we do not believe there is currently a mechanism through which it is likely that "regimen" discounts can be negotiated or administered in the US health care system. If this could be achieved, value-based price benchmarks for newer drugs would be higher, as shown in Tables 17 and 18.

The draft value-based price benchmark results are shown in Table 22 for second-line treatments. As noted previously, the potential budget impact of each of these regimens does not exceed our stated threshold when annualized over a five-year time horizon. The price of each drug that could be charged and not exceed the $904 million annual benchmark is higher than the price range that would achieve $100,000 to $150,000 per QALY gained.

Therefore, the draft ICER value-based price benchmark for second-line CFZ, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $673 to $1,267 per vial. This price represents a 32%-64% discount from the estimated cost of CFZ. The draft ICER value-based price benchmark for second-line ELO is $267 to $588 per 400 mg vial, representing a 75%-89% discount from the cost per vial. The draft ICER value-based price benchmark for second-line IX is $181 to $587 per capsule, representing an 80%-94% discount from the WAC price. Greater discounts are required for those regimens with "treat to progression" dosing schedules.

Table 22. Draft value-based price benchmarks for second-line regimens

Regimen	WAC Price per Vial/Capsule	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Draft Value-Based Price Benchmark
CFZ+LEN+DEX	$1,862	$673	$1,267	$673 to $1,267
ELO+LEN+DEX	$2,368	$267	$588	$267 to $588
IX+LEN+DEX	$2,890	$181	$587	$181 to $587

Our draft value-based benchmark prices for each third-line regimen are shown in Table 23. As above, none of the evaluated drugs are projected to exceed the $904 million budget impact threshold. The price range for each third-line regimen based on cost-effectiveness thresholds is

lower than the annual cost for these patients using list price for each regimen, except for PAN. This reflects the results of our cost-effectiveness analyses, which found cost/QALY ratios greater than $150,000/QALY for all third-line regimens except PAN+BOR+DEX, which was found to be cost-saving relative to LEN+DEX.

Therefore, the draft ICER value-based price benchmark for CFZ as a third-line MM treatment, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $432 to $974 per vial. This price represents a 48%-77% discount from the WAC price. The draft ICER value-based price benchmark for third-line ELO is $178 to $466 per vial, representing an 80%-93% discount from the per-vial cost. The draft ICER value-based price benchmark for third-line IX would be $74 to $440 per capsule, or an 85%-97% discount. Finally, the draft ICER value-based price benchmark for third-line PAN is $2,933 to $3,886 per capsule, which is substantially higher than the list price. The price benchmarks for PAN are listed in relation to use of this agent with BOR+DEX versus BOR+DEX alone, based on the results of our scenario analyses, as this would be the more realistic comparator for pricing considerations.

Table 23. Draft value-based price benchmarks for third-line regimens

Regimen	WAC Price per Vial/Capsule	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Draft Value-Based Price Benchmark
CFZ+LEN+DEX	$1,862	$432	$974	$432 to $974
ELO+LEN+DEX	$2,368	$178	$466	$178 to $466
IX+LEN+DEX	$2,890	$74	$440	$74 to $440
PAN+BOR+DEX*	$1,222	$2,933	$3,886	$2,933 to $3,886

*Compared to BOR+DEX

6.6 Summary and Comment

The primary aim of this analysis was to estimate the cost-effectiveness of various treatments for multiple myeloma patients who have received one or two previous therapies (i.e., second- or third-line treatment), focusing on patients with relapsed and/or refractory disease, who were not currently on maintenance treatment, and were not being considered for stem cell transplant. For second-line treatment, our primary analysis generated incremental cost-effectiveness ratios of approximately $200,000/QALY for CFZ+LEN+DEX, $428,000/QALY for ELO+LEN+DEX, and approximately $434,000/QALY for IX+LEN+DEX, relative to comparator treatment with LEN+DEX alone. These ratios are all well above commonly-cited thresholds for the cost-effectiveness of health interventions (i.e., $50,000-$150,000 per QALY gained), and would require substantial discounts in many cases to achieve these thresholds. Similar results were observed for these regimens in our analysis of third-line therapy.

We also analyzed PAN+BOR+DEX in the third-line population, and we found it be both less expensive and more effective than LEN+DEX treatment. Reduced costs are largely due to the lower acquisition cost of BOR relative to LEN as well as the time-limited nature of the PAN+BOR+DEX regimen. We do note, however, that these results should be interpreted with caution as our estimate of treatment effect for this regimen was far more uncertain than that for the other regimens, and that overall efficacy findings from the Phase III trial of PAN+BOR+DEX were questioned by regulators and HTA agencies due to unusually high rates of censoring and toxicity-related discontinuation.

Because the discounts required to achieve commonly-accepted cost-effectiveness thresholds exceeded 90% in some instances above, we explored this issue further. Health technology assessments have dealt with the issue of health care interventions that are not cost-effective even at or close to zero price in the past.[41] In most of these cases, the situation arises when clinically effective treatments were leading to patients spending additional time in high-cost health care states. Because of these additional costs, the treatment would not appear cost-effective, even if its cost were reduced to zero. One solution to this issue which has been proposed in the literature is to treat those additional costs as unrelated, and so exclude them from the evaluation of the cost-effectiveness of the intervention.[45] However, this approach is not without controversy, [46,47] and so we did not attempt its calculation for this review.

We also estimated the potential budget impact of each regimen, assuming 75% uptake across all second-line (i.e., 25% for each of the three regimens) and third-line treatments (i.e., 18.75% for each of the four regimens). With these assumptions, no regimen approached the budget impact threshold of $904 million for a new drug. If we assume greater uptake rates, the potential budget impact for CFZ+LEN+DEX would approach an annual threshold of $904 million only at an assumed uptake of 100%. Uptake of IX+LEN+DEX would need to approach 75% of eligible patients to exceed this annual threshold, while the potential budget impact of ELO+LEN+DEX would exceed the

threshold at around 60% uptake. None of the third-line regimens would exceed the $904 million annual threshold, even assuming 100% uptake for each regimen.

We note several limitations of our analysis. The cost-effectiveness analysis was conducted from a health system perspective, and so does not incorporate costs and effects that might be relevant from a societal perspective, such as productivity, transportation, or caregiver costs. However, the largest cost driver and a highly sensitive parameter in our model was the costs of the drugs themselves, and all patients were assumed to have a similar severity of disease. Any residual differences in transportation time or time in treatment would be unlikely to have materially affected our findings. We also assumed that there would be no vial sharing for any infused drug, in the absence of published and credible data on the frequency of this practice in MM. If vial sharing does occur in actual practice for some patients, our analysis would overestimate drug costs for the affected regimens, although to a currently unknown extent.

While our analysis included reported adverse events that occurred in at least 5% of patients for any regimen of interest, we did exclude adverse events that occurred in <5% of patients across *all* regimens, which may have ruled out certain rare but expensive events. However, given that drug costs represented 85-90% of total costs for any given regimen in our analysis, the effects of adding rare adverse events to our analysis would not have materially changed our findings.

In the absence of complete data on overall survival, we assumed that progression-free survival had a predictable and consistent relationship to overall survival based on a published systematic review focused specifically on MM.[40] The observed relationship in any individual study may have been different. We did test this relationship in sensitivity and scenario analyses, and found that, while the assumed relationship of PFS to OS was a sensitive parameter, its impact was far less than that of varying PFS hazard ratios. We also note that we used overall hazard ratios for PFS from available studies rather than those for subgroups defined by number of prior lines of treatment, as we found no consistent evidence of a differential treatment effect according to this stratification across studies, and the trials of interest were powered to detect differences in the overall effect in the full intent-to-treat population.

We also note that the proportional hazards assumption has been challenged in prior studies of MM populations, which may have affected any network-derived estimates of treatment effect.[96] However, given the requirement to use a fixed-effects model based on the number of single-study connections, and our use of LEN+DEX as the universal comparator, the clinical effects of CFZ, ELO, and IX in combination with LEN+DEX are very close to those observed in the key clinical trials. As described previously, the regimen with the greatest uncertainty is PAN+BOR+DEX. However, in a recent NICE submission, findings of a matched patient-level indirect comparison of PAN+BOR+DEX versus LEN+DEX also found an incremental benefit for the former, albeit a smaller effect than that observed in our analysis.[111] While the magnitude of estimated costs and benefits would differ between these approaches, the general conclusions of the primary analysis (i.e., lower costs and

greater QALYs for PAN+BOR+DEX versus LEN+DEX) would remain the same, acknowledging all of the previously-mentioned caveats with the PAN+BOR+DEX clinical evidence.

Finally, our assumed levels of regimen uptake in the marketplace by five years were based on reasoned assumptions, but actual uptake and market share may vary from these estimates. We also present potential budget impact across a range of uptake possibilities in sensitivity analyses. Additionally, costs for drugs already on the market (i.e., CFZ) were not considered as part of the background treatment costs; rather, the potential budget impact analysis was performed from the perspective of adding each newer drug to LEN+DEX (or BOR+DEX) alone.

In summary, the introduction of newer regimens for second- and third-line use in multiple myeloma appears to confer clinical benefits in terms of lengthening progression-free and overall survival as well as improved quality of life. However, at current wholesale acquisition costs, the estimated cost-effectiveness of these regimens exceeds commonly-cited thresholds. Achieving levels of value more closely aligned with patient benefit would require substantial discounts from the list price in many cases.

7. Summary of the Votes and Considerations for Policy

7.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of the Midwest CEPAC Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation, and they help form recommendations with the Midwest CEPAC Panel on ways the evidence can be applied to policy and practice.

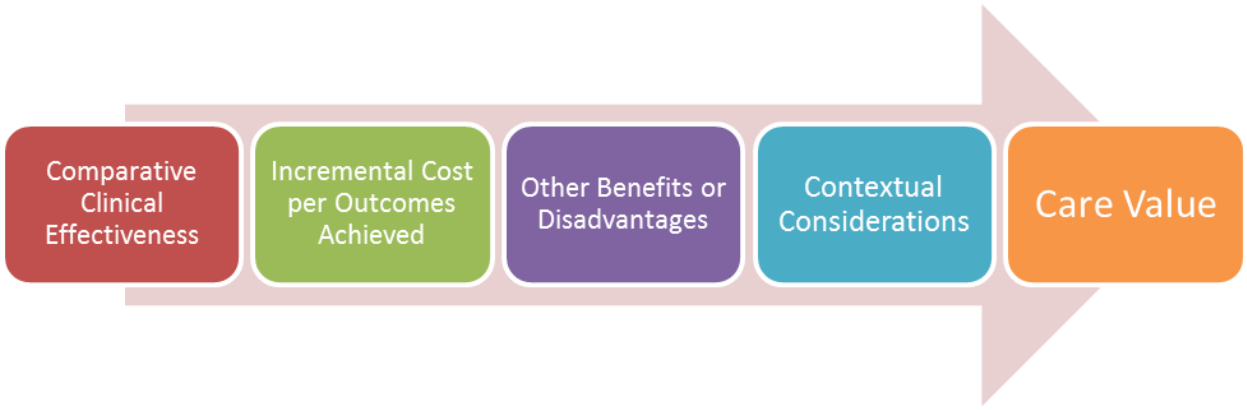
At each meeting, after the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the May 26, 2016 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the treatment of relapsed or refractory multiple myeloma. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 01:35:00), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for relapsed or refractory multiple myeloma. These questions are developed by the ICER research team for each assessment, with input from the Midwest CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented below, along with comments reflecting considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel made use of a value assessment framework with four different components of care value, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, other benefits or disadvantages, and contextual considerations regarding the illness or therapy.

Once they made an overall assessment of care value as low, intermediate, or high considering these four components, the Midwest CEPAC Panel then explicitly considered the affordability of the regimens reviewed in assessing provisional health system value as low, intermediate, or high (see Figure 7 and Figure 8, as well as the detailed explanation that follows).

Figure 9. Care Value Framework



There are four elements to consider when deliberating on care value:

c) ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

d) ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.

e) ***Other benefits or disadvantages*** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.

f) ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

7.2 Clinical Effectiveness Voting Results

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:

1. Is the evidence adequate to demonstrate that the net health benefit of treatment of each regimen listed below is greater than that of treatment with lenalidomide and dexamethasone?

    a) carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)

Yes: 11 votes	*No: 0 votes*

    b) elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)

Yes: 10 votes	*No: 1 votes*

    c) ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 9 votes	*No: 2 votes*

Comments: Members of the Midwest CEPAC voting yes commented that, while they felt there to be adequate evidence of improved net health benefit with each of these newer regimens, more evidence would be helpful to guide clinical practice. In particular, further study should confirm improvements in overall survival, identify patient subpopulations that may benefit from specific treatments, and provide head-to-head comparisons of different treatment sequences of available agents.

2. Is the evidence adequate to distinguish the net health benefit of treatment among these three regimens?

    - carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
    - elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
    - ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 2 votes	***No: 9 votes***

Comments: The primary justification given for the "no" votes was that there were no head-to-head studies and that the indirect comparison performed by ICER staff through a network meta-analysis found that the relative benefits of these treatment regimens were very similar across the study populations.

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:

3. Is the evidence adequate to demonstrate that the net health benefit of treatment with the regimens listed below is greater than that of comparator treatment listed?

    a) carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX) vs. LEN+DEX

Yes: 10 votes	*No: 1 votes*

    b) elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX) vs. LEN+DEX

Yes: 11 votes	*No: 0 votes*

    c) ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX) vs. LEN+DEX

Yes: 11 votes	*No: 0 votes*

d) panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX) vs. BOR+DEX

Yes: 5 votes	***No: 6 votes***

Comments: As illustrated by the votes, members of the Midwest CEPAC were most concerned with the evidence on PAN+BOR+DEX, largely due to concerns about toxicity. Members voting yes believed that the levels of toxicity seen in the Phase III trial might be mitigated by the use of subcutaneous BOR rather than the intravenous administration used for most patients in the trial. A member voting no shared that while he was tempted to vote yes as a result of this possibility, the weight of the evidence remained equivocal.

4. Is the evidence adequate to distinguish the net health benefit of treatment among these regimens:

   - carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX)
   - elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX)
   - ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX)

Yes: 3 votes	***No: 8 votes***

Comments: As with the similar voting results for this question regarding net health benefit in second-line use, the primary justification given for the "no" votes was that there were no head-to-head studies and that the indirect comparison performed by ICER staff through a network meta-analysis found that the relative benefits of these treatment regimens were very similar across the study populations.

5. 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: 4 votes	***No: 6 votes***

**1 member abstained*

Comments: At the time of this vote, clinical experts shared that there was new evidence, soon to be publicly released, that may change opinion on the usage of daratumumab in earlier lines of therapy. Members were counseled to consider only the currently-available evidence as they

did for the other regimens of interest. One member abstained from voting as a result. Members wanted to highlight that this is a "point in time vote" and that they would like to revisit this question as more evidence emerges.

7.3 Comparative Care Value Voting Results

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:

6. Given the available evidence, what is the ***care value*** of treatment with each of the following three regimens listed below versus treatment with lenalidomide and dexamethasone:

    a) carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX):

Low : 2 votes	***Intermediate: 9 votes***	*High: 0 votes*

    b) elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX):

Low : 4 votes	***Intermediate: 7 votes***	*High: 0 votes*

    c) ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX):

Low : 4 votes	***Intermediate: 7 votes***	*High: 0 votes*

Comments: A majority of the Council found each of the second-line regimens to be of intermediate value. While no members voted that the regimens were high value, those voting for intermediate value cited the significant clinical benefit provided by these regimens in spite of cost-effectiveness results that exceeded commonly-cited thresholds. Members also mentioned the challenge of achieving cost-effectiveness thresholds when new treatments are added to regimens already containing very expensive medications. However, one clinical expert cautioned that some of the cost estimates may be systematically understated because the regimens with indications for treatment of fixed duration are in practice given on a "treat to progression" basis, thereby increasing their costs in clinical practice.

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:

7. Given the available evidence, what is the ***care value*** of treatment with any of the regimens listed below versus that of comparator treatment (either lenalidomide and dexamethasone OR bortezomib and dexamethasone):

    a) carfilzomib with lenalidomide and dexamethasone (CFZ+LEN+DEX):

Low : 2 votes	***Intermediate: 9 votes***	*High: 0 votes*

    b) elotuzumab with lenalidomide and dexamethasone (ELO+LEN+DEX):

Low : 6 votes	*Intermediate: 5 votes*	*High: 0 votes*

    c) ixazomib with lenalidomide and dexamethasone (IX+LEN+DEX):

Low : 5 votes	***Intermediate: 6 votes***	*High: 0 votes*

    d) panobinostat with bortezomib and dexamethasone (PAN+BOR+DEX):

Low: 4 votes	***Intermediate: 4 votes***	*High: 3 votes*

Comments: The voting splits for the first three regimens were similar to those for second-line use, although more Council members voted low value given that the incremental cost-effectiveness ratios were even higher for third-line use. For PAN-BOR-DEX, while the regimen has the lowest cost and most favorable cost-effectiveness ratio, voting was influenced by the view of one of the clinical experts that no myeloma expert would consider panibinostat clinically superior to carfilzomib, elotuzumab or ixazomib.

7.4 Roundtable Discussions and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion about the treatment options for relapsed or refractory multiple myeloma with a Policy Roundtable that included two clinical experts, two patient representatives, a payer representative and a pharmacy benefit manager representative. The policy roundtable discussion with the Midwest CEPAC Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below.

Roundtable Participant	Association
Yelak Biru	North Texas Myeloma Support Group Leader and Member, Board of Directors, International Myeloma Foundation
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

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Clinical Research Community

Researchers, funding agencies, manufacturers, and patients should work together to design and conduct clinical research to address critical evidence gaps, including the lack of information on the comparative effectiveness and value of different sequences of available drugs.

The current drug development policy structure is dominated by the goal of getting new, effective drugs onto the market as quickly and efficiently as possible. Such a system favors clinical trial design with relatively short-term outcomes and without examination of different options for how to sequence treatment regimens for patients who will be cycling through different treatments over several years. Constructed with this goal in mind, these studies fail to address many of the key clinical questions facing patients, clinicians, and insurers once the drugs do reach clinical practice. Prominent among the evidence gaps is the lack of information on the comparative effectiveness and value of different approaches to sequencing regimens for patients with differing levels of "aggressive" disease. Much research is also needed to evaluate different protocols for maintenance

treatment during remission. Patients need to know if they can gain the same benefits while avoiding months of additional treatment, with its attendant side effects and costs.

It will take a concerted effort by all stakeholders to work together to address these evidence gaps. Patients and clinicians must become more committed to engagement in clinical trials, becoming more willing to accept randomization and other clinical trial requirements as needed. Drug manufacturers should facilitate funding and conduct of studies of different options for maintenance therapy when there are important questions left outstanding following FDA approval. And funding agencies, such as the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI), should prioritize research on new drugs in the first few years after entry into clinical practice, especially given the increasing number of drugs entering use following accelerated regulatory approval pathways. This research is needed to provide patients, clinicians, and insurers the information they need on the comparative benefits, harms, and costs of different treatment options.

Patients

Patient organizations should be given a leadership role in efforts to change the way clinical trials are designed and to advocate for ongoing and rigorous study in real-world populations. Through this effort patient organizations should seek to reduce barriers that impede high participation in clinical research that will guide future clinical practice.

Patient groups have long advocated for the ability to provide input to manufacturers and researchers regarding the outcomes most important to them, the benefits that might be afforded by alternative settings of treatment or drug delivery mechanisms, and other key concerns. Most importantly, this input should occur when key clinical trials are in the conception and design phases to ensure that the information most important to patients is available at the time of drug approval.

A patient representative on the policy roundtable also called on patient groups to look beyond FDA approval, stating that regulatory approval should not be considered the endpoint for most research. In particular, the development of rigorous patient registries can provide key data on how approved regimens work under a variety of real-world conditions and may allow for streamlined study of the effects of treatment sequences and variations of protocols for maintenance treatment.

Clinical experts on the roundtable also discussed challenges in enrolling patients in cancer clinical studies, as many individuals are reluctant to be randomized due to concerns regarding possible negative impacts on their own disease course. Patient organizations can play a critical role in educating the patient community regarding the intent and value of clinical trials as well as reassuring patients that tools exist (e.g., study stopping rules, compassionate use requirements) to get therapies with demonstrated clinical benefits to patients who need them.

Manufacturers

Drug manufacturers should improve the quality of evidence available around the time of drug approval and adoption to better inform treatment decisions.

The lack of high-quality evidence around new treatment regimens for multiple myeloma was mentioned repeatedly by patients, clinical experts, and Midwest CEPAC panel members during both the voting and roundtable discussions. Given that many important decisions about clinical use, pricing, and coverage must be made near the time of FDA approval, drug manufacturers should work together with the FDA and with patient organizations to establish more consistent approaches to descriptions of patient characteristics as well as to the measurement of both risk factors and outcomes. Doing so would give all stakeholders – patients, clinicians, and payers – enhanced ability to perform more robust indirect comparisons of risks and benefits across treatment options. In addition, drug manufacturers should try to gather comprehensive information about genetic and other patient characteristics that would allow for more robust analyses of outcomes in different patient subpopulations. The inability to understand which drugs may work best for which kinds of patients greatly limits the universal desire for more targeted, individualized treatment.

Manufacturers should consider extensions to both survival and time on treatment in their pricing strategies for new therapies.

Price points set by manufacturers must reflect the new reality of multiple myeloma patients in the current decade, following significant treatment advances that have increased the overall survival of most patients. Manufacturers should consider the increased value that patients are returning to the industry by living longer, and consequently remaining on treatment for longer periods of time, when pricing new therapies.

Manufacturers should take the lead in designing mechanisms to discount all components of a treatment regimen, as advances in multiple myeloma therapy often involve increasing the number of drugs provided to patients during a given treatment course.

Roundtable participants discussed the issues associated with replacing two-drug regimens with three- and even four-drug combinations. As noted in the ICER report, some of the newer drugs do not reach common cost-effectiveness thresholds when added to existing regimens, even with discounts approaching or exceeding 100%, because other expensive drugs in the regimen are also used for longer periods of time. One possible solution is to create "regimen-based" discounts that

reflect better alignment between regimen costs and the value brought to patients, as well as more realistic levels of discounting from the manufacturer perspective. However, this will require manufacturers to cooperate in developing administratively straightforward and scalable agreements with payers and pharmacy benefit managers.

Insurers

Multiple myeloma is a condition in which many patients will cycle through most or all available treatments, and there is substantial variation in drug mechanisms of action and in the personal patient values that guide consideration of the trade-offs between extended survival and different side effect profiles. Given this background, and in the absence of better evidence, payers should not consider step therapy or "fail first" coverage policies for myeloma treatments.

During roundtable discussions, insurers and pharmacy benefit managers mentioned that step therapy or other policies that restrict access are typically employed in situations where populations are relatively homogenous, outcomes are straightforward to measure, and comparisons between treatment options can be clearly made. Multiple myeloma does not fit this description due to its heterogeneity and lack of robust comparative data. For this and most other cancers, payers currently require adherence to the FDA-labeled indication and generally follow national guidelines from NCCN and other clinical societies. However, generation of better and more detailed evidence as described above could lead to the development of step-therapy requirements and/or treatment pathways for certain conditions, such as in the case of tyrosine kinase inhibitors for chronic myeloid leukemia.

Even if insurers do not employ step-therapy or other access restrictions for particular cancers, they should still seek to negotiate discounts on drug prices that better reflect the degree of clinical benefit provided to patients. As noted above, one method for doing so could involve cooperation with manufacturers to develop and implement mechanisms to achieve discounts on all individual drugs in a given treatment regimen. Doing so would not only reduce the magnitude of discount being sought on each individual agent, thereby creating incentives for further innovation, but will likely be a more realistic approach to achieving lower overall drug prices. This will reduce both the financial burden borne by patients and the pressure for payers to restrict access to innovative treatment regimens for multiple myeloma.

Clinicians

Clinicians should consider costs and cost-effectiveness in discussing the sequencing of treatment options for multiple myeloma.

In instances where the clinical evidence does not clearly designate a better treatment or treatment sequence, clinicians should consider the cost to the patient and the health system in their treatment decision. Given the inevitability of relapse in all multiple myeloma patients, and subsequent shorter courses of treatment with each successive relapse, use of less costly regimens earlier in the disease trajectory will lessen the financial burden to the health system and reduce out-of-pocket expenses for patients and their families. One of the roundtable participants, Dr. Vincent Rajkumar of the Mayo Clinic, described the example of use of lower-cost BOR+LEN+DEX as followed by a more expensive regimen at relapse (when the period of remission is likely to be shorter). In contrast, use of a more expensive regimen such as CFZ+LEN+DEX or ELO+LEN+DEX earlier in the disease ahead of BOR+LEN+DEX would increase costs when used during the typically longer period of remission seen at that point in the disease course.

Provider groups that bear financial risk for costs of care should seek mechanisms to manage costs across the health system and avoid too narrow a focus on drug costs within individual classes or patient populations.

As accountable care organizations and other integrated health systems begin to bear greater degrees of financial risk for overall costs of care, the primary mechanisms for cost control should be focused on the entire spectrum of health care services, not solely drug costs for specific classes or certain patient populations. For example, a "silo" approach to drug cost management in cancer might fail to account for the application of mechanisms known to reduce costs, such as multi-disciplinary care coordination or delivery of palliative care services in appropriate patient populations, and may preclude an appropriate focus on areas of excessive spending or waste.

This is the first Midwest CEPAC review of treatment options for relapsed and refractory multiple myeloma.

References

1. Multiple Myeloma Research Foundation. What is multiple myeloma? http://www.themmrf.org/multiple-myeloma/what-is-multiple-myeloma/. Accessed January, 2016.
2. National Cancer Institute. Surveillance E, and End Results (SEER) Program., . SEER Stat Fact Sheets: Myeloma. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed January, 2016.
3. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia.* 2012;26(1):149-157.
4. Rajkumar SV. Overview of the management of multiple myeloma. In: UpToDate. Kyle RA, ed. *UpToDate*. Waltham, MA. Accessed April 5, 2016.
5. Blinman P, King M, Norman R, Viney R, Stockler MR. Preferences for cancer treatments: an overview of methods and applications in oncology. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2012;23(5):1104-1110.
6. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *American journal of hematology.* 2012;87(1):78-88.
7. Rajkumar SV. Treatment of multiple myeloma. *Nature reviews. Clinical oncology.* 2011;8(8):479-491.
8. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood.* 2011;118(12):3205-3211.
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma Version 3.2016. 2016; https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed April 7, 2016.
10. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia.* 2015.
11. Roy A, Kish JK, Bloudek L, et al. Estimating the costs of therapy in patients with relapsed and/or refractory multiple myeloma: A model framework. *American Health and Drug Benefits.* 2015;8(4):204-214.
12. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clinic proceedings.* 2015;90(4):500-504.
13. Light DW, Kantarjian H. Market spiral pricing of cancer drugs. *Cancer.* 2013;119(22):3900-3902.
14. Banegas MP, Guy GP, Jr., de Moor JS, et al. For Working-Age Cancer Survivors, Medical Debt And Bankruptcy Create Financial Hardships. *Health affairs (Project Hope).* 2016;35(1):54-61.
15. Ramsey S, Blough D, Kirchhoff A, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health affairs (Project Hope).* 2013;32(6):1143-1152.
16. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *The New England journal of medicine.* 2015;372(2):142-152.
17. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *The New England journal of medicine.* 2015;373(7):621-631.
18. San-Miguel JF, Hungria VTM, Yoon S-S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *The Lancet. Oncology.* 2014;15(11):1195-1206.

19. U.S. Food and Drug Administration. Ninlaro (ixazomib) Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.
20. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet (London, England).* 2016.
21. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016;374(17):1621-1634.
22. San-Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *The Lancet. Oncology.* 2013;14(11):1055-1066.
23. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(12):1277-1280.
24. San-Miguel JF, Hungria VTM, Yoon SS, et al. Final analysis of overall survival from the phase 3 panorama 1 trial of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. *Blood.* 2015;126(23):3026.
25. *ELOQUENT-2 Update: A Phase 3, Randomized, Open-Label Study of Elotuzumab in Combination with Lenalidomide/Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma -- 3-Year Safety and Efficacy Follow-up*. Orlando, FL: American Society of Hematology Annual Meeting and Exposition; 2015.
26. U.S. Food and Drug Administration. Transcript for the November 6, 2014 Meeting of the Oncologic Drugs Advisory Committee (ODAC). 2014; http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM430828.pdf.
27. U.S. Food and Drug Administration. Farydak (Panobinostat) Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf.
28. U.S. Food and Drug Administration. Pomalyst (Pomalidomide) Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204026s005s006s008lbl.pdf. Accessed March, 2016.
29. U.S. Food and Drug Administration. Transcript for the June 20, 2012 Meeting of the Oncologic Drugs Advisory Committee (PM Session). 2012; http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM314709.pdf.
30. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(10):1030-1033.
31. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood.* 2010;116(23):4745-4753.
32. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol.* 2011;12(5):431-440.
33. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(6):587-600.

34. Hansen V, Coleman M, Elkins S, et al. 3027 An Expanded Treatment Protocol of Panobinostat Plus Bortezomib and Dexamethasone in Patients with Previously Treated Myeloma. 57th Annual Society for Hematology Conference; December 6, 2015; Orlando, FL.
35. Silverman B. FDA Used Regulatory Loophole to Save Novartis' Farydak. *"The Pink Sheet".* August 17, 2015.
36. U.S. Food and Drug Administration. Farydak (Panobinostat) Approval Letter. 2015; http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed March, 2016.
37. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;357(21):2133-2142.
38. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007;357(21):2123-2132.
39. Stadtmauer E, Weber D, Dimopoulos M, et al. Lenalidomide in Combination with Dexamethasone Is More Effective Than Dexamethasone at First Relapse in Relapsed Multiple Myeloma. *Blood.* 2006;108(11):3552. Accessed at http://www.myeloma.cz/res/file/2009-bilovice/celgen-core-slides-mm3009-mm3010.pdf.
40. Felix J, Aragao F, Almeida JM, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. *BMC Cancer.* 2013;13:122.
41. Davis S. Assessing technologies that are not cost-effective at zero price: Report by the Decision Support Unit. Decision Support Unit, School of Health and Related Research, University of Sheffield. 2014.
42. Rappange DR, van Baal PH, van Exel NJ, Feenstra TL, Rutten FF, Brouwer WB. Unrelated medical costs in life-years gained: should they be included in economic evaluations of healthcare interventions? *PharmacoEconomics.* 2008;26(10):815-830.
43. van Baal PH, Feenstra TL, Hoogenveen RT, de Wit GA, Brouwer WB. Unrelated medical care in life years gained and the cost utility of primary prevention: in search of a 'perfect' cost-utility ratio. *Health economics.* 2007;16(4):421-433.
44. National Cancer Institute. Surveillance E, and End Results (SEER) Program., . SEER Cancer Statistics Factsheets: Myeloma. 2016. Accessed April 7, 2016.
45. Grima DT, Bernard LM, Dunn ES, McFarlane PA, Mendelssohn DC. Cost-effectiveness analysis of therapies for chronic kidney disease patients on dialysis: a case for excluding dialysis costs. *PharmacoEconomics.* 2012;30(11):981-989.
46. van Baal P, Meltzer D, Brouwer W. Pharmacoeconomic guidelines should prescribe inclusion of indirect medical costs! A response to Grima et Al. *PharmacoEconomics.* 2013;31(5):369-373; discussion 375-366.
47. Gandjour A, Lauterbach KW. Does prevention save costs? Considering deferral of the expensive last year of life. *Journal of health economics.* 2005;24(4):715-724.
48. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
49. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood.* 2008;111(5):2516-2520.
50. Dimopoulos MA, Terpos E, Niesvizky R, Palumbo A. Clinical characteristics of patients with relapsed multiple myeloma. *Cancer treatment reviews.* 2015;41(10):827-835.
51. Mohty B, El-Cheikh J, Yakoub-Agha I, Avet-Loiseau H, Moreau P, Mohty M. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and 'retreatment' approaches in the era of novel agents. *Leukemia.* 2012;26(1):73-85.

52. Haessler J, Shaughnessy JD, Jr., Zhan F, et al. Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(23):7073-7079.
53. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. *Blood.* 1992;80(4):887-890.
54. Masdehors P, Merle-Beral H, Maloum K, Omura S, Magdelenat H, Delic J. Deregulation of the ubiquitin system and p53 proteolysis modify the apoptotic response in B-CLL lymphocytes. *Blood.* 2000;96(1):269-274.
55. LeBlanc R, Catley LP, Hideshima T, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. *Cancer research.* 2002;62(17):4996-5000.
56. Hideshima T, Richardson P, Chauhan D, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer research.* 2001;61(7):3071-3076.
57. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): And randomised, phase 3, open-label, multicentre study. *The Lancet Oncology.* 2016;17(1):27-38.
58. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science (New York, N.Y.).* 2010;327(5971):1345-1350.
59. Zhu YX, Braggio E, Shi C-X, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. *Blood.* 2011;118(18):4771-4779.
60. Lopez-Girona A, Mendy D, Ito T, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia.* 2012;26(11):2326-2335.
61. Zhu YX, Kortuem KM, Stewart AK. Molecular mechanism of action of immune-modulatory drugs thalidomide, lenalidomide and pomalidomide in multiple myeloma. *Leukemia & lymphoma.* 2013;54(4):683-687.
62. Lacy MQ. "IM iD"eally treating multiple myeloma. *Blood.* 2013;121(11):1926-1928.
63. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Molecular cancer therapeutics.* 2011;10(11):2034-2042.
64. Lonial S, Durie B, Palumbo A, San-Miguel J. Monoclonal antibodies in the treatment of multiple myeloma: current status and future perspectives. *Leukemia.* 2016;30(3):526-535.
65. Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. *American journal of clinical pathology.* 2004;121(4):482-488.
66. Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2008;14(9):2775-2784.
67. Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood.* 2012;120(3):552-559.
68. Anthem. Cancer Care Quality Program Treatment Pathways: Multiple Myeloma. 2016; https://anthem.aimoncology.com/pdf/pathways/Cancer_Pathways_Clinical_Detail.pdf. Accessed April 7, 2016.
69. National Institute for Health and Care Excellence (NICE). NICE Myeloma Pathway. 2016; http://pathways.nice.org.uk/pathways/myeloma#path=view%3A/pathways/myeloma/myeloma-overview.xml&content=view-index, April 6, 2016.

70. National Institute for Health and Care Excellence (NICE). NICE Guidance in develeopment: multiple myeloma - carfilzomib (with lenalidomide and dexamethasone, after prior therapy). 2016; https://www.nice.org.uk/guidance/indevelopment/gid-tag511. Accessed April 7, 2016.
71. National Institute for Health and Care Excellence (NICE). Proposed Health Technology Appraisal: Daratumumab for treating relapsed and refractory multiple myeloma 2016; https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Proposed-appraisals-no-wave/multiple-myeloma-daratumumab-draftscope.pdf. Accessed April 7, 2016.
72. National Institute for Health and Care Excellence (NICE). NICE Guidance In Development: Multiple myeloma (previously treated) - elotuzumab. 2016; https://www.nice.org.uk/guidance/indevelopment/gid-ta10015. Accessed April 7, 2016.
73. National Institute for Health and Care Excellence (NICE). NICE Proposed Health Technology Appraisal: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma. 2015; https://www.nice.org.uk/guidance/GID-TA10043/documents/draft-scope-pre-referral. Accessed April 7, 2015.
74. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
75. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
76. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *The New England journal of medicine.* 2015;373(13):1207-1219.
77. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. *Blood.* 2013;121(11):1968-1975.
78. Sehgal K, Das R, Zhang L, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: Impact of immune activation and cereblon targets. *Blood.* 2015;125(26):4042-4051.
79. Richardson PG, Jagannath S, Moreau P, et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. *The Lancet. Haematology.* 2015;2(12):e516-527.
80. Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. *Blood.* 2016;127(6):713-721.
81. Weisel K, Dimopoulos M, Song KW, et al. Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial. *Clinical Lymphoma, Myeloma and Leukemia.* 2015;15(9):519-530.
82. San-Miguel JF, Weisel KC, Song KW, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. *Haematologica.* 2015;100(10):1334-1339.
83. Dimopoulos MA, Weisel KC, Song KW, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. *Haematologica.* 2015;100(10):1327-1333.
84. Morgan G, Palumbo A, Dhanasiri S, et al. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone. *British journal of haematology.* 2015;168(6):820-823.

85. Anderson KC, Kyle RA, Rajkumar SV. Clinically relevant end points and new drug approvals for myeloma. *Leukemia.* 2008;22:231-239.
86. San-Miguel J, Weisel K, Song KW, et al. Patient outcomes by prior therapies and depth of response: Analysis of MM-003, a phase 3 study comparing pomalidomide + low-dose dexamethasone (POM + LoDEX) Vs high-dose dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM). *Blood.* 2013;122(21).
87. U.S. Food and Drug Administration. Ninlaro Medical Review (208462Orig1s000). In: Center for Drug Evaluation and Research, ed2015.
88. Avet-Loiseau H, Fonseca R, Siegel D, et al. Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone in patients with relapsed multiple myeloma based on cytogenetic risk status: Subgroup analysis from the phase 3 study aspire (NCT01080391). *Blood.* 2015;126(23):731.
89. U.S. Food and Drug Administration. Empliciti Medical/Statistical Review (761035Orig1s000). In: Research CfDEa, ed2015.
90. Moreau P, Masszi T, Grzasko N, et al. Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRD), significantly extends progression-free survival (PFS) for patients (PTS) with relapsed and/or refractory multiple myeloma (RRMM): The phase 3 tourmaline-MM1 study (NCT01564537). *Blood.* 2015;126(23):727.
91. Dimopoulos MA, Stewart AK, Rajkumar SV, et al. Effect of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) by line of therapy: Secondary analysis from an interim analysis of the phase III study ASPIRE (NCT01080391). *Journal of Clinical Oncology.* 2015;33(15).
92. San-Miguel JF, Hungria VTM, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1. *Journal of Clinical Oncology.* 2015;33(15).
93. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ (Clinical research ed.).* 2005;331(7521):897-900.
94. Cameron C, Coyle D, Richter T, et al. Systematic review and network meta-analysis comparing antithrombotic agents for the prevention of stroke and major bleeding in patients with atrial fibrillation. *BMJ open.* 2014;4(6):e004301.
95. Ip S PJ, Balk EM, Dahabreh IJ, Avendano EE, Lau J. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. Research White Paper. (Prepared by Tufts Evidence-based Practice Center under Contract No. 290-2007-10055-I.) AHRQ Publication No. 13-EHC007-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2013.
96. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. *Research synthesis methods.* 2010;1(3-4):258-271.
97. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(1):89-96.
98. U.S. Food and Drug Administration. Carfilzomib (Kyprolis) Prescribing Information. 2016; http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202714s010lbl.pdf. Accessed March, 2016.
99. U.S. Food and Drug Administration. Elotuzumab (Empliciti) Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf. Accessed March, 2016.

100. Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma from a US Perspective. *Journal of medical economics.* 2016:1-44.
101. Talamo G, Zhu J, Dolloff N, et al. Retrospective Study of Body Weight in Patients with Multiple Myeloma through Different Stages of the Disease. *Metab Nutr Oncol.* 2013;01(01):e7-e11.
102. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol.* 2011;11:139.
103. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. . http://www.nice.org.uk/guidance/ta338.
104. Farr AM, Stott-Miller M, Varker H, Spencer D, Shah M, Chen C. Treatment Sequencing Patterns Associated with Elderly Patients with Relapsed/Refractory Multiple Myeloma (MM) in the US Community Setting. *Blood.* 2016;126(23):5392.
105. Amgen. Data provided in response to ICER data request. QOL/Utility Data from ASPIRE Cost Effectiveness Model. Data on file.
106. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer.* 2013;21(2):599-607.
107. Potluri R, Farr AM, Hirji I, Davis C, Bhandari H, Oukessou A. Treatment Sequencing Patterns And Costs of Care in Patients with Relapsed/Refractory Multiple Myeloma. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2015;18(7):A450.
108. U.S. Census Bureau. Population Division. Table 1. Annual Estimates of the Resident Population for the United States, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2015 (NST-EST2015-01). *State Totals: Vintage 2015* 2015. Accessed April 7, 2016.
109. U.S. Census Bureau. Population Division. Table 1. Projections of the Population and Components of Change for the United States: 2015 to 2060 (NP2014-T1). *2014 National Population Projections: Summary Tables* 2014. Accessed April 7, 2016.
110. Song X, Cong Z, Wilson K. Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. *Current Medical Research and Opinion.* 2016;32(1):95-103.
111. National Institute for Health and Care Excellence (NICE). Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]. 2016; https://www.nice.org.uk/guidance/TA380/documents/committee-papers. Accessed March, 2016.
112. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
113. U.S. Preventive Services Task Force. *Appendix VII. Criteria for Internal Validity: Assessing Individual Studies.* Procedure Manual;2011.
114. Dimopoulos MA, Stewart AK, Rajkumar SV, et al. Effect of carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone in patients with relapsed multiple myeloma by line of therapy: Interim results from the phase 3 aspire study. *Haematologica.* 2015;100:151-152.
115. Palumbo A, Stewart AK, Rajkumar SV, et al. Efficacy and safety of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients (pts) with relapsed multiple myeloma (RMM) based on age: Secondary analysis from the phase 3 study aspire (nct01080391). *Clinical Lymphoma, Myeloma and Leukemia.* 2015;15:e75-e76.

116. Dimopoulos MA, Lonial S, White D, et al. Eloquent-2 update: A phase 3, randomized, open-label study of elotuzumab in combination with lenalidomide/dexamethasone in patients with relapsed/refractory multiple myeloma-3-year safety and efficacy follow-up. *Blood.* 2015;126(23):28.
117. Jagannath S, Lonial S, Jakubowiak AJ, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in high-risk and/or stage 23 relapsed and/or refractory multiple myeloma: A retrospective subset analysis of the phase 2 study. *Blood.* 2011;118(21).
118. Richardson PG, Jagannath S, Moreau P, et al. A phase 2 study of elotuzumab (elo) in combination with lenalidomide and low-dose dexamethasone (ld) in patients (pts) with relapsed/refractory multiple myeloma (r/r mm): Updated results. *Blood.* 2012;120(21).
119. Richardson PG, Jagannath S, Moreau P, et al. Final results for the 1703 phase 1b/2 study of elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood.* 2014;124(21).
120. Richardson PG, Hungria VTM, Yoon SS, et al. Subgroup analysis by prior treatment of the efficacy and safety of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study. *Clinical Lymphoma, Myeloma and Leukemia.* 2015;15:e78.
121. Richardson PG, Hungria VTM, Yoon SS, et al. Characterization of the incidence and management of gastrointestinal toxicity in the phase 3 panorama 1 study of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. *Blood.* 2014;124(21).
122. Einsele H, Richardson P, Hungria V, et al. Subgroup analysis by prior treatment among patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone. *Haematologica.* 2015;100:1.
123. Weisel K, Dimopoulos M, Moreau P, et al. Analysis of MM-003 patients with moderate renal impairment using pomalidomide + low-dose dexamethasone (POM + lodex) vs. high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM). *Haematologica.* 2013;98:105.
124. Weisel KC, San Miguel JF, Song KW, et al. Phase 3 study of pomalidomide + low-dose dexamethasone vs. High-dose dexamethasone in relapsed/refractory multiple myeloma: MM-003 subanalysis of elderly patients (>65 and >70 years of age). *Haematologica.* 2014;99:364-365.
125. Weisel K, San Miguel J, Song K, et al. Impact of ecog performance status on overall survival and hrqol in relapsed/refractory multiple myeloma patients from the MM-003 trial of pomalidomide + low-dose dexamethasone (DEX) vs high-dose dex. *Haematologica.* 2014;99:518.
126. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2005;352(24):2487-2498.
127. Dimopoulos MA, Orlowski RZ, Facon T, et al. Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma. *Haematologica.* 2015;100(1):100-106.
128. Roy A, Kish JK, Bloudek L, et al. Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework. *Am Health Drug Benefits.* 2015;8(4):204-215.
129. Center for Medicare and Medicaid Services. Acute Inpatient Prospective Payment System. 2015; http://www.cms.hhs.gov/AcuteInpatientPPS.
130. National Institute for Health and Care Excellence (NICE). Panobinostat for treating multiple myeloma after 2 previous treatments. In: guidance Nta, ed2016.

131. National Institute for Health and Care Excellence (NICE). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib In: guidance Nta, ed2015.
132. Pan-Canadian Oncology Drug Review (pCDOR). Pomalidomide (Pomalyst) for Multiple Myeloma. In: Recommendation pERCF, ed2014.
133. Richardson PG, Lee JH, Majer I, Krishna A, Woodman RC. Efficacy of treatments in relapsed or relapsed and refractory multiple myeloma: An indirect treatment comparison. *Blood.* 2014;124(21).
134. Sheng Z, Liu G. Pooled analysis of the reports of pomalidomide after failure of lenalidomide and (or) bortezomib for multiple myeloma. *Hematological Oncology.* 2015.
135. Sun J-J, Zhang C, Zhou J, Yang H-L. Pooled analysis of pomalidomide for treating patients with multiple myeloma. *Asian Pacific journal of cancer prevention : APJCP.* 2015;16(8):3163-3166.
136. Nooka A, Kaufman JL, Behera M. Efficacy and safety of triplet versus doublet salvage therapies among patients with multiple myeloma (MM) experiencing early relapse: Meta-analysis of Phase III randomized controlled trials (RCTs). Paper presented at: Blood2015.
137. Ruggeri K, Maguire Á, Schmitz S, et al. Estimating the relative effectiveness of treatments in relapsed/refractory multiple myeloma through a systematic review and network meta-analysis. *Blood.* 2015;126(23):2103.

APPENDICES

A. Evidence Review Methods

B. PRISMA and Evidence Review Table

C. Additional Results from Evidence Review

D. Network Meta-Analysis Methods and Results

E. Comparative Value Supplemental Information

F. Previous Technology Assessments and Systematic Reviews

G. Ongoing Studies

Appendix A. Evidence Review Methods

Table A1. PRISMA 2009 Checklist

TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

RESULTS (*continued*)		
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies

Table A2. Medline 1996 to Present with Daily Update, Cochrane Database of Systematic Reviews 2005 to January 20, 2016, Cochrane Central Register of Controlled Trials December 2015

1	exp multiple myeloma/
2	myelom$.ti,ab.
3	plasm$ cell myelom$.ti,ab.
4	myelomatosis.ti,ab.
5	(plasm$ adj3 neoplas$).ti,ab.
6	kahler.ti,ab.
7	(pomalidomide or pomalyst or imnovid).ti,ab.
8	(panobinostat or farydak).ti,ab.
9	(ixazomib or ninlaro).ti,ab.
10	(elotuzumab or empliciti).ti,ab.
11	(daratumumab or darzalex).ti,ab.
12	(carfilzomib or kyprolis).ti,ab.
13	1 or 2 or 3 or 4 or 5 or 6
14	7 or 8 or 9 or 10 or 11 or 12
15	13 and 14
16	limit 15 to english language
17	limit 16 to humans
18	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or interview or lectures or letter or monograph or news or practice guideline or "review" or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.
19	17 not 18

Table A3. Search strategy of Embase on February 9, 2016

#18	#17 AND ('clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'controlled study'/de OR 'human'/de OR 'in vivo study'/de OR'intention to treat analysis'/de OR 'multicenter study'/de OR 'normal human'/de OR 'open study'/de OR 'phase 1 clinical trial'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial'/de OR 'phase 3 clinical trial (topic)'/de OR 'randomized controlled trial (topic)'/de) AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it)
#17	#16 NOT [medline]/lim
#16	#15 NOT #1
#15	#12 AND #13 AND #14
#14	[humans]/lim
#13	[english]/lim
#12	#9 AND #11
#11	#2 AND #10
#10	'myeloma':ti OR 'myeloma':ab
#9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
#8	'pomalidomide':ti OR 'pomolidomide':ab OR 'pomalyst':ti OR 'pomalyst':ab
#7	'panobinostat':ti OR 'panobinostat':ab OR 'farydak':ti OR 'farydak':ab
#6	'daratumumab':ti OR 'daratumumab':ab OR 'darzalex':ti OR 'darzalex':ab
#5	'ixazomib':ti OR 'ixazomib':ab OR 'ninlaro':ti OR 'ninlaro':ab
#4	'elotuzumab':ti OR 'elotuzumab':ab OR 'empliciti':ti OR 'emplicity':ab
#3	'carfilzomib':ti OR 'carfilzomib':ab OR 'kyprolis':ti OR 'kyprolis':ab
#2	'multiple myeloma'/exp
#1	'case report'/it OR 'case study'/it OR 'letter'/it OR 'editorial'/it

Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study; a third investigator resolved any discrepancies in selection as necessary.

We also included FDA documents related to the agents of interest. These included manufacturer submissions to the agency, internal FDA review documents, and transcripts of Advisory Committee deliberations and discussions. These documents as well as all other literature that did not undergo a formal peer review process are described separately.

Data Extraction and Quality Assessment

Summary tables of extracted data are available in Appendix B. We abstracted outcome data only for dosing regimens included in the FDA labelling for each agent. Of note, while carfilzomib has indications for use as monotherapy, as well as in combination with dexamethasone alone or with lenalidomide and dexamethasone, our review focused only on combination therapy with lenalidomide and dexamethasone based on clinical input regarding the regimen of greatest clinical interest.

We used criteria published by the U.S. Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories “good,” “fair,” or “poor.”[112,113]

Guidance for quality ratings using these criteria is presented below.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

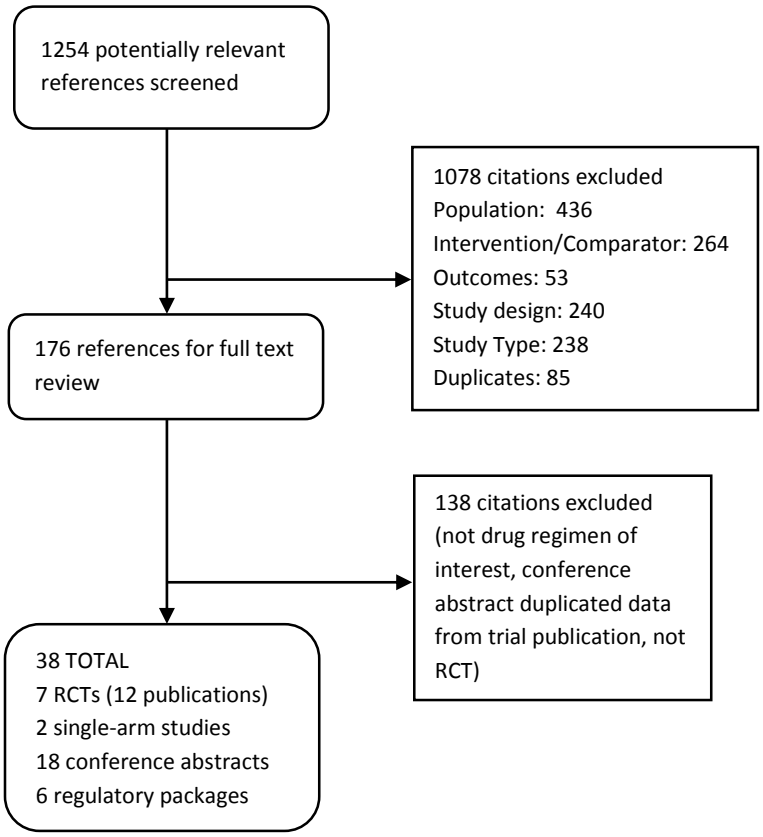
Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies identified provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature. This did not culminate in the suggestion of a publication bias in our literature review.

Appendix B. PRISMA and Evidence Review Table

Figure B1. PRISMA flow chart showing results of literature search for multiple myeloma



Note: results of the Phase III trial of IX+LEN+DEX versus LEN+DEX were published in the interim following posting of our draft report. This publication is not reflected in the above PRISMA but our summary of findings has been updated accordingly.

Table B1. Summary evidence table

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Carfilzomib (Kyprolis)						
Publication **Stewart AK** **N Engl J Med 2015**[16] **(ASPIRE)** ***fair***	RCT Multicenter Open-label Phase III ITT Median months 1) 32.3 2) 31.5	1) CFZ+LEN+DEX (n=396) 2) LEN+DEX (n=396) <u>Dosing schedule</u>: CFZ 20mg/m^2→ 27mg/m^2 on Days 1, 2, 8, 9, 15, 16 for 12 cycles and on Days 1, 2, 15, 16 on Cycles 13-18 LEN 25mg on Days 1-21 DEX 40mg on Days 1, 8, 15, 22 *Beyond Cycle 18, pt received only LEN+DEX*	Adults w/ relapsed MM s/p 1-3 prior tx Prior BOR w/o dz progression Prior LEN+DEX w/o AEs or dz progression	Age, median yr (range) 1) 64.0 (38.0-87.0) 2) 65.0 (31.0-91.0) Grade 2 ECOG performance status, n (%) 1) 40 (10.1) 2) 35 (8.8) High cytogenetic risk, n (%) 1) 48 (12.1) 2) 52 (13.1) CrCl mean mL/min (SD) 1) 85.0 (28.9) 2) 85.9 (30.2) Number previous regimens, median (range) 1) 2.0 (1-3) 2) 2.0 (1-3)	<u>Primary endpoint</u> PFS, median months (95% CI) 1) 26.3 (23.3-30.5) 2) 17.6 (15.0-20.6) HR for progression or death 0.69 (0.57-0.83); p=0.0001 <u>Secondary endpoints</u> Interim OS, 24-month % (95% CI) 1) 73.3 (68.6-77.5) 2) 65.0 (59.9-69.5) HR for death 0.79 (0.63-0.99); p=0.04 Overall response % (95% CI) 1) 87.1 (83.4-90.3) 2) 66.7 (61.8-71.3) p<0.001 HrQoL, (using QLQ-C30) Improvement in treatment arm p<0.001	Discont'n % d/t AEs 1) 15.3 2) 17.7 CFZ arm AEs ≥ 5% of comparator arm (%): Hypokalemia (27.6 vs. 13.4) Cough (28.8 vs. 17.2) URI (28.6 vs. 19.3) Diarrhea (42.3 vs. 33.7) Pyrexia (28.6 vs. 19.3) HTN (14.3 vs. 6.9) Thrombocytopenia nasopharyngitis Grade ≥3 AEs 1) 83.7% 2) 80.7% Grade ≥3 Hypokalemia, n (%) 1) 37 (9.4) 2) 19 (4.9)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Avet-Louiseau H Blood 2015[88]** **(ASPIRE)**	ASPIRE	*See ASPIRE* Subgroup analysis of cytogenetic risk High-risk cytogenetics (n=100) Standard-risk cytogenetics (n=317)	*See ASPIRE*	*See ASPIRE*	High-risk cytogenetics: PFS, median months (95% CI) 1) 23.1 (12.5-24.2) 2) 13.9 (9.5-16.7) HR 0.639 (0.369-1.106) ORR, % (95% CI) 1) 79.2 (65.0-89.5) 2) 59.6 (45.1-73.0) Standard-risk cytogenetics: PFS, median months (95% CI) 1) 29.6 (24.1-not estim) 2) 19.5 (14.8-26.0) HR 0.657 (0.480-0.901) ORR, % (95% CI) 1) 91.2 (85.4-95.2) 2) 73.5 (66.2-80.0)	High-risk cytogenetics: Grade ≥3 AEs 1) 89.1% 2) 78.4% HTN Grade ≥3 AEs, n (%) 1) 1 (2.2) 2) 0 Standard-risk cytogenetics: Grade ≥3 AEs 1) 85.6% 2) 84.5% HTN Grade ≥3 AEs, n (%) 1) 9 (6.2) 2) 3 (1.8)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Dimopoulos MA J Clin Oncol 2015[91]** **(ASPIRE)**	ASPIRE	*See ASPIRE* Subgroup analysis of lines of prior therapy 1 prior line (n=341) ≥2 prior lines (n=451)	*See ASPIRE*	*See ASPIRE*	1 prior line: PFS, median months (95% CI) 1) 29.6 (23.3-33.5) 2) 17.6 (15.0-22.2) HR 0.694; p=0.0083 ≥2 prior lines: PFS, median months (95% CI) 1) 25.8 (22.2-31.0) 2) 16.7 (13.9-22.0) HR 0.688; p=0.0017	1 prior line: No Grade ≥3 AEs occurred ≥5% more frequently in treatment arm ≥2 prior lines: Grade ≥3 AEs occurring ≥5% more frequently in treatment arm Hypokalemia 1) 11.0% 2) 3.4% Grade ≥3 neutropenia occurring ≥5% more frequently between lines of therapy: 1 prior line (26.4%) ≥2 prior lines (32.4%)
Abstract **Dimopoulos MA Haematologica 2015[114]** **(ASPIRE)**	ASPIRE	*See ASPIRE*	*See ASPIRE*	*See ASPIRE*	ORR 1 prior line 1) 87.0% 2) 70.1% ≥2 prior lines 1) 87.3% 2) 64.4%	AES ≥ Grade 3 1 prior line 1) 85.7% 2) 79.9% ≥2 prior lines 1) 81.9% 2) 81.3%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Palumbo A 15th Int'l Myeloma Workshop 2015[115]** **(ASPIRE)**	ASPIRE	*See ASPIRE* Subgroup analysis of age 1) ≥70 years (n=103) <70 years (n=293) 2) ≥70 years (n=115) <70 years (n=281)	*See ASPIRE*	*See ASPIRE*	≥70 years: PFS, median months (95% CI) 1) 23.8 (18.3-29.6) 2) 16.0 (14.0-21.3) HR 0.739; p=0.0521 ORR, % 1) 90.3 2) 66.1 p<0.0001 <70 years: PFS, median months (95% CI) 1) 28.6 (24.1-32.3) 2) 17.6 (14.5-22.2) HR 0.668; p=0.0002 ORR, % 1) 86.0 2) 66.9 p<0.0001	≥70 years: Grade ≥3 AEs ≥5% more in treatment arm Neutropenia 1) 36.9% 2) 23.2% Thrombocytopenia 1) 20.4% 2) 15.2% Hypokalemia 1) 15.5% 2) 6.3% <70 years: Grade ≥3 AEs ≥5% more in treatment arm Hypophosphatemia 1) 9.0% 2) 2.5%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Daratumumab (Darzalex)						
Publication **Lonial** **Lancet** **2016**[20] **(SIRIUS)** ***poor***	Randomized Single-arm Multicenter Open-label Phase II Median f/u: 9.3 months; study is ongoing	Daratumumab monotherapy <u>Part 1, stage 1</u> 1) DARA 16 mg/kg (n=16) 2) DARA 8 mg/kg (n=18) <u>Part 1, stage 2</u> 1) DARA 16 mg/kg (n=41) <u>Part 2</u> 1) DARA 16 mg/kg (n=106)	Age ≥18 years 3+ prior tx or refractory to both proteasome inhibitors and immunomodulatory drugs	Age, median (range): 63.5 (31-84) Male, n (%): 52 (49) White, n (%): 84 (79) ECOG score, n (%) 0: 29 (27) 1: 69 (65) 2: 8 (8) ISS stage, n (%): I: 26 (25) II: 40 (38) III: 40 (38) Previous lines of therapies, median (range): 5 (2-14) Received autologous stem cell transplantation, n (%): 85 (80)	<u>Primary endpoint</u> ORR, n (%) 31 (29%) <u>Secondary endpoints</u> PFS, Median 3.7 months (95% CI 2.8-4.6) OS at 12 months 64.8% (95% CI 51.2-75.5) Median OS: 17.5 (95% CI 13.7-NE) Subgroup (ORR): Age, sex, ethnicity, ISS stage, No. of lines of therapy, refractory to, type of MM (IgG/non-IgG), renal function, bone marrow % plasma cells, cytogenetic risk, extramedullary plasmacytoma	Discontinuation due to AE: 5% Grade 3/4 AEs, n (%) Fatigue: 3 (3) Anemia: 25 (24) Thrombocytopenia: 20 (19) Neutropenia: 13 (12) Back pain: 3 (3)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Lokhorst N Engl J Med 2015**[76] ***poor***	Nonrandomized Multicenter Open-label Phase I/II	Part 1: dose-escalation daratumumab 0.005 - 24 mg/kg (n=32) Part 2: Dose-expansion 1) DARA 8 mg/kg (n=30) 2) DARA 16 mg/kg (n=42) m) (5 dosing schedules in part 2—3 for 8 mg and 2 for 16 mg doses)	Relapsed/ refractory myeloma requiring systemic therapy and 2+ prior tx (incl. immunomodulatory agents, proteasome inhibitors, chemotherapy, autologous stem-cell transplantation. Age ≥18 Life expectancy ≥3 m ECOGPS ≤2 measurable level of M protein or free light chains	Age, median (range): 1) 59 (38-76) 2) 64 (44-76) % Male: 1) 70% 2) 64% ECOG score=2, n (%) 1) 1(3) 2) 2(5) Prior therapies, median (range): 1) 4 (3-10) 2) 4 (2-12) Stem-cell transplantation: 76%	Primary endpoint Safety (frequencies and severities of AEs) Secondary endpoints ORR 1) 10% 2) 36% Median PFS, mos (95% CI) 1) 2.4 (1.4 to 3.5) 2) 5.6 (4.2-8.1) OS at 12 months (95% CI) 1): 77% (52-90) 2): 77% (58-88)	Grade3/4 AEs, n(%) Fatigue 1) 1 (3) 2) 0 (0) Pyrexia 1) 0(0) 2) 1 (2)

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td colspan="7">Elotuzumab (Empliciti)</td></tr>
<tr>
<td>Publication

Lonial
N Engl J Med 2015[17]

(ELOQUENT-2)

fair</td>
<td>RCT
Multicenter
Open-label
Phase 3

Median f/u: 24.5m

Median duration of treatment
1) 17
2) 12</td>
<td>1) ELO+LEN+DEX (n=321)

2) LEN+DEX (n=325)

<u>Dosing schedule:</u>
ELO 10mg/kg on Days 1, 8, 15, 22 during 1st two cycles, and on Days 1 and 15 starting with the third cycle

LEN 25mg on Days 1-21

DEX 40mg QWK w/o ELO and 8mg IV + 28mg PO on day of ELO administration</td>
<td>Age ≥18; measurable disease; 1-3 prior therapies; documented disease progression; CrCl≥30mL/min</td>
<td>Median age (range)
1) 67 (37-88)
2) 66 (38-91)

ISS Stage III, n (%)
1) 66 (21)
2) 68 (21)

n (%)
1 prev. regimen
1) 151 (47)
2) 159 (49)

2 prev. regimens
1) 118 (37)
2) 114 (35)

≥3 prev. regimens
1) 52 (16)
2) 52 (16)

Previous tx, n (%)
<table>
<tr><th></th><th>1)</th><th>2)</th></tr>
<tr><td>BOR</td><td>219 (86)</td><td>231 (71)</td></tr>
<tr><td>LEN</td><td>16 (5)</td><td>21 (6)</td></tr>
</table>
</td>
<td>1-yr PFS:
1) 68%
2) 57%

2-yr PFS:
1) 41%
2) 27%

Median PFS:
1) 19.4m
2) 14.9m
HR=0.70 (0.57-0.85); p<0.001

Overall response rate:
1) 79%
2) 66%
p<0.001

Interim Mortality, n (%)
1) 210 (30)
2) 116 (37)

Change from baseline in pain and HrQoL NS between groups (Brief Pain Inventory-Short Form, EORTC QLQ-C30, EORTC QLQ-MY20)</td>
<td>Discontinuation due to AEs (drug toxicity + AEs unrelated to study drug), n (%)
1) 43 (13.4)
2) 68 (20.9)

Grade 3/4 events, n (%)

Lymphocytopenia
1) 244 (77)
2) 154 (49)

Neutropenia
1) 107 (34)
2) 138 (44)

Serious adverse events:
1) 65%
2) 57%</td>
</tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract and Presentation **Dimopoulos Blood 2015[116]** **(ELOQUENT-2)**	ELOQUENT-2	*See ELOQUENT-2*	*See ELOQUENT-2*	*See ELOQUENT-2*	3-year PFS 1) 26% 2) 18% HR=0.73 (0.60-0.89) Time to next Treatment, mos (95% CI) 1) 33 (26.15, 40.21) 2) 21 (18.07, 23.20) Interim Median OS, mos (95% CI) 1) 43.7 (40.3, NE) 2) 39.6 (33.3, NE) HR=0.77 (0.61, 0.97) p=0.0257	Patients who experienced Grade 3/4 AEs, n (%) 1) 248 (78) 2) 212 (67)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Richardson Lancet Haematol 2015**[79] **(1703 study)** ***fair***	RCT Multicenter Open-label Dose-escalation Phase Ib-II Median duration of f/u, mos (range) 1) 21.2 (3.9-45.8) 2) 16.8 (2.1-47.2) Median no. treatment cycles (range) 1) 21.5 (4-49) 2) 16.0 (1-51)	1) ELO 10 mg/kg + LEN+DEX (n=36) 2) ELO 20 mg/kg + LEN+DEX (n=37) <u>Dosing schedule</u>: ELO on Days 1, 8, 15, 22 for cycles 1-2 and on Days 1 and 15 for subsequent cycles LEN 25mg on Days 1–21 DEX 40mg QWK	Age ≥18; confirmed MM diagnosis; ECOG PS 0–2; 1-3 prior therapies; evidence of disease progression since, or refractory to, most previous treatment; measurable disease measurable (M-protein component in serum or urine)	Male, n (%) 1) 19 (53) 2) 24 (65) Mean age (range) 1) 60.6 (39-77) 2) 63.3 (41-82) ISS Stage III, n (%) 1) 11 (31) 2) 16 (43) High risk, n (%) 1) 1 (3) 2) 3 (8) Lines of prev. therapy, n (%) Prev. BOR, n (%) 1) 22 (61) 2) 22 (59)	Overall response, n (%) 1) 33 (92) 2) 28 (76) Median PFS 1) 32.49 (95% CI: 14.88-NA) 2) 25.00 (95% CI: 14.00-35.71) Median duration of response 1) 34.8 (IQR 12.7-NE) 2) 29 (15.1-NE)	Grades 3/4 treatment-emergent AEs, n (%) 1) 32 (89) 2) 25 (68) Total Grade 3/4 treatment-emergent AEs Anemia: 11 (15) Lymphopenia: 15 (21) Thrombocytopenia: 13 (18) Neutropenia: 14 (19) Leucopenia: 7 (10) Diarrhea: 7 (10) Peripheral neuropathy: 0 Upper respiratory tract infections: 2 (3)

	1)	2)
1	16 (44)	17 (50)
2	16 (44)	16 (43)
3	4 (11)	4 (11)

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Abstract

Jagannath Blood 2011[117]

(1703 study)</td>
<td>1703 study</td>
<td>See 1703 study</td>
<td>See 1703 study</td>
<td>(Treatment arms pooled)

n (%)
High risk cytogenetics: 10 (14)

Bortezomib refractory: 17 (23)

Thalidomide refractory: 14 (19)

Refractory to last line of therapy: 24 (33)</td>
<td>Overall response
<table>
<tr><th></th><th>n (%)</th></tr>
<tr><td>High cytogenetic risk</td><td>8 (80)</td></tr>
<tr><td>Standard cytogenetic risk</td><td>52 (83)</td></tr>
<tr><td>BOR refractory</td><td>12 (71)</td></tr>
<tr><td>Not BOR refractory</td><td>48 (86)</td></tr>
<tr><td>THAL refractory</td><td>11 (79)</td></tr>
<tr><td>Not THAL refractory</td><td>49 (84)</td></tr>
<tr><td>Refractory to last therapy</td><td>17 (71)</td></tr>
<tr><td>Not refractory to last therapy</td><td>43 (90)</td></tr>
</table>
</td>
<td>See 1703 study</td>
</tr>
</table>

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td>Abstract

Richardson Blood 2012[118]

(1703 study)</td><td>1703 study</td><td>See 1703 study</td><td>See 1703 study</td><td>See 1703 study</td><td>(Treatment arms pooled)

<table><tr><td></td><td>ORR</td><td>PFS</td></tr><tr><td>1 prior therapy</td><td>91%</td><td>25 mos</td></tr><tr><td>≥2 prior therapies</td><td>78%</td><td>21.3 mos</td></tr></table></td><td>See 1703 study</td></tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Richardson Blood 2014[119]** **(1703 study)**	1703 study	*See 1703 study*	*See 1703 study*	*See 1703 study*	*(Treatment arms pooled)* Median PFS not reached for patients with sCR Median PFS for patients with VGPR (n=31): 36 mos Median PFS for patients with PR (n=20): 31 mos	Patients who experienced a serious AE: 58%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Ixazomib (Ninlaro)						
Publication **Moreau N Engl J Med 2016[21]** **(TOURMALINE-MM1)** ***good***	RCT Multicenter Double-blind Phase III *all oral triplet therapy Median f/u at first analysis: 14.8 months for treatment group, 14.6 months for control group; Survival analysis ongoing	1) IX+LEN+DEX (n=360) 2) Placebo +LEN+DEX (n=362) <u>Dosing schedule</u>: Ixazomib 4mg PO or placebo on Days 1, 8, 15 LEN 25mg on Days 1-21 DEX 40mg on Days 1, 8, 15, 22 28-day cycle repeated until disease progression or toxicity	Relapsed and/or refractory MM Measurable disease s/p 1-3 prior lines Not refractory to prior LEN or PI 18yr+ ECOG PS 0-2 Adequate hematologic and hepatic function	Median age, years (range) 1) 66 (38-91) 2) 66 (30-89) % Male 1) 58 2) 56 White n (%) 1) 310 (86) 2) 301 (83) ECOG Grade 2, n (%) 1) 18 (5) 2) 24 (7) ISS Stage III, n (%) 1) 45 (12) 2) 42 (12) High-risk, n (%) 1) 75 (21) 2) 62 (17)	<u>Primary endpoint</u> PFS events n (%) 1) 129 (36) 2) 157 (43) Median months 1) 20.6 (17.0-unk.) 2) 14.7 (12.9-17.6) HR=0.74 (0.59-0.94); p=0.01 <u>Secondary endpoint</u> Overall response rate n (%) 1) 282 (78.3) 2) 259 (71.5) p=0.04 Complete response n (%) 1) 42 (12) 2) 24 (7) p=0.02 Partial response n (%) 1) 240 (67) 2) 235 (65) Median DOR months 1) 20.5 2) 15.0	Discontinuation d/t AEs 1) 17% 2) 14% Grade 3/4 AEs (%) Neutropenia 1) 22% 2) 23.7% Thrombocytopenia 1) 19.1% 2) 13.4% Anemia 1) 9% 2) 13% Diarrhea 1) 6% 2) 3% Thromboembolism 1) 3.0% 2) 3.3%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Moreau P ASH 2015[90]** **(TOURMALINE-MM1)**	TOURMALINE-MM1	*See TOURMALINE-MM1*	*See TOURMALINE-MM1*	*See TOURMALINE-MM1*	High-risk cytogenetics [del(17p)]: PFS 1) HR 0.543 Overall response rate, % 1) 78.3 2) 71.5 OR 1.44; p=0.035 OS data not mature Deaths on treatment 1) 3% 2) 5%	Grade ≥3 AEs rate 1) 68% 2) 61% Discontinuation d/t AEs: 1) 13% 2) 11% Grade ≥3 thrombocytopenia 1) 13% 2) 5%

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td colspan="7">Panobinostat (Farydak)</td></tr>
<tr>
<td>Publication

San-Miguel Lancet Oncol 2014[18]

(PANORAMA-1)

good</td>
<td>RCT
Multicenter
Double-blind
Phase 3
Crossover not permitted

Median f/u:
1) 6.4 m
2) 5.9 m</td>
<td>1) PAN+BOR+DEX (n=387)

2) Placebo + BOR + DEX (n=381)

<u>Dosing schedule</u>:
<u>Ph1</u>: 8 3-wk cycles (max 12 cycles)

PAN 20mg 3x/wk for 2 wks

BOR 1.3mg/m^2 on Days 1, 4, 8, 11

DEX 20mg on days of/after BOR

<u>Ph2</u>: Proceed if clinical benefit
4 6-wk cycles

PAN/placebo same schedule

BOR 1x/wk on Wk 1, 2, 4, 5

DEX on days of/after BOR</td>
<td>Age ≥18 years

1-3 prior tx regimens

ECOG status ≤2

Exclude primary refractory, BOR-refractory, previous tx w/ deacetylase inhibitor</td>
<td>Age (years)
1) 63 (56-69)
2) 63 (56-68)

Male n (%)
1) 202 (52)
2) 205 (54)

ECOG, status 2, n (%)
1) 19 (5)
2) 29 (8)

ISS, Stage III, n (%)
1) 77 (20)
2) 86 (23)

Previous line tx, n (%)
<table>
<tr><th></th><th>1</th><th>2</th><th>3</th></tr>
<tr><td>1)</td><td>197 (51)</td><td>124 (32)</td><td>64 (17)</td></tr>
<tr><td>2)</td><td>198 (52)</td><td>108 (28)</td><td>75 (20)</td></tr>
</table>
Prior BOR+DEX, n (%)
1) 147 (38)
2) 143 (38)</td>
<td><u>Primary endpoint:</u>
PFS, months (95% CI)
1) 11.99 (10.33-12.94)
2) 8.08 (7.56-9.23)
HR$_{adj}$ 0.58 (0.48-0.71);
p<0.001

<u>Secondary endpoints:</u>
OS, months (95% CI), not mature
1) 33.64 (31.34-not estim)
2) 30.39 (26.87-not estim)
HR 0.87 (0.69-1.10); p=0.26

Overall response rate, % (95% CI):
1) 60.7 (55.7-65.6)
2) 54.6 (49.4-59.7)
3) P=0.09

Similar subgroup PFS outcomes: Relapsed and refractory, Stage II-III MM, age ≥65 years, previous BOR users</td>
<td>Discontinuation d/t AEs, n (%)
1) 138 (36)
2) 77 (20)

Grade 3 AEs, %
<table>
<tr><th></th><th>1)</th><th>2)</th></tr>
<tr><td>Diarrhea</td><td>24</td><td>7</td></tr>
<tr><td>Asthenia, fatigue</td><td>23</td><td>12</td></tr>
<tr><td>Nausea</td><td>5</td><td><1</td></tr>
<tr><td>Vomiting</td><td>7</td><td>1</td></tr>
</table>
Plt ct abnormality, %
<table>
<tr><th></th><th>Grade3</th><th>Grade4</th></tr>
<tr><td>1)</td><td>33</td><td>35</td></tr>
<tr><td>2)</td><td>19</td><td>12</td></tr>
</table>
Absolute lymphocyte ct abnormality, %
<table>
<tr><th></th><th>Grade3</th><th>Grade4</th></tr>
<tr><td>1)</td><td>42</td><td>12</td></tr>
<tr><td>2)</td><td>33</td><td>7</td></tr>
</table>
ANC abnormality, n (%)
<table>
<tr><th></th><th>Grade3</th><th>Grade4</th></tr>
<tr><td>1)</td><td>28</td><td>7</td></tr>
<tr><td>2)</td><td>9</td><td>2</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Publication

Richardson PG Blood 2016[80]

(PANORAMA-1)

good</td>
<td>PANORAMA-1</td>
<td>See PANORAMA-1
Subgroup analysis based on prior treatment</td>
<td>See PANORAMA-1</td>
<td>See PANORAMA-1</td>
<td colspan="2">Median PFS, months (95% CI)
<table>
<tr><th></th><th>1)</th><th>2)</th><th>HR</th></tr>
<tr><td>Prior IMiD</td><td>12.3 (10.3-13.8)</td><td>7.4 (6.0-7.9)</td><td>0.54 (0.43-0.68)</td></tr>
<tr><td>Prior BOR & IMiD</td><td>10.6 (7.6-13.8)</td><td>5.8 (4.4-7.1)</td><td>0.52 (0.36-0.76)</td></tr>
<tr><td>≥2 prior lines</td><td>12.5 (7.3-14.0)</td><td>4.7 (3.7-6.1)</td><td>0.47 (0.31-0.72)</td></tr>
</table>
ORR, % (95% CI)
<table>
<tr><th></th><th>1)</th><th>2)</th><th>p-value</th></tr>
<tr><td>Prior IMiD</td><td>62 (55.6-68.1)</td><td>50 (43.5-56.5)</td><td>0.00954</td></tr>
<tr><td>Prior BOR & IMiD</td><td>58.5 (47.9-68.6)</td><td>41.4 (31.6-51.8)</td><td>0.01893</td></tr>
<tr><td>≥2 prior lines</td><td>58.9 (46.8-70.3)</td><td>39.2 (28.0-51.2)</td><td>0.01703</td></tr>
</table>
*Harms not presented here</td>
<td></td>
</tr>
<tr>
<td>Abstract

Richardson PG Clin Lymphoma Myeloma Leuk 2015[120]

(PANORAMA-1)</td>
<td>PANORAMA-1</td>
<td>See PANORAMA-1
Subanalysis of pts who received ≥2 prior lines tx, incl. BOR and an IMiD (n=147)</td>
<td>See PANORAMA-1</td>
<td>See PANORAMA-1</td>
<td>Median PFS, months (95% CI)
1) 12.5
2) 4.7
HR 0.47 (0.31-0.72)

ORR, % (95% CI)
1) 58.9 (46.8-70.3)
2) 39.2 (28.0-51.2)</td>
<td>Grade 3/4 AEs, %
<table>
<tr><th></th><th>1)</th><th>2)</th></tr>
<tr><td>Thrombo-cytopenia</td><td>68.1</td><td>44.4</td></tr>
<tr><td>Neutro-penia</td><td>40.3</td><td>16.4</td></tr>
<tr><td>Diarrhea</td><td>33.3</td><td>15.1</td></tr>
<tr><td>Asthenia/ fatigue</td><td>26.4</td><td>13.7</td></tr>
</table></td>
</tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Richardson PG Blood 2014[121]** **(PANORAMA-1)**	PANORAMA-1	*See PANORAMA-1* Subanalysis of patients who experienced diarrhea as AE	See *PANORAMA-1*	See *PANORAMA-1*	See *PANORAMA-1*	Discontinuation d/t diarrhea 1) 4.5% 2) 1.6% Diarrhea AE reported 1) 260/381 (68.2%) 2) 157/377 (41.6%) Serious AEs of diarrhea 1) 11.3% 2) 2.4% Grade 4 diarrhea AE 1) 1.3% 2) 0.5%
Abstract **San-Miguel JF Blood 2015[24]** **(PANORAMA-1)**	PANORAMA-1	*See PANORAMA-1* Final analysis of secondary endpoint	*See PANORAMA-1*	See *PANORAMA-1*	Secondary endpoint, median OS, months (95% CI), mature results: 1) 40.3 (35.0-44.8) 2) 35.8 (29.0-40.6) HR 0.94 (0.78-1.14); p=0.5435 Subanalysis, OS of pt who received ≥2 prior lines incl. BOR and IMiD: 1) 25.5 (19.6-34.3) 2) 19.5 (14.1-32.5)	NR

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Einsele H Haematologica 2015[122]** **(PANORAMA-1)**	PANORAMA-1	*See PANORAMA-1* Subanalysis by prior treatment	*See PANORAMA-1*	*See PANORAMA-1*	ORR by prior therapy IMiD tx, % (95% CI) 1) 62 (55.6-68.1) 2) 50 (43.3-56.5)	*See PANORAMA-1*

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **San-Miguel JF J Clin Oncol 2015[92]** **(PANORAMA-1)**	PANORAMA-1	*See PANORAMA-1* Subanalysis of 193 (25%) patients who received prior BOR and IMiDs 1) n=94 2) n=99	*See PANORAMA-1*	*See PANORAMA-1*	Median PFS, months (95% CI) 1) 10.6 (7.6-13.8) 2) 5.8 (4.4-7.1) HR 0.56 (0.39-0.80); p=0.0011 Median PFS of those who received ≥2 prior lines: 1) 12.5 (7.3-14.0) 2) 4.7 (3.7-6.1) HR 0.47 (0.32-0.72); p=0.0003 ORR % (95% CI) 1) 58.5 (47.9-68.6) 2) 41.4 (31.6-51.8) p=0.0179	*See PANORAMA-1*

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td colspan="7">Pomalidomide (Pomalyst)</td></tr>
<tr>
<td>Publication

San Miguel J Lancet Oncol 2013[22]

(MM-003)

fair</td>
<td>RCT
Multicenter
Open-label
Phase III

Median f/u for final OS: 10 months

Median f/u for final PFS and interim OS: 4.2 months (IQR 2.0-.1)

45 patients in the high-dose DEX group crossed over and received POM</td>
<td>1) POM + low-dose DEX (n=302)

2) High-dose DEX (n=153)

<u>Dosing schedule</u>:
POM 4mg on Days 1-21 of each 28-day cycle

Low-dose DEX 40mg QWK

High-dose DEX 40mg on Days 1-4, 9-12, 17-20 of 28-day cycle

Tx until progressive disease or toxicity</td>
<td>Age >18; relapsed/refractory MM; refractory to previous treatment; ≥2 previous consecutive cycles of BOR and LEN (alone or in combination); adequate alkylator treatment; failed treatment with BOR or LEN</td>
<td>Med age, (range)
1) 64 (35-84)
2) 65 (35-87)

Male, n (%)
1) 181 (60)
2) 87 (57)

ECOG PS 2, n (%)
1) 52 (17)
2) 25 (16)

ISS III
1) 93 (31)
2) 54 (35)

Prior therapies (med)
1) 5 (2-14)
2) 5 (2-17)

Refractory, n (%)
<table>
<tr><th></th><th>1)</th><th>2)</th></tr>
<tr><td>BOR</td><td>238 (79)</td><td>121 (79)</td></tr>
<tr><td>LEN</td><td>286 (95)</td><td>141 (92)</td></tr>
<tr><td>Both</td><td>225 (75)</td><td>113 (74)</td></tr>
</table>
</td>
<td><u>Primary endpoint</u>: PFS median months (95% CI)
1) 4.0 (3.6-4.7)
2) 1.9 (1.9-2.2)
HR 0.48
(95% CI: 0.39-0.60) p<0.0001

<u>Secondary endpoint</u>: OS median months (95% CI)
1) 12.4 (10.4-15.3)
2) 8.0 (6.9-9.0)
HR 0.70
(95% CI: 0.54-0.92)
p=0.009

Overall response n (%)
1) 95 (31)
2) 15 (10)</td>
<td>Grade 3/4 AEs n (%)
1) 259 (86.3)
2) 127 (84.7)

Grade 3 AEs
Infections & infestations
1) 72 (24)
2) 28 (19)

Neutropenia, n (%)
1) 77 (26)
2) 13 (9)

Leukopenia, n (%)
1) 20 (7)
2) 2 (1)

Discontinuation due to AEs, n (%)
1) 26 (8.6)
2) 16 (10.5)</td>
</tr>
</table>

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Publication

Dimopoulos M Haematologica 2015[83]

(MM-003)

fair</td>
<td>Updated median f/u: 15.4 m

Crossover permitted (56%)
46% of high risk
64% of standard risk</td>
<td>See MM-003</td>
<td>See MM-003</td>
<td>High risk cytogenetics:
del(17p) n (%)
1) 44 (15)
2) 23 (15)

t(4;14)
1) 44 (15)
2) 15 (10)

ECOG, PS 2-3, n (%)
1) 52 (17)
2) 28 (18)

ISS, Stage III, n (%)
1) 92 (30)
2) 53 (35)

CrCl<60mL/min
1) 95 (31)
2) 59 (39)</td>
<td><u>PFS</u>
Updated overall PFS
1) 4.0m
2) 1.9m
HR 0.50; p<0.001

<table>
<tr><th></th><th>1) m</th><th>2) m</th><th>HR</th></tr>
<tr><td>del(17p)</td><td>4.6</td><td>1.1</td><td>0.34 p<0.001</td></tr>
<tr><td>t(4;14)</td><td>2.8</td><td>1.9</td><td>0.49 p=0.028</td></tr>
<tr><td>Standard risk</td><td>4.2</td><td>2.3</td><td>0.55 p<0.001</td></tr>
</table>

<u>Median OS</u>
Updated overall OS
1) 13.1m
2) 8.1m
HR 0.72; p=0.009

del(17p)
HR 0.45; p<0.008

t(4;14)
HR 1.12; p=0.761

Standard risk cytogenetics
HR 0.85; p=0.380</td>
<td>Grade 3/4 AEs in patients treated with POM + LoDEX ≥1 year, n (%)

Neutropenia: 28 (52)
Anemia: 5 (9)

Thrombocytopenia: 5 (9)

Leukopenia: 5 (9)

Infections: 23 (43)

Pneumonia: 11 (20)

Bone pain: 4 (7)

Fatigue: 4 (7)

Asthenia: 1 (2)

Glucose intolerance: 2 (4)

Discontinuation due to AE: 2 (4)</td>
</tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **San Miguel JF Haematologica 2015[82]** **(MM-003)** ***fair***	*See MM-003*	*See MM-003*	*See MM-003*	*See MM-003*	ORR refractory in POM + LoDEX LEN: 30% BOR: 31% LEN & BOR: 29% <u>Progression-free survival</u> HR (95% CI) ≤3 prior tx: 0.63 (0.4-1.0) >3 prior tx: 0.45 (0.35-0.57) LEN ref: 0.51 (0.41-0.64) BOR ref: 0.50 (0.40-0.64) LEN & BOR ref: 0.53 (0.42-0.68) <u>Overall survival</u> HR (95% CI) ≤3 prior tx: 0.56 (0.33-0.96) >3 prior tx: 0.76 (0.58-1.0) LEN ref: 0.70 (0.55-0.90) BOR ref: 0.77 (0.58-1.01) LEN & BOR ref: 0.77 (0.58-1.02)	*See MM-003*

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Weisel K Clin Lymphoma Myeloma Leuk 2015[81]** **(MM-003)** ***fair***	*See MM-003*	*See MM-003*	*See MM-003*	*See MM-003*	In 7/8 domains, greater percentage of POM + LoDEX had improved HrQoL vs. HiDEX (EORTC QLQ-C30) Statistically significant OR with POM + LoDEX vs. HiDEX for physical functioning, emotional functioning, fatigue (EORTC QLQ-C30) Median time to first clinically meaningful first HrQoL worsening significantly prolonged for POM + LoDEX vs. HiDEX for physical functioning, emotional functioning, side effects of treatment, health utility	*See MM-003*

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td>Publication

Morgan G Br J Haematology 2015[84]

(MM-003)

fair</td><td>See MM-003

Two-stage Weibull method used to adjust estimates of treatment effect on overall survival due to crossover</td><td>See MM-003</td><td>See MM-003</td><td>See MM-003</td><td>Overall survival after crossover adjustment
Median months
1) 12.7
2) 5.7
HR=0.52
95% CI: 0.39 – 0.68)

Lifetime extrapolation Mean overall survival (months)
1) 28.0
2) 13.4</td><td>See MM-003</td></tr>
<tr><td>Abstract

San Miguel JF Blood 2013[86]

(MM-003)</td><td>See MM-003</td><td>See MM-003</td><td>See MM-003</td><td>See MM-003</td><td colspan="2">POM + LoDEX vs. HiDEX
<table>
<tr><th></th><th>PFS, mos (p-value)</th><th>OS, mos (p-value)</th><th>ORR, % (p-value)</th></tr>
<tr><td>≤3 prior Tx</td><td>3.7 vs. 1.9 (0.02)</td><td>11.1 vs. 6.9 (0.02)</td><td>26 vs. 3 (0.005)</td></tr>
<tr><td>>3 prior Tx</td><td>4.4 vs. 2.0 (<0.001)</td><td>13.1 vs. 8.7 (0.19)</td><td>33 vs. 12 (<0.001)</td></tr>
<tr><td>LEN refractory</td><td>3.9 vs. 1.9 (<0.001)</td><td>12.7 vs. 8.0 (0.02)</td><td>30 vs. 9 (<0.001)</td></tr>
<tr><td>BOR refractory</td><td>3.9 vs. 2.0 (<0.001)</td><td>11.9 vs. 7.7 (0.07)</td><td>30 vs. 12 (<0.001)</td></tr>
<tr><td>LEN & BOR refractory</td><td>3.7 vs. 2.0 (<0.001)</td><td>11.1 vs. 7.7 (0.10)</td><td>28 vs. 12 (<0.001)</td></tr>
</table></td></tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Weisel K Haematologica 2013[123]** **(MM-003)**	*See MM-003* Subanalysis of patients with or without moderate renal impairment (RI) (creatinine clearance <60 vs. ≥60 mL/min)	*See MM-003*	*See MM-003*	Moderate renal impairment, n (%) 1) 94 (31) 2) 59 (39) 64% with RI >65	<u>Normal renal function</u> Median PFS, mos 1) 3.7 2) 1.8 HR=0.47 p<0.001 Median OS, mos 1) Not reached 2) 9.2 HR=0.57 P=0.021 <u>Moderate RI</u> Median PFS, mos 1) 3.2 2) 1.6 HR=0.44 p<0.001 Median OS, mos 1) 10.3 2) 4.6 HR=0.51 p=0.008	(Normal renal function, moderate RI) Discontinuation due to AEs 1) 5%, 11% 2) 7%, 5% Neutropenia 1) 41%, 44% 2) 15%, 15% Anemia 1) 24%, 33% 2) 26%, 34% Infection 1) 23%, 28% 2) 23%, 24%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Weisel K Haematologica 2014_1**[124] **(MM-003)**	*See MM-003* Subanalysis of elderly patients (>65 and >70 years)	*See MM-003* Median duration of POM Tx 4.4 mos and 4.0 mos in patients ≤65 yrs and >65 yrs respectively Relative POM dose intensity 90% for both age groups	*See MM-003*	Pts. ≤65 vs. >65 Prior stem cell transplant 91% vs. 45% CrCl ≥60 mL/min 78% vs. 51% ISS stage 3 28% vs. 37%	ORR in pts. ≤65 1) 32% 2) 11% ORR in pts. >65 1) 33% 2) 11% ORR in pts. ≤70 1) 31% 2) 13% ORR in pts. >65 1) 35% 2) 7% p<0.001 for all comparisons	(≤65, >65) Discontinuation due to AEs 1) 6%, 13% 2) 10%, 11% Neutropenia 1) 51%, 45% 2) 22%, 13% Anemia 1) 35%, 30% 2) 41%, 37% Infections 1) 34%, 31% 2) 20%, 30%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Weisel K Haematologica 2014_2[125]** **(MM-003)**	*See MM-003* Analysis of impact of ECOG Performance Status on overall survival and HrQoL 2 Cox proportional hazards models: <u>Model 1:</u> Controlled for treatment and ECOG PS improvement (y/n) <u>Model 2:</u> Controlled for treatment, ECOG PS improvement, progressive disease, and subsequent POM Tx	After unblinding 56% of HiDEX patients subsequently received POM	*See MM-003*	*See MM-003*	Impact of ECOG PS improvement on OS Model 1 (95% CI) HR=0.62 (0.44-0.86) P=0.04 Model 2 (95% CI) HR=0.61 (0.44-0.85) P=0.004 Impact of progressive disease on OS HR=4.97 (2.99-8.25) p<0.001 Impact of crossover on OS HR=0.12 (0.05-0.30) p<0.001 Association between better ECOG PS and better function/reduced symptom burden	*See MM-003*

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Publication

Leleu X
Blood
2013[77]

(IFM 2009-02)

fair</td>
<td>RCT
Multicenter
Open-label
Phase II
ITT

Median f/u 22.8 months</td>
<td>1) POM + DEX for 21/28 days (n=43)

2) POM + DEX for 28/28 days (n=41)

<u>Dosing schedule</u>:
POM 4mg po on Days 1-21 of 28-day cycle
-or-
Days 1-28 of 28-day cycle

DEX 40mg po qwk</td>
<td>Relapsed MM

S/p 1+ prior tx</td>
<td>Median age, years (range)
1) 60 (45-81)
2) 60 (42-83)

ISS, Stage 3 %
1) 24
2) 17

Median prior lines, n (range)
1) 5 (1-13)
2) 5 (2-10)</td>
<td><u>Primary endpoint</u>:
ORR, n (%)
1) 15 (35)
2) 14 (34)

PFS, median mos (95% CI)
1) 5.4 (3-9)
2) 3.7 (2-7)
HR 1.28 (0.8-2.0); p=0.29

Deaths, n (%)
1) 25 (58)
2) 28 (68)

Median OS (95% CI)
1) 14.9 (9-NE)
2) 14.8 (9-20)
HR 1.23 (0.7-2.0); p=0.45

<table>
<tr><td colspan="2">PFS, median months (95% CI)</td></tr>
<tr><td>>6 lines prior</td><td>3.2 (2-5)</td></tr>
<tr><td>High-risk cytogenetics</td><td>2.6 (2-4)</td></tr>
</table>

<table>
<tr><td colspan="2">OS, median months (95% CI)</td></tr>
<tr><td>>6 lines prior</td><td>9.2 (3-NE)</td></tr>
<tr><td>High-risk cytogenetic</td><td>5.4 (3-9)</td></tr>
</table>
</td>
<td>Grade ≥3 AEs, n (%)
1) 40 (93)
2) 35 (85)

Discontinuation d/t AEs, n
1) 0
2) 2

Grade ≥3 AEs with ≥5% difference between arms, n (%)
<table>
<tr><td></td><td>1)</td><td>2)</td></tr>
<tr><td>Neutro-penia</td><td>28 (65)</td><td>24 (58.5)</td></tr>
<tr><td>Asthenia</td><td>6 (14)</td><td>2 (5)</td></tr>
<tr><td>Infection</td><td>8 (19)</td><td>11 (27)</td></tr>
<tr><td>PNA</td><td>3 (7)</td><td>8 (19.5)</td></tr>
<tr><td>Bone pain</td><td>6 (14)</td><td>3 (7)</td></tr>
<tr><td>Renal failure</td><td>7 (16)</td><td>2 (5)</td></tr>
<tr><td>Resp. d/o</td><td>8 (19)</td><td>2 (5)</td></tr>
<tr><td>Dyspnea</td><td>5 (12)</td><td>0</td></tr>
</table>
</td>
</tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Sehgal K Blood 2015**[78] ***fair***	RCT Phase II	1) POM 2 mg-28/28 + DEX 40 mg (n=19) 2) POM 4 mg-21/28 + 40 DEX mg (n=20) POM on continuous (2 mg/day for 28/28 days) or intermittent dosing (4 mg/day for 21/28 days); POM alone for cycle 1 and DEX 40 mg QWK at cycle 2 and beyond (patients >70 yrs received 20 mg DEX)	Age ≥18; relapsed MM following ≥2 prior standard lines of therapy including LEN; refractory to prior LEN therapy; measurable disease; ECOG PS 0-2;	Median age 1) 63 2) 61 Male, n (%) 1) 10 (52) 2) 12 (60) Prior therapy (median) 1) 4 2) 4 LEN & BOR refractory, n (%) 1) 15 (79) 2) 16 (80)	Objective Response (≥PR) 1) 4 (21) 2) 9 (45) p=0.17 Deaths 1) 10 2) 11 Event-free survival, mos 1) 4.3 2) 5.3 p=0.59 Overall survival, mos 1) 21.7 2) 17.8 p=0.78 ORR in LEN/BOR dble refractory: 32% Absence of deletion 17p associated with survival (HR=0.291; p=0.0367)	n (%) Any Grade 3/4 AE 1) 13 (68) 2) 18 (90) p=0.12 Thrombocytopenia 1) 4 (21) 2) 1 (5) Febrile neutropenia 1) 3 (16) 2) 1 (5) Fatigue 1) 3 (16) 2) 2 (10) Respiratory disorders 1) 1 (5) 2) 3 (15) Dyspnea 1) 1 (5) 2) 2 (10)

Appendix C. Additional Results from Evidence Review

Overall Survival Subgroup Results

Table C1. OS subgroup results: number of lines of prior therapy

	PANORAMA-1					
	PAN+BOR+DEX	BOR+DEX			PAN+BOR+DEX	BOR+DEX
	All patients[24]	All patients[24]			Patients with 2 or more prior lines, including BOR & IMiD[24]	Patients with 2 or more prior lines, including BOR & IMiD[24]
Median months	40.3	35.8			25.5	19.5
(95% CI)	(35.0-44.8)	(29.0-40.6)			(19.6-34.3)	(14.1-32.5)
HR	0.94				NR	
(95% CI)	(0.78-1.14); p=0.54				NR	
	MM-003					
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
	All patients[22]	All patients[22]	Patients with 3 or fewer lines[82,86]	Patients with 3 or fewer lines[86 82]	Patients with more than 3 lines[82,86]	Patients with more than 3 lines[86 82]
Median months	12.7	8.1	11.1	6.9	13.1	8.7
(95% CI)	(10.4-15.5)	(6.9-10.8)	(NR); p=0.02		p=0.19	
HR	0.74		0.56		0.76	
(95% CI)	(0.56-0.97); p=0.03		(0.33-0.96)		(0.58-1.00)	

Table C2. OS subgroup results: refractory to prior IMiD/proteasome therapy

	MM-003[22]			
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
	All patients	All patients	Patients refractory to BOR & LEN	Patients refractory to BOR & LEN
Median months	12.7	8.1	11.1	7.7
(95% CI)	(10.4-15.5)	(6.9-10.8)	(9.2-15.5)	(5.4-10.1)
HR	0.74		NR	
(95% CI)	(0.56-0.97); p=0.03		p=0.10	

Progression-Free Survival Subgroup Results

Table C3. PFS subgroup results: cytogenetic risk

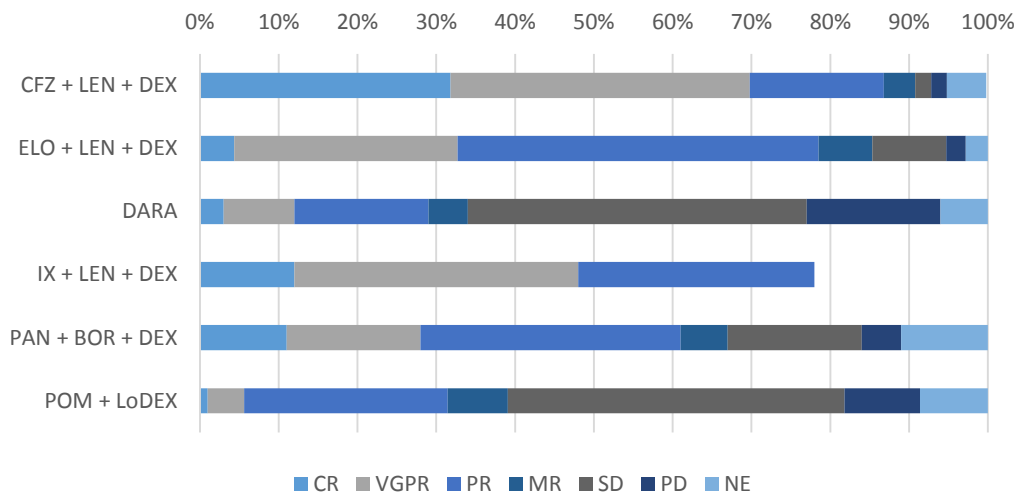
	ASPIRE					
	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX
	All patients[16]	All patients[16]	Patients with high-risk cytogenetics[88]	Patients with high-risk cytogenetics[88]	Patients with standard-risk cytogenetics[88]	Patients with standard-risk cytogenetics[88]
Median months	26.3	17.6	23.1	13.9	29.6	19.5
(95% CI)	(23.3-30.5)	(15.0-20.6)	(12.5-24.2)	(9.5-16.7)	(24.1-not estim.)	(14.8-26.0)
HR	0.69		0.64		0.66	
(95% CI)	(0.57-0.83); p=0.0001		(0.37-1.11)		(0.48-0.90)	
	ELOQUENT-2					
	ELO+LEN+DEX	LEN+DEX	ELO+LEN+DEX	LEN+DEX	ELO+LEN+DEX	LEN+DEX
	All patients[17]	All patients[17]	Patients with high-risk cytogenetics[89]	Patients with high-risk cytogenetics[89]	Patients with standard-risk cytogenetics[89]	Patients with standard-risk cytogenetics[89]
Median months	19.4	14.9	NR	NR	NR	NR
(95% CI)	(16.6-22.2)	(12.1-17.2)	NR	NR	NR	NR
HR	0.70		0.64		0.77	
(95% CI)	(0.57-0.85); p<0.001		(0.41-0.99)		(0.60-0.97)	
	TOURMALINE-MM1					
	IX+LEN+DEX	LEN+DEX	IX+LEN+DEX	LEN+DEX		
	All patients[19]	All patients[19]	Patients with high-risk cytogenetics[90]	Patients with high-risk cytogenetics[90]		
Median months	20.6	14.7	~20.6	NR		
(95% CI)	(17.0-not estim.)	(12.9-17.6)	NR	NR		
HR	0.74		0.54			
(95% CI)	(0.59-0.94); p=0.012		NR			
	MM-003[22]					
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
	All patients	All patients	Patients with high-risk cytogenetics	Patients with high-risk cytogenetics	Patients with standard-risk cytogenetics	Patients with standard-risk cytogenetics
Median months	4.0	1.9	NR	NR	NR	NR
(95% CI)	(3.6-4.7)	(1.9-2.2)	NR	NR	NR	NR
HR	0.48		0.46		0.50	
(95% CI)	(0.39-0.60); p<0.0001		(0.30-0.72)		(0.33-0.74)	

Table C4. PFS subgroup results: refractory to prior IMiD/proteasome therapy

	ASPIRE[16]					
	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX	CFZ+LEN+DEX	LEN+DEX
	All patients	All patients	Patients nonresponsive to BOR & refractory to IMiD	Patients nonresponsive to BOR & refractory to IMiD	Patients responsive to BOR & refractory to IMiD	Patients responsive to BOR & refractory to IMiD
Median months	26.3	17.6	NR		NR	NR
(95% CI)	(23.3-30.5)	(15.0-20.6)	NR		NR	NR
HR	0.69		0.89		0.7	
(95% CI)	(0.57-0.83); p=0.0001		(0.45-1.77)		(0.57-0.85)	
	MM-003					
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX		
	All patients[222]	All patients[222]	Patients refractory to BOR & LEN[22,86]	Patients refractory to BOR & LEN[22,86,]		
Median months	4.0	1.9	3.7	2.0		
(95% CI)	(3.6-4.7)	(1.9-2.2)	NR	NR		
HR	0.48		0.52			
(95% CI)	(0.39-0.60); p<0.0001		(0.41-0.68)			

Additional Response Rate Results

Figure C1. Treatment response



CR=Complete response; VGPR=Very good partial response; MR=Minimal response; SD=stable disease; PD=Progressive disease; NE= Not evaluated

Overall Response Rate Subgroup Results

Subgroup Analyses to Inform Second- versus Third- or Later-Line Use

In general, the ORR by number of prior therapies and by prior-refractory or prior-exposure to lenalidomide or bortezomib did not dramatically differ from the overall ORR in each of the key studies' intervention groups.[20,80,82,114] Among patients treated with POM+LoDEX and DARA, overall response was slightly higher in the subgroups treated with more than three previous therapies (34% and 30% for POM+LoDEX and DARA respectively) compared to those who received fewer prior therapies (26% for both regimens), although differences may have been due to the small number of patients who had received less than three prior therapies (POM+LoDEX n=17; DARA n=7). Subgroup data of ORR are presented in Table C5.

Other Subgroups

Additional subgroup analyses were performed to evaluate ORR by cytogenetic risk in the ASPIRE, MM-003, and SIRIUS trials (see Table C6 for definitions of risk). In the ASPIRE trial, ORR was improved for CFZ+LEN+DEX versus LEN+DEX in both standard- and high-risk subgroups.[88]

In contrast, overall response rates in the MM-003 trial differed dramatically between cytogenetic risk groups. Patients with del(17p) treated with POM+LoDEX had an ORR similar to that in patients with standard cytogenetic risk (31.8% vs. 35.1%), both of which were statistically superior to HiDEX treatment, whereas the response rate was much lower in patients with t(4;14) (15.9%) and did not differ between subgroups.[83]

Table C5. ORR subgroup results

		Standard risk	High risk	1 prior treatment	≥2 prior treatments	LEN refractory	BOR refractory	LEN+BOR refractory
ASPIRE	CFZ + LEN + DEX	91.2%[88]	79.2%[88]	87.0%[114]	87.3%[114]			
	LEN + DEX	73.5%[88]	59.6%[88]	70.1%[114]	64.4%[114]			
SIRIUS	DARA	29.4% (19.0-41.7)[20]	20.0% (5.7-43.7)[20]	≤3 prior Tx: 26.3% (9.1-51.2) >3 prior TX: 29.9% (20.5-40.6)[20]		28% (19.1-38.2)[20]	27.4% (18.7-37.5)[20]	26.4% (17.6-37.0)[20]
PANORAMA-1	PAN + BOR + DEX				58.9% (46.8- 70.3)[80]			
	BOR + DEX				39.2% (28.0-51.2)[80α]			
MM-003	POM + LoDEX	35.2%[83]	del(17p): 31.8% t(4;14): 15.9%[83]	≤3 prior Tx: 26% >3 prior TX: 34%[82]		30%[82]	31%[82]	29%[82]
	HiDEX	9.7%[83]	del(17p): 4.3%[83] t(4;14): 13.3%					

α At least two prior regimens including bortezomib and an IMiD; ORR subgroup data not available for ixazomib or elotuzumab

Table C6. Risk definitions

	High-Risk	Standard-Risk
ASPIRE	t(4;14), t(14;16), or del(17p) in ≥60% of plasma cells	All other patients with known baseline cytogenetics
ELOQUENT-2	t(4;14), t(14;16) or del(17p) in ≥60% of plasma cells	Not reported
SIRIUS	IMWG risk stratification: ISS II/III and t(4;14) or 17p13 del	Patients who are neither high-risk or low-risk by IMWG risk criteria
TOURMALINE-MM1	t(4;14), t(14;16), or del(17)	Not reported
PANORAMA-1	t(4; 14), t(14; 16), or del(17)	All other patients with known baseline cytogenetics
MM-003	Del(17p), t(4;14)	Not reported

Appendix D. Network Meta-Analysis Methods and Results

Network Meta-Analysis Methods

In addition to summary evidence tables, we performed quantitative indirect comparisons using Bayesian network meta-analysis (NMA) where possible.[93] Results are summarized in the report text. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points was used to assess the best model fit under multiple alternative assumptions. Given the large number of comparisons to be made among multiple myeloma treatments, and the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. However, the available network is constructed of primarily single-study connections, which made the only feasible approach a fixed-effects model (to preserve statistically-significant effects observed in trials) and selected subgroup analyses (to address heterogeneity).[94]

Quantitative analyses focused attention on the effects of the regimens of interest on progression-free and/or overall survival, and were conducted using the NetMetaXL tool (http://www.netmetaxl.com/), a publicly-available and validated Excel-based tool for specifying and analyzing Bayesian indirect comparisons in a WinBUGS environment. For these outcomes, adjusted hazard ratios from the randomized trials were log-transformed and entered into the spreadsheet, and 95% confidence intervals were used to specify variance estimates (i.e., standard errors). A total of 40,000 iterations each were employed for both "burn-in" (for model convergence) and model (for model results) simulations.

We also conducted sensitivity analyses in which digitized information from the progression-free survival curves for each regimen of interest were used to inform assessment of hazard ratios at multiple timepoints to determine whether the assumption of a proportional hazard holds true, based on established methods.[96] We did this both for the overall dataset and a subset of data from the carfilzomib, ixazomib, and elotuzumab trials, to assess whether inclusion of more contemporary data for lenalidomide+dexamethasone had a material impact on results. In this instance, 30,000 iterations were used for both burn-in and model simulations.

Results of Network Meta-Analysis

Figure D1. Overall survival network diagram

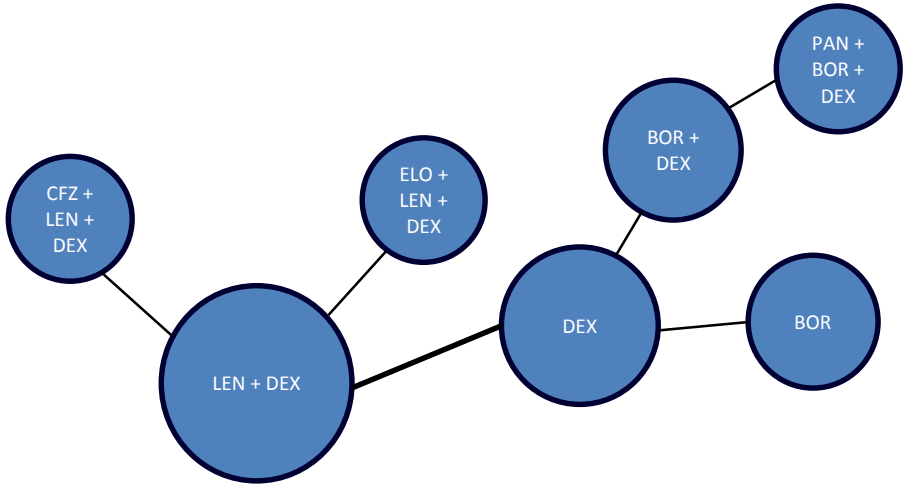


Table D1. Overall survival studies

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
ASPIRE[16]	LEN+DEX	CFZ+LEN+DEX	396	396	-0.24	0.12
ELOQUENT-2[25]	LEN+DEX	ELO+LEN+DEX	325	321	-0.26	0.12
MM-010[38]	DEX	LEN+DEX	175	176	-0.42	0.19
MM-009[37]	DEX	LEN+DEX	176	177	-0.82	0.20
APEX[126]	DEX	BOR	336	333	-0.56	0.18
Dimopoulos 2015[127]	BOR	BOR+DEX	109	109	-0.04	0.29
PANORAMA-1[24]	BOR+DEX	PAN+BOR+DEX	381	387	-0.06	010

Table D2. Network meta-analysis: Overall survival

ELO LEN DEX						
0.98 (0.70 to 1.35)	**CFZ LEN DEX**					
0.81 (0.37 to 1.79)	0.84 (0.38 to 1.83)	**PAN BOR DEX**				
0.77 (0.36 to 1.64)	0.79 (0.37 to 1.68)	0.94 (0.78 to 1.14)	**BOR DEX**			
0.77 (0.61 to 0.97)	0.79 (0.63 to 0.99)	0.95 (0.45 to 2.01)	1.01 (0.49 to 2.09)	**LEN DEX**		
0.73 (0.44 to 1.21)	0.75 (0.45 to 1.24)	0.90 (0.49 to 1.64)	0.96 (0.54 to 1.69)	0.95 (0.61 to 1.49)	**BOR**	
0.42 (0.29 to 0.60)	0.43 (0.30 to 0.61)	0.51 (0.25 to 1.03)	0.54 (0.28 to 1.07)	0.54 (0.41 to 0.71)	0.57 (0.40 to 0.81)	**DEX**

FE Model:
resdev, 8.17 vs. 7;
DIC = 1.362

Figure D2. Progression-free survival network diagram

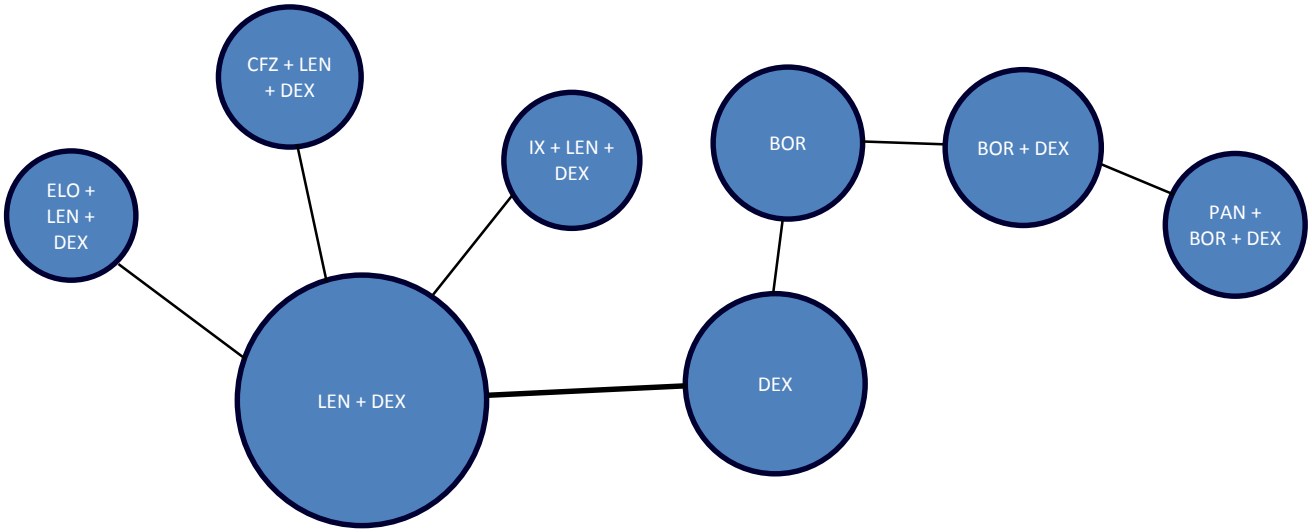


Table D3. Progression-free survival studies

Study name	Treatment 1	Treatment 2	n1	n2	LogHr	LogSE
ASPIRE[16]	LEN+DEX	CFZ+LEN+DEX	396	396	-0.37	0.10
TOURMALINE-MM1[21]	LEN+DEX	IX+LEN+DEX	362	360	-0.30	0.12
ELOQUENT-2[17]	LEN+DEX	ELO+LEN+DEX	325	321	-0.36	0.10
MM-010[38]	DEX	LEN+DEX	175	176	-1.05	0.14
MM-009[37]	DEX	LEN+DEX	176	177	-1.05	0.14
APEX[87,126]	DEX	BOR	336	333	-0.60	0.11
Dimopoulos 2015[127]	BOR	BOR+DEX	109	109	-0.52	0.27
PANORAMA-1[18]	BOR+DEX	PAN+BOR+DEX	381	387	-0.46	0.10

Note: Because PFS was unavailable for MM-009 and MM-010, TTP was used; this approach has been used in other indirect comparisons of the agents of interest[111]

Table D4. Network meta-analysis: Overall PFS

PAN BOR DEX							
0.78 (0.41 to 1.51)	**CFZ LEN DEX**						
0.77 (0.40 to 1.50)	0.99 (0.75 to 1.30)	**ELO LEN DEX**					
0.73 (0.37 to 1.44)	0.93 (0.69 to 1.26)	0.95 (0.70 to 1.28)	**IX LEN DEX**				
0.58 (0.48 to 0.71)	0.74 (0.39 to 1.39)	0.75 (0.40 to 1.41)	0.80 (0.42 to 1.52)	**BOR DEX**			
0.54 (0.29 to 1.02)	0.69 (0.57 to 0.83)	0.70 (0.57 to 0.86)	0.74 (0.59 to 0.93)	0.93 (0.51 to 1.71)	**LEN DEX**		
0.34 (0.20 to 0.60)	0.44 (0.31 to 0.62)	0.45 (0.31 to 0.64)	0.47 (0.32 to 0.69)	0.59 (0.35 to 1.01)	0.64 (0.47 to 0.86)	**BOR**	
0.19 (0.10 to 0.35)	0.24 (0.18 to 0.32)	0.25 (0.19 to 0.32)	0.26 (0.19 to 0.35)	0.33 (0.18 to 0.58)	0.35 (0.29 to 0.42)	0.55 (0.44 to 0.69)	**DEX**

FE Model:
resdev, 6.996 vs. 8;
DIC = -4.288

Figure D3. Network diagram for analysis of progression-free survival by number of prior lines of therapy

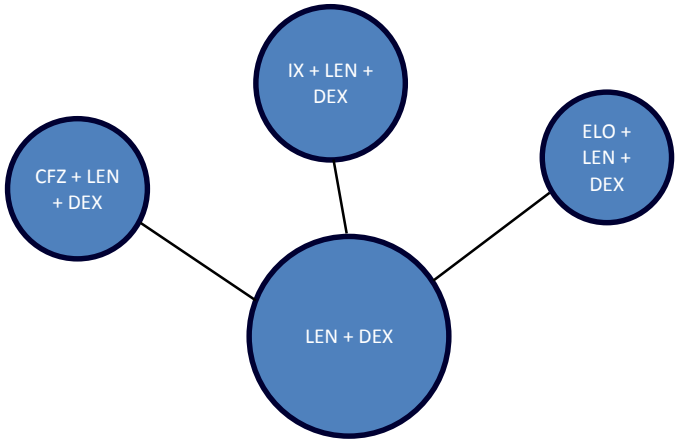


Table D5. Progression-free survival studies by prior line of therapy

Study name	Treatment 1	Treatment 2	n1	n2	1 Prior Line of Therapy		2-3 Prior Lines of Therapy	
					LogHr	LogSE	LogHr	LogSE
ASPIRE[91]	LEN+DEX	CFZ+LEN+DEX	157	184	-0.37	0.14	-0.37	0.12
TOURMALINE-MM1[87]	LEN+DEX	IX+LEN+DEX	213	212	-0.13	0.16	-0.54	0.19
ELOQUENT-2[17]	LEN+DEX	ELO+LEN+DEX	159	151	-0.29	0.15	-0.43	0.15

Table D6. Network meta-analysis: Subgroup analysis of PFS, 1 prior line of therapy

CFZ LEN DEX			
0.92 (0.62 to 1.38)	**ELO LEN DEX**		
0.79 (0.52 to 1.18)	0.85 (0.56 to 1.30)	**IX LEN DEX**	
0.69 (0.53 to 0.91)	0.75 (0.56 to 1.00)	0.88 (0.65 to 1.19)	**LEN DEX**

FE Model:
resdev, 2.986 vs. 3;
DIC = -0.002

Table D7. Network meta-analysis: Subgroup analysis of PFS, 2-3 prior lines of therapy

IX LEN DEX			
0.89 (0.56 to 1.42)	**ELO LEN DEX**		
0.84 (0.54 to 1.30)	0.95 (0.65 to 1.37)	**CFZ LEN DEX**	
0.58 (0.40 to 0.84)	0.65 (0.49 to 0.87)	0.69 (0.54 to 0.87)	**LEN DEX**

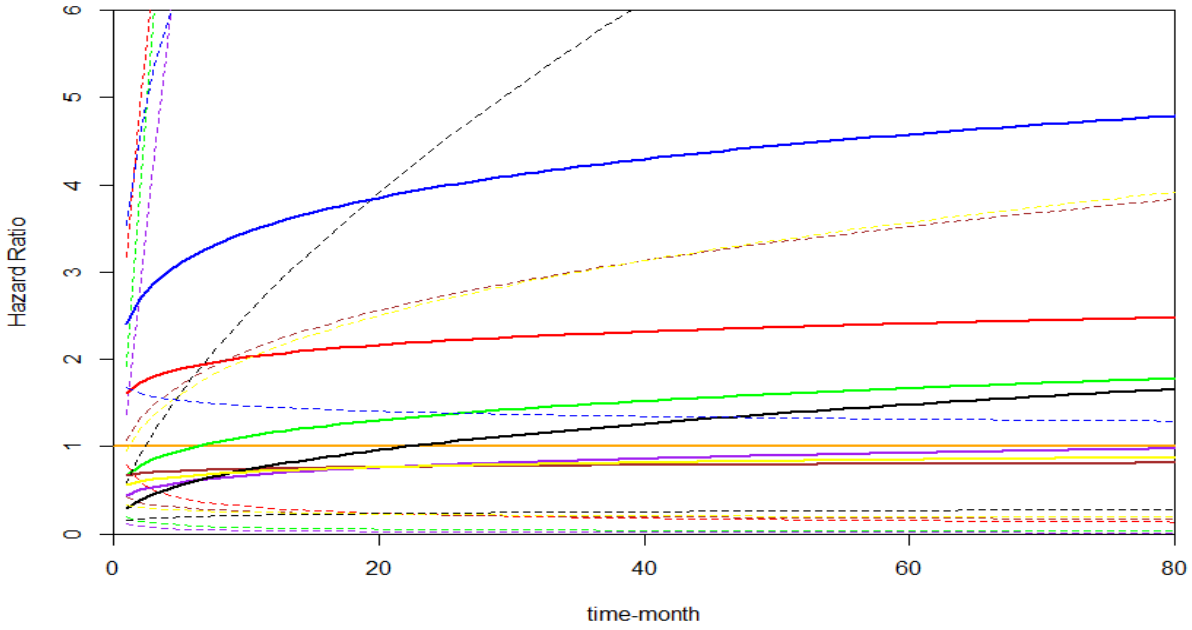
FE Model:
resdev, 2.986 vs. 3;
DIC = 0.055

WinBUGS Code for Network Meta-Analysis Using Digitized Progression-Free Survival Curves

```
Model{
for (i in 1:N){
r[i]~ dbin(p[i],n[i])
p[i]<-1-exp(-h[i]*dt[i])

#random effects model
h[i]<-exp(nu[i]+log(time[i])*theta[i])
nu[i]<-mu[s[i],1]+md[s[i],1]*(1-equals(t[i],b[i]))
theta[i]<-mu[s[i],2]+ md[s[i],2]*(1-equals(t[i],b[i]))
}

for(k in 1 :NS){

md[k,1]<-d[ts[k],1]-d[bs[k],1]
md[k,2]<-d[ts[k],2]-d[bs[k],2]
}

# priors
d[1,1]<-0
d[1,2]<-0

for(j in 2 :NT){
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}


for(k in 1 :NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
}

}
```

Figures D4 (Hazard ratios) and D5 (Survival curves) over time for network meta-analysis using digitized progression-free survival data

Orange: LEN+DEX
Blue: DEX
Yellow: ELO+LEN
Black: CFZ+LEN+DEX
Brown: IX+LEN+DEX
Red: BOR
Green: BOR+DEX
Purple: PAN+BOR+DEX



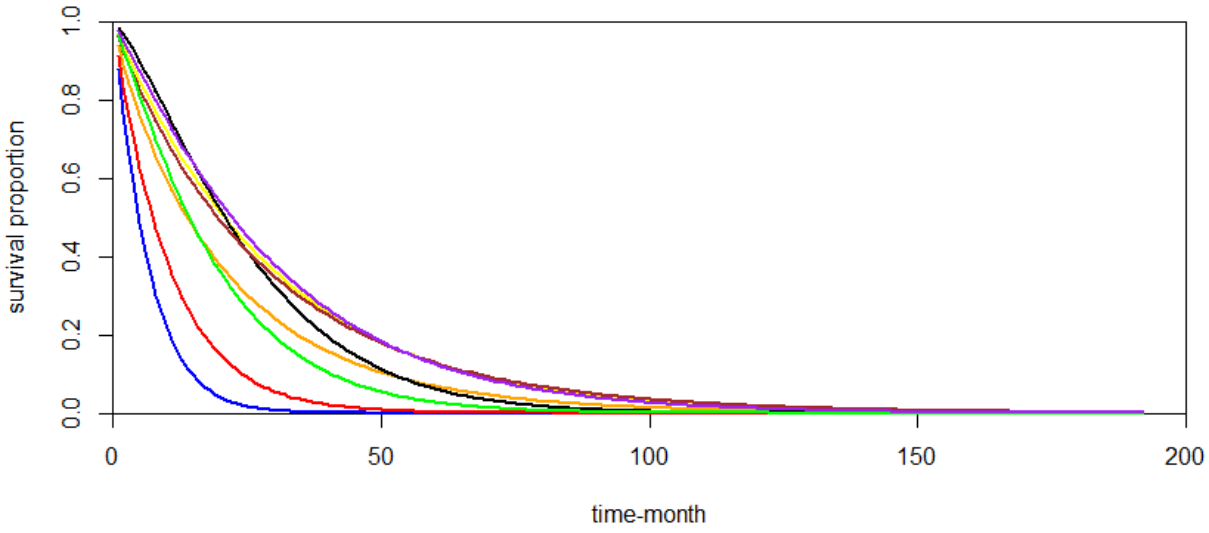


Table D8. Hazard ratios for progression-free survival at 1, 2, and 5 years based on full evidence network

ref=LEN DEX	12 months			24months			60 months		
	median	LL	UL	median	LL	UL	median	LL	UL
PAN BOR DEX	0.692	0.035	17.151	0.785	0.025	34.685	0.927	0.016	87.993
CFZ LEN DEX	0.786	0.217	2.82	1.033	0.238	4.399	1.482	0.269	7.921
ELO LEN DEX	0.722	0.244	2.123	0.774	0.223	2.655	0.85	0.197	3.57
IX LEN DEX	0.746	0.251	2.206	0.769	0.218	2.699	0.801	0.18	3.524
BOR DEX	1.162	0.067	23.803	1.358	0.05	48.004	1.667	0.033	121.338
BOR	2.059	0.291	14.904	2.203	0.22	22.949	2.408	0.152	40.608
DEX	3.557	1.45	8.756	3.966	1.39	11.273	4.579	1.316	15.743

Table D9. Hazard ratios for progression-free survival at 1, 2, and 5 years based on limited evidence network with lenalidomide+dexamethasone as uniform comparator

ref=LEN DEX	12 months			24months			60 months		
	median	LL	UL	median	LL	UL	median	LL	UL
CFZ LEN DEX	0.781	0.175	3.469	1.017	0.188	5.628	1.441	0.206	10.673
ELO LEN DEX	0.72	0.25	2.057	0.768	0.229	2.565	0.837	0.204	3.434
IX LEN DEX	0.75	0.243	2.241	0.777	0.208	2.753	0.814	0.17	3.613

Appendix E. Comparative Value Supplemental Information

Table E1. Adverse event inputs

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

Table E2. Treatment regimen recommended dosage

	Treatment Initiation				Subsequent Treatment (if different)			
	Days/Cycle	Cycle 1 Dose	To Cycle:	Admin. Days	Days/Cycle	Subs. Doses	To Cycle:	Admin. Days
Bortezomib with dexamethasone								
Bortezomib	21	1.3 mg/m^2	8	1,4,8,11	35	1.3 mg/m^2	to progression	1,8,15,22
Dexamethasone	28	20 mg	to progression	1,8,15,22				
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

Table E3. Dose intensity estimates

LEN+DEX[α]	
Lenalidomide	100.0%
Dexamethasone	100.0%
BOR+DEX[α]	
Bortezomib	100.0%
Dexamethasone	100.0%
CFZ+LEN+DEX[16]	
Carfilzomib	91.0%
Lenalidomide	80.5%
Dexamethasone	85.3%
ELO+LEN+DEX[89]	
Elotuzumab cycles 1-2	100.0%
Elotuzumab subsequent cycles	96.0%
Lenalidomide	82.3%
Dexamethasone	86.0%
Dexamethasone (IV)	86.0%
IX+LEN+DEX[21]	
Ixazomib	97.4%
Lenalidomide	93.8%
Dexamethasone	92.2%
PAN+BOR+DEX[18]	
Panobinostat	80.7%
Bortezomib	75.7%
Dexamethasone	87.5%

α Assumed maximum dose intensity

Table E4. Cost per Grade 3/4 adverse event

Adverse Event	Cost per event	Source
Anemia	$971	Roy et al.[128]
Arrhythmias	$6,998	Roy et al.[128]
Back Pain	$10,728	Roy et al.[128]
Cataract	$3,700	CMS[129]
Deep Vein Thrombosis	$31,645	Roy et al.[128]
Diarrhea	$9,738	Roy et al.[128]
Fatigue	$8,437	Roy et al.[128]
Hyperglycemia	$166	Roy et al.[128]
Hypocalcemia	$1,155	Roy et al.[128]
Hypokalemia	$1,707	Roy et al.[128]
Lymphopenia	$166	Roy et al.[128]
Nausea	$11,934	Roy et al.[128]
Neutropenia	$166	Roy et al.[128]
Peripheral/Sensory Neuropathy	$783	Roy et al.[128]
Pneumonia	$14,855	Roy et al.[128]
Thrombocytopenia	$166	Roy et al.[128]
Vomiting	$11,934	Roy et al.[128]

Abbreviations: DRG: Diagnosis related group; CMS: Center for Medicare and Medicaid Services

Table E5. Scenario with BOR+DEX as comparator in the second-line

Second-Line			
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX
ICER	$364,366	$652,463	$719,372

Table E6. Scenario with BOR+DEX as comparator in the third-line

Third-Line				
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX	PAN+BOR+DEX
ICER	$420,177	$727,983	$797,178	$10,230

Table E7. Scenario with unadjusted OS to PFS ratio derived from included studies in the second-line

Second-Line			
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX
ICER	$171,181	$364,090	$369,784

Table E8. Scenario with unadjusted OS to PFS ratio derived from included studies in the third-line

Third-Line				
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX	PAN+BOR+DEX
ICER	$201,163	$401,221	$403,674	Dominant

Table E9. Scenario with ASPIRE-derived LEN+DEX baseline curve in the second-line

Second-Line			
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX
ICER	$184,097	$433,720	$444,020

Table E10. Scenario with ASPIRE-derived LEN+DEX baseline curve in the third-line

Third-Line				
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX	PAN+BOR+DEX
ICER	$232,822	$483,063	$487,985	Dominant

Table E11. Scenario with ASPIRE-derived triplet versus doublet regimen utilities in the second-line

Second-Line			
	CFZ+LEN+DEX	ELO+LEN+DEX	IX+LEN+DEX
ICER	$182,959	$389,928	$389,595

Table E12. Second-line probabilistic sensitivity analysis

Results by Regimen

2nd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
Total Costs	**$284,400**	**$285,776**	**($219,381 - $363,695)**	**$457,350**	**$460,694**	**($352,625 - $592,289)**	**$638,144**	**$644,673**	**($471,047 - $858,205)**	**$582,428**	**$592,211**	**($431,105 - $805,467)**
Drug Costs	$240,913	$243,469	($181,675 - $316,141)	$398,767	$403,962	($301,855 - $530,271)	$569,796	$577,739	($415,422 - $781,520)	$532,873	$544,144	($389,688 - $752,640)
Supportive Care Costs	$528	$533	($439 - $649)	$1,882	$1,892	($1,683 - $2,133)	$2,607	$2,654	($2,045 - $3,468)	$2,491	$2,540	($1,923 - $3,338)
Administration Costs				$8,377	$8,354	($6,690 - $10,051)	$14,698	$14,984	($10,683 - $20,633)			
Progression Costs	$38,901	$37,716	($27,308 - $51,361)	$44,103	$42,256	($30,242 - $52,845)	$43,886	$42,128	($30,080 - $52,799)	$43,062	$41,521	($29,641 - $52,835)
Adverse Event Costs	$4,057	$4,058	($3,246 - $5,037)	$4,221	$4,231	($3,403 - $5,198)	$7,156	$7,169	($5,965 - $8,584)	$4,001	$4,006	($3,225 - $4,928)
Total QALYs	**2.59**	**2.66**	**(1.89 - 3.74)**	**3.45**	**3.57**	**(2.42 - 5.22)**	**3.41**	**3.53**	**(2.42 - 5.20)**	**3.27**	**3.40**	**(2.28 - 5.00)**
PFS QALYs	1.41	1.43	(1.17 - 1.73)	1.91	1.94	(1.49 - 2.54)	1.89	1.92	(1.46 - 2.54)	1.81	1.84	(1.39 - 2.44)
Progression QALYs	1.17	1.24	(0.62 - 2.15)	1.54	1.63	(0.80 - 2.86)	1.52	1.61	(0.80 - 2.85)	1.46	1.55	(0.77 - 2.74)
Total Life Years (OS)	**3.53**	**3.65**	**(2.53 - 5.21)**	**4.71**	**4.88**	**(3.24 - 7.27)**	**4.66**	**4.83**	**(3.24 - 7.20)**	**4.46**	**4.64**	**(3.04 - 6.91)**
PFS LYs	1.73	1.75	(1.45 - 2.10)	2.34	2.38	(1.84 - 3.10)	2.31	2.35	(1.81 - 3.09)	2.21	2.25	(1.70 - 2.97)
Progression LYs	1.80	1.90	(0.97 - 3.28)	2.37	2.50	(1.25 - 4.37)	2.34	2.48	(1.24 - 4.33)	2.25	2.39	(1.19 - 4.19)

Incremental Results vs. LEN-DEX

2nd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
ICER (vs. L+Dex)	--	--	--	**$199,982**	**$211,701**	**($105,098 - $377,210)**	**$427,607**	**$454,634**	**($260,581 - $835,126)**	**$433,794**	**$550,487**	**($259,337 - $1,084,988)**
Total Costs	--	--	--	**$172,951**	**$174,918**	**($94,817 - $262,112)**	**$353,744**	**$358,897**	**($222,650 - $529,616)**	**$298,028**	**$306,435**	**($179,900 - $465,166)**
Drug Costs	--	--	--	$157,854	$160,493	($81,929 - $246,611)	$328,883	$334,270	($202,738 - $501,615)	$291,960	$300,675	($176,695 - $458,542)
Supportive Care Costs	--	--	--	$1,354	$1,358	($1,205 - $1,529)	$2,079	$2,120	($1,575 - $2,852)	$1,963	$2,007	($1,454 - $2,716)
Administration Costs	--	--	--	$8,377	$8,354	($6,690 - $10,051)	$14,698	$14,984	($10,683 - $20,633)			
Progression Costs	--	--	--	$5,202	$4,540	(-$2,930 - $8,698)	$4,985	$4,412	(-$2,774 - $8,668)	$4,161	$3,805	(-$2,207 - $8,036)
Adverse Event Costs	--	--	--	$164	$173	(-$963 - $1,353)	$3,099	$3,111	($1,759 - $4,601)	-$56	-$52	(-$1,248 - $1,123)
Total QALYs	--	--	--	**0.86**	**0.91**	**(0.38 - 1.69)**	**0.83**	**0.87**	**(0.32 - 1.69)**	**0.69**	**0.74**	**(0.18 - 1.51)**
PFS QALYs	--	--	--	0.50	0.52	(0.22 - 0.91)	0.48	0.50	(0.18 - 0.93)	0.39	0.42	(0.10 - 0.83)
Progression QALYs	--	--	--	0.37	0.39	(0.14 - 0.80)	0.35	0.38	(0.13 - 0.80)	0.29	0.32	(0.07 - 0.72)
Total Life Years (OS)	--	--	--	**1.17**	**1.23**	**(0.52 - 2.31)**	**1.12**	**1.19**	**(0.44 - 2.31)**	**0.93**	**1.00**	**(0.24 - 2.08)**
PFS LYs	--	--	--	0.61	0.63	(0.27 - 1.11)	0.58	0.61	(0.22 - 1.13)	0.48	0.51	(0.12 - 1.01)
Progression LYs	--	--	--	0.56	0.60	(0.22 - 1.23)	0.54	0.58	(0.20 - 1.23)	0.45	0.49	(0.11 - 1.09)

Table E13. Third-line probabilistic sensitivity analysis

Results by Regimen

3rd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX			PAN-BOR-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
Total Costs	**$258,609**	**$257,105**	**($204,778 - $316,116)**	**$427,027**	**$425,444**	**($334,321 - $529,296)**	**$583,531**	**$585,030**	**($446,164 - $744,738)**	**$530,228**	**$534,523**	**($398,945 - $695,425)**	**$196,021**	**$192,321**	**($156,995 - $225,638)**
Drug Costs	$216,151	$216,173	($167,864 - $270,132)	$369,865	$369,851	($283,424 - $467,754)	$517,785	$520,623	($390,696 - $673,051)	$481,956	$487,601	($358,302 - $641,759)	$136,366	$136,087	($105,645 - $165,473)
Supportive Care Costs	$473	$474	($415 - $539)	$1,779	$1,784	($1,608 - $1,969)	$2,364	$2,390	($1,919 - $2,949)	$2,255	$2,289	($1,803 - $2,868)	$415	$415	($378 - $438)
Administration Costs				$8,113	$8,097	($6,450 - $9,730)	$13,394	$13,521	($9,884 - $17,753)				$3,128	$3,115	($2,459 - $3,819)
Progression Costs	$37,928	$36,416	($26,667 - $48,141)	$43,049	$41,498	($29,607 - $53,051)	$42,833	$41,345	($29,669 - $53,029)	$42,016	$40,642	($28,819 - $52,512)	$46,984	$43,571	($30,662 - $53,191)
Adverse Event Costs	$4,057	$4,042	($3,233 - $4,999)	$4,221	$4,214	($3,380 - $5,198)	$7,156	$7,151	($5,961 - $8,508)	$4,001	$3,990	($3,222 - $4,898)	$9,128	$9,134	($7,995 - $10,359)
Total QALYs	**2.04**	**2.09**	**(1.47 - 2.88)**	**2.74**	**2.82**	**(1.90 - 3.96)**	**2.71**	**2.79**	**(1.91 - 3.97)**	**2.60**	**2.69**	**(1.78 - 3.88)**	**3.46**	**3.73**	**(1.95 - 6.36)**
PFS QALYs	1.00	1.01	(0.77 - 1.25)	1.37	1.39	(1.02 - 1.82)	1.36	1.37	(1.00 - 1.82)	1.30	1.32	(0.94 - 1.78)	1.82	1.96	(1.05 - 3.36)
Progression QALYs	1.03	1.08	(0.55 - 1.80)	1.37	1.43	(0.73 - 2.40)	1.36	1.42	(0.72 - 2.39)	1.30	1.37	(0.68 - 2.32)	1.63	1.77	(0.78 - 3.26)
Total Life Years (OS)	**3.25**	**3.32**	**(2.43 - 4.48)**	**4.37**	**4.47**	**(3.13 - 6.21)**	**4.32**	**4.44**	**(3.11 - 6.18)**	**4.14**	**4.27**	**(2.93 - 6.07)**	**5.27**	**5.67**	**(3.02 - 9.40)**
PFS LYs	1.55	1.56	(1.37 - 1.76)	2.12	2.14	(1.73 - 2.64)	2.09	2.12	(1.69 - 2.62)	2.00	2.03	(1.59 - 2.55)	2.59	2.78	(1.55 - 4.56)
Progression LYs	1.70	1.76	(0.95 - 2.82)	2.25	2.34	(1.24 - 3.82)	2.23	2.32	(1.24 - 3.73)	2.14	2.24	(1.17 - 3.70)	2.68	2.89	(1.35 - 5.16)

Incremental Results vs. LEN-DEX

3rd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX			PAN-BOR-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
ICER (vs. L+Dex)	--	--	--	**$238,560**	**$250,394**	**($129,580 - $444,839)**	**$481,244**	**$515,226**	**($299,957 - $918,525)**	**$484,582**	**$494,807**	**($277,941 - $1,210,118)**	**-$44,084**	**-$27,887**	**(-$420,181 - $1,117)**
Total Costs	--	--	--	**$168,418**	**$168,338**	**($92,910 - $245,030)**	**$324,922**	**$327,925**	**($212,645 - $465,635)**	**$271,619**	**$277,417**	**($162,733 - $411,674)**	**-$62,588**	**-$64,784**	**(-$127,099 - -$6,440)**
Drug Costs	--	--	--	$153,714	$153,678	($79,491 - $227,449)	$301,634	$304,450	($195,105 - $436,021)	$265,805	$271,428	($160,022 - $403,247)	-$79,784	-$80,087	(-$139,723 - -$24,431)
Supportive Care Costs	--	--	--	$1,307	$1,310	($1,157 - $1,460)	$1,891	$1,916	($1,472 - $2,433)	$1,783	$1,815	($1,360 - $2,359)	-$58	-$59	(-$134 - $3)
Administration Costs	--	--	--	$8,113	$8,097	($6,450 - $9,730)	$13,394	$13,521	($9,884 - $17,753)				$3,128	$3,115	($2,459 - $3,819)
Progression Costs	--	--	--	$5,121	$5,082	($1,588 - $9,138)	$4,905	$4,929	($1,424 - $9,073)	$4,087	$4,226	($752 - $8,634)	$9,055	$7,155	(-$1,924 - $14,249)
Adverse Event Costs	--	--	--	$164	$172	(-$993 - $1,318)	$3,099	$3,109	($1,698 - $4,574)	-$56	-$52	(-$1,207 - $1,074)	$5,071	$5,092	($3,771 - $6,496)
Total QALYs	--	--	--	**0.71**	**0.73**	**(0.32 - 1.27)**	**0.68**	**0.71**	**(0.27 - 1.29)**	**0.56**	**0.60**	**(0.15 - 1.22)**	**1.42**	**1.64**	**(0.09 - 3.89)**
PFS QALYs	--	--	--	0.37	0.38	(0.16 - 0.66)	0.35	0.37	(0.13 - 0.66)	0.29	0.31	(0.07 - 0.61)	0.82	0.95	(0.06 - 2.29)
Progression QALYs	--	--	--	0.34	0.35	(0.13 - 0.68)	0.32	0.34	(0.12 - 0.69)	0.27	0.29	(0.07 - 0.65)	0.60	0.69	(0.02 - 1.73)
Total Life Years (OS)	--	--	--	**1.12**	**1.16**	**(0.50 - 1.98)**	**1.07**	**1.12**	**(0.43 - 2.06)**	**0.89**	**0.95**	**(0.23 - 1.91)**	**2.02**	**2.35**	**(0.07 - 5.58)**
PFS LYs	--	--	--	0.57	0.58	(0.26 - 0.96)	0.54	0.56	(0.22 - 0.97)	0.45	0.47	(0.11 - 0.91)	1.04	1.22	(0.03 - 2.95)
Progression LYs	--	--	--	0.55	0.58	(0.22 - 1.10)	0.53	0.56	(0.20 - 1.12)	0.44	0.48	(0.11 - 1.03)	0.98	1.13	(0.04 - 2.75)

Results by Regimen

3rd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX			PAN-BOR-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
Total Costs	**$261,718**	**$260,467**	**($207,019 - $315,703)**	**$482,576**	**$483,817**	**($388,186 - $594,757)**	**$457,129**	**$472,605**	**($366,191 - $608,273)**	**$506,041**	**$511,780**	**($384,974 - $671,825)**	**$186,877**	**$184,559**	**($149,855 - $218,435)**
Drug Costs	$216,151	$216,149	($166,786 - $267,521)	$427,021	$429,458	($340,549 - $534,562)	$391,837	$408,368	($309,439 - $535,781)	$459,683	$466,471	($343,654 - $617,912)	$136,366	$136,724	($106,435 - $166,969)
Supportive Care Costs	$473	$474	($414 - $542)	$1,779	$1,786	($1,611 - $1,976)	$2,364	$2,390	($1,906 - $2,956)	$2,255	$2,291	($1,823 - $2,899)	$415	$415	($379 - $439)
Administration Costs				$8,113	$8,124	($6,464 - $9,791)	$13,394	$13,499	($10,024 - $17,543)				$3,128	$3,119	($2,469 - $3,783)
Progression Costs	$37,929	$36,671	($27,203 - $48,423)	$43,048	$41,833	($30,199 - $53,349)	$42,833	$41,640	($29,990 - $53,323)	$42,015	$40,937	($29,398 - $53,133)	$46,968	$44,301	($31,091 - $53,218)
Adverse Event Costs	$7,166	$7,172	($6,019 - $8,538)	$2,614	$2,617	($2,093 - $3,232)	$6,702	$6,708	($5,574 - $8,044)	$2,087	$2,082	($1,571 - $2,675)	$8,203	$8,199	($7,112 - $9,380)
Total QALYs	**2.04**	**2.09**	**(1.49 - 2.87)**	**2.74**	**2.82**	**(1.93 - 4.01)**	**2.71**	**2.79**	**(1.94 - 3.96)**	**2.60**	**2.69**	**(1.83 - 3.84)**	**3.46**	**3.75**	**(2.01 - 6.21)**
PFS QALYs	1.00	1.00	(0.78 - 1.25)	1.37	1.38	(1.01 - 1.82)	1.36	1.37	(0.99 - 1.80)	1.30	1.31	(0.94 - 1.77)	1.82	1.98	(1.06 - 3.36)
Progression QALYs	1.03	1.08	(0.58 - 1.80)	1.37	1.44	(0.75 - 2.44)	1.36	1.42	(0.74 - 2.38)	1.30	1.37	(0.72 - 2.34)	1.63	1.77	(0.82 - 3.14)
Total Life Years (OS)	**3.25**	**3.33**	**(2.44 - 4.48)**	**4.37**	**4.50**	**(3.16 - 6.25)**	**4.32**	**4.45**	**(3.13 - 6.22)**	**4.14**	**4.28**	**(3.01 - 6.02)**	**5.27**	**5.72**	**(3.14 - 9.21)**
PFS LYs	1.55	1.56	(1.36 - 1.77)	2.12	2.14	(1.73 - 2.64)	2.09	2.12	(1.68 - 2.63)	2.00	2.03	(1.61 - 2.58)	2.59	2.81	(1.58 - 4.60)
Progression LYs	1.70	1.78	(0.97 - 2.84)	2.25	2.36	(1.28 - 3.81)	2.23	2.34	(1.25 - 3.77)	2.14	2.25	(1.21 - 3.67)	2.67	2.90	(1.36 - 5.02)

Incremental Results vs. LEN-DEX

3rd Line	LEN-DEX			CFZ-LEN-DEX			ELO-LEN-DEX			IX-LEN-DEX			PAN-BOR-DEX		
	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range	Deterministic	Mean	Credible Range
ICER (vs. L+Dex)	**--**	**--**	**--**	**$313,052**	**$330,803**	**($207,017 - $550,544)**	**$289,607**	**$328,157**	**($194,989 - $592,695)**	**$436,087**	**$497,021**	**($264,507 - $1,116,447)**	**-$52,828**	**-$107,009**	**(-$336,117 - -$2,732)**
Total Costs	**--**	**--**	**--**	**$220,858**	**$223,350**	**($161,150 - $295,591)**	**$195,411**	**$212,138**	**($119,920 - $325,329)**	**$244,324**	**$251,314**	**($148,064 - $379,989)**	**-$74,840**	**-$75,907**	**(-$138,188 - -$16,351)**
Drug Costs	--	--	--	$210,870	$213,308	($153,843 - $282,972)	$175,686	$192,219	($104,546 - $302,163)	$243,532	$250,321	($150,274 - $375,816)	-$79,784	-$79,425	(-$139,480 - -$21,917)
Supportive Care Costs	--	--	--	$1,307	$1,312	($1,165 - $1,465)	$1,891	$1,916	($1,468 - $2,456)	$1,783	$1,817	($1,379 - $2,391)	-$58	-$59	(-$130 - $5)
Administration Costs	--	--	--	$8,113	$8,124	($6,464 - $9,791)	$13,394	$13,499	($10,024 - $17,543)				$3,128	$3,119	($2,469 - $3,783)
Progression Costs	--	--	--	$5,120	$5,161	($1,735 - $9,168)	$4,904	$4,969	($1,401 - $9,244)	$4,087	$4,266	($803 - $8,605)	$9,040	$7,630	(-$1,114 - $14,439)
Adverse Event Costs	--	--	--	-$4,552	-$4,555	(-$5,929 - -$3,330)	-$464	-$464	(-$2,073 - $1,128)	-$5,078	-$5,090	(-$6,462 - -$3,835)	$1,038	$1,027	(-$613 - $2,640)
Total QALYs	**--**	**--**	**--**	**0.71**	**0.74**	**(0.32 - 1.29)**	**0.67**	**0.70**	**(0.27 - 1.30)**	**0.56**	**0.60**	**(0.15 - 1.22)**	**1.42**	**1.66**	**(0.12 - 3.78)**
PFS QALYs	--	--	--	0.37	0.38	(0.17 - 0.65)	0.35	0.36	(0.13 - 0.65)	0.29	0.31	(0.07 - 0.63)	0.82	0.97	(0.06 - 2.34)
Progression QALYs	--	--	--	0.34	0.36	(0.14 - 0.68)	0.32	0.34	(0.12 - 0.68)	0.27	0.29	(0.07 - 0.63)	0.60	0.69	(0.04 - 1.58)
Total Life Years (OS)	**--**	**--**	**--**	**1.12**	**1.17**	**(0.52 - 2.01)**	**1.07**	**1.12**	**(0.43 - 2.04)**	**0.89**	**0.95**	**(0.23 - 1.95)**	**2.02**	**2.38**	**(0.11 - 5.42)**
PFS LYs	--	--	--	0.57	0.58	(0.27 - 0.97)	0.54	0.56	(0.22 - 0.99)	0.45	0.47	(0.11 - 0.94)	1.04	1.26	(0.06 - 3.03)
Progression LYs	--	--	--	0.55	0.58	(0.23 - 1.10)	0.53	0.56	(0.20 - 1.09)	0.44	0.48	(0.11 - 1.02)	0.98	1.13	(0.06 - 2.52)

Appendix F. Previous Technology Assessments and Systematic Reviews

We identified three completed technology assessments: two from the National Institute for Health and Care Excellence (NICE) in the UK and one from the Pan-Canadian Oncology Drug Review (pCODR). These reviews of panobinostat and pomalidomide are summarized below. We also identified five systematic reviews of the newer MM drugs; three of these were abstracts of systematic reviews and meta-analyses that have not been published in longer formats.

Technology Assessments

Panobinostat:

- National Institute for Health and Care Excellence (NICE) technology appraisal guidance: Panobinostat for treating multiple myeloma after 2 previous treatments (January 27, 2016) (https://www.nice.org.uk/guidance/ta380/resources/panobinostat-for-treating-multiple-myeloma-after-at-least-2-previous-treatments-82602842988229)[130]

PAN+BOR+DEX is recommended for treating relapsed and/or refractory MM who have received two or more prior regimens including BOR and an IMiD, provided the manufacturer gives a pricing discount (which remains confidential). Although the Committee noted that the subgroup analyses supporting the marketing authorization were not pre-specified in the trial publication, they concluded that these subgroup results were relevant and useful for this population.

Pomalidomide:

- NICE technology appraisal guidance: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (March 25, 2015) (https://www.nice.org.uk/guidance/ta338/resources/pomalidomide-for-relapsed-and-refractory-multiple-myeloma-previously-treated-with-lenalidomide-and-bortezomib-82602554094277)[131]

POM+LoDEX is not recommended for treating relapsed and refractory MM in adults who have had two or more previous treatments including LEN and BOR and whose disease has progressed on the most recent therapy. The Evidence Review Group was concerned that HiDEX was the comparator in the MM-003 trial, as this is not consistent with clinical practice for salvage therapy in the UK. They also suggested that patients in the MM-003 trial may have been healthier than in other MM trials despite the double-refractory nature of their disease. For comparator studies, the company used two unpublished observational studies that reported results of a small number of patients who had relapsed after prior MM treatments. The Appraisal Committee believed these comparator data

were insufficient to judge pomalidomide's comparative effectiveness. Multiple cost-effectiveness analyses using BOR+DEX as the referent comparator resulted in ratios >£50,000 per QALY gained. Ultimately, the Committee determined that even if POM+LoDEX extends life for three or more months for pre-treated MM patients, the drug is not cost effective.

- Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee Final Recommendation: Pomalidomide (Pomalyst) for Multiple Myeloma (July 31, 2014) (https://www.cadth.ca/sites/default/files/pcodr/pcodr-pomalyst-mm-fn-rec.pdf) and https://www.cadth.ca/sites/default/files/pcodr/pcodr-pomalyst-mm-fn-egr.pdf)[132]

The pCODR expert review committee issued a final recommendation (based on the MM-003 trial) that pomalidomide should be funded for patients with relapsed and/or refractory MM who failed two or more prior lines of therapy including BOR and LEN, and who demonstrated disease progression on their last treatment, provided that cost-effectiveness is improved to an "acceptable" level. They included an additional provision for patients for whom BOR is contraindicated. The Patient Advocacy Group appreciated that POM is an oral agent. They considered POM to provide a net clinical benefit with a poor incremental cost-effectiveness ratio (CAN $132,217 - $173,430 per QALY, depending on time horizon) at its current price. One of their suggestions was to price the drug per milligram rather than per capsule.

Systematic Reviews

Of the five systematic reviews identified, one pertained to panobinostat, two to pomalidomide, and two to meta-analyses of multiple newer MM drugs. These publications and abstracts are summarized below.

Panobinostat:

- Richardson PG, Lee JH, Majer I, et al. Efficacy of treatments in relapsed or relapsed and refractory multiple myeloma: An Indirect treatment comparison. *Blood.* 2014;(21) (abstract https://ash.confex.com/ash/2014/webprogram/Paper70196.html)[133]

In an ASH abstract, Richardson and colleagues shared the results from an indirect treatment comparison using data from PANORAMA-1 in combination with data from a systematic literature review of studies published from January 2003-April 2014 that examined IV BOR, LEN, thalidomide, and doxorubicin use in patients with relapsed or refractory multiple myeloma. A fixed effects model was used with the five trials identified to estimate HRs of PFS and TTP and odds ratios of near complete response and complete response. PAN+BOR+DEX showed the lowest risk of progression or death compared to other regimens. Using PAN+BOR+DEX as the referent category, the hazard of progression was significantly increased for BOR+DEX, 1.60; BOR, 2.77; and DEX, 5.11 (the HR confidence intervals for LEN+DEX and doxorubicin+BOR were not significant).

Pomalidomide:

- Sheng Z, Liu G. Pooled analysis of the reports of pomalidomide after failure of lenalidomide and (or) bortezomib for multiple myeloma. *Hematol Oncol.* 2015;doi:10.1002/hon.2192[134]
- Sun JJ, Zhang C, Zhou J, and Y HL. Pooled analysis of pomalidomide for treating patients with multiple myeloma. *Asian Pac J Cancer Prev*. 2015;16(8):3163-3166[135]

Sheng and colleagues conducted a review of the literature published on or before September 2014, focusing on LEN- or BOR-refractory MM patients, with the objective of determining the response rate of POM+LoDEX. They identified six studies of 641 total patients with a combined ORR of 31%; heterogeneity was minimal. They described similar results for subgroup analyses: patients older than 65 years; patients with high-risk cytogenetics; and patients with double-refractory disease. The most common Grade 3 or 4 AEs were neutropenia (53%), anemia (27%), thrombocytopenia (23%), pneumonia (13%), and fatigue (11%). There were very few thromboembolic events and episodes of treatment-emergent peripheral neuropathy.

Similarly, a PUBMED search of pomalidomide and MM articles published prior to January 2015 identified four papers from which Sun et al. generated their pooled analysis of pomalidomide treatment effects. Published clinical studies were included that examined POM in combination with DEX or prednisone. Outcomes included 120/291 (41.2%) total patients achieving complete or partial response. Major adverse events included anemia, thrombocytopenia, and neutropenia, and no treatment-related death occurred.

Other Meta-Analyses:

- Nooka AK, Kaufman JL, Behera M, et al. Efficacy and safety of triplet versus doublet salvage therapies among patients with multiple myeloma (MM) experiencing early relapse: Meta-analysis of Phase III randomized controlled trials (RCTs). *Blood.* 2015;126(23):5344 (abstract http://www.bloodjournal.org/content/126/23/5344.full.pdf)[136]
- Ruggeri K, Maguire A, Schmitz S, et al. Estimating the relative effectiveness of treatments in relapsed/refractory multiple myeloma through a systematic review and network meta-analysis. *Blood*. 2015;126(23):2103 (abstract http://www.bloodjournal.org/content/126/23/2103.full.pdf)[137]

The abstract by Nooka et al. described a traditional fixed and random effects model meta-analysis of RCTs (January 2000-July 2015) comparing triplet to doublet salvage therapy in early relapsed MM patients who had been treated with 1-3 prior lines of therapy. Data from four trials (PANORAMA-1, IFM 2005-04, ASPIRE, and ELOQUENT-2) were pooled for a total of 2,475 patients to reveal an improved ORR odds ratio of 1.94 (95% CI 1.61-2.32) and an improved PFS HR of 0.66 (95% CI 0.60-0.73) in triplet versus doublet therapy. The relative risk of Grade 3 diarrhea, fatigue, and thrombocytopenia was higher with triplet therapy.

Ruggeri et al. conducted a literature search through December 2014, which included RCTs with median PFS, OS, or TTP as primary or secondary outcomes in relapsed/refractory MM. A Bayesian network meta-analysis was used with a fixed effects model since direct comparisons in the network were limited to one or two clinical trials. Trials conducted in patients treated with three or more prior lines of therapy were excluded to reduce heterogeneity across studies. Sixteen regimens were incorporated within two networks, as it was not possible to link all regimens within a single network. The larger of these networks revealed CFZ+LEN+DEX to be the most effective treatment followed by LEN+DEX and then BOR. The smaller of these networks suggested that PAN+BOR+DEX was the most effective.

Appendix G. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants with Relapsed or Refractory Multiple Myeloma (NCT02136134) **Sponsor** **Janssen Research & Development, LLC**	Phase III open-label RCT	DARA + BOR + DEX vs. BOR + DEX	N=497 • ≥1 prior therapy • Progressive disease • ECOG PS ≤2 • ≥Partial response to ≥ 1 prior regimen	Primary • PFS (3 years) Secondary • TTP • ORR • DOR • Time to response • OS	March 2017
A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma (NCT02076009) **Sponsor** **Janssen Research & Development, LLC**	Phase III open-label RCT	DARA + LEN + DEX vs. LEN + DEX	N=571 • Measurable disease • ≥1 prior therapy • Progressive disease • ECOG PS ≤2 • ≥Partial response to ≥ 1 prior regimen	Primary • PFS (until 3 years) Secondary • TTP • ORR • DOR • OS	September 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
A Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly Versus Twice-weekly Carfilzomib Dosing (ARROW) (NCT02412878) **Sponsor** **Onyx Therapeutics, Inc.**	Phase III open-label RCT	Once-weekly CFZ (70 mg/m^2) + DEX vs. twice-weekly CFZ (27 mg/m^2) + DEX	N=460 • Relapsed & refractory MM • 2-3 prior therapies • Prior exposure to an IMiD • Prior exposure to a PI • ≥Partial response to ≥ 1 prior regimen • Measurable disease • ECOG PS ≤1 • Left ventricular ejection fraction (LVEF) ≥ 40% • Adequate organ and bone marrow function	Primary • ORR (19 months) Secondary • PFS • OS • AEs	April 2017

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
Trial of Elotuzumab with or without Pomalidomide and Low-dose Dexamethasone to Treat Refractory and Relapsed and Refractory Multiple Myeloma (NCT02654132) **Sponsor** **Bristol-Myers Squibb**	Phase II open-label RCT	ELO + POM + DEX vs. POM + DEX	N=121 • ≥2 prior lines of therapy which included ≥2 consecutive cycles of LEN and a PI (alone or in combination) • Refractory or relapsed and refractory MM • ≥Partial response to previous treatment with PI, LEN, or both, but progressed within 6 months, and refractory to last treatment • Measurable disease • ECOG PS ≤2	Primary • PFS (14 months) Secondary • ORR • OS	May 2017

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
Phase II Randomised Trial of Cyclophosphamide and Dexamethasone in Combination with Ixazomib in Relapsed or Refractory Multiple Myeloma. (NCT02461888) **Sponsor** **University of Leeds**	Phase II open-label RCT	IX + cyclophosphamide + DEX vs. cyclophosphamide + DEX	N=250 • Age ≥18 • Measurable disease • Relapsed or relapsed & refractory MM following exposure to thalidomide, LEN and BOR • ECOG PS ≤2 • Platelet count ≥50x109/L • Absolute neutrophil count ≥1.0 x 109/L • Haemoglobin > 9 g/dL • ALT and/or AST ≤3 x upper limit of normal • Creatinine clearance ≥ 30 ml/min • Bilirubin ≤1.5 x upper limit of normal	Primary • PFS (36 months) Secondary • Maximum response • TTP • DOR • OS • AEs • Treatment compliance • QoL • Cost effectiveness	May 2017
Panobinostat/ Bortezomib/ Dexamethasone in Relapsed or Relapsed-and-refractory Multiple Myeloma (NCT02654990) **Sponsor** **Novartis Pharmaceuticals**	Phase II open-label RCT	PAN (20 mg 3x week) + BOR (s.c.) + DEX PAN (20 mg 2x week) + BOR (s.c.) + DEX PAN (10 mg 3x week) + BOR (s.c.) + DEX	N=240 • Relapsed or refractory MM • Measurable disease • 1-3 prior therapies • Prior IMiD exposure • Acceptable lab values • Not primary refractory or refractory to BOR	Primary • ORR up to 8 cycles Secondary • ORR (70 months) • Complete response rate • TTP • Time to response • DOR • EORTC-QoL	October 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
Study of Pomalidomide and Low Dose Dexamethasone with or without Pembrolizumab (MK-3475) in Refractory or Relapsed and Refractory Multiple Myeloma (rrMM) (MK-3475-183/KEYNOTE-183) (NCT02576977) **Sponsor** **Merck Sharp & Dohme Corp.**	Phase III open-label RCT	Pembrolizumab + POM + DEX vs. POM + DEX	N=300 • Measurable disease • ≥2 prior therapies • Prior IMiD and PI (alone or in combination) • Failed therapy with IMiD or PI • ECOG PS ≤1	Primary • PFS (33 months) • OS Secondary • ORR	June 2018
Safety and Efficacy of Pomalidomide, Bortezomib and Low-dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma (NCT01734928) **Sponsor** **Celgene Corporation**	Phase III open-label RCT	POM + BOR + LoDEX vs. BOR + LoDEX	N=544 • Age ≥18 • Measurable disease • Relapsed or refractory MM • 1-3 prior therapies • Prior LEN for at least 2 cycles	Primary • PFS (1 year) Secondary • OS (5 years) • AEs • ORR • DOR	April 2022

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Outcomes	Estimated Completion Date
Pomalidomide in Relapsed and Refractory Multiple Myeloma (RRMM) (NCT02406222) **Sponsor** **University of Leeds**	Phase II open-label RCT	POM + DEX + Cyclophosphamide vs. POM + DEX	N=250 • Measurable disease • Relapsed and/or refractory MM • ≥2 prior therapies • Prior LEN and PI • Failed tx with LEN and PI • Adequate prior alkylator therapy • Life expectancy ≥3 months • Absolute neutrophil count ≥ 1.0 x109 /L • Platelet count ≥ 30 x 109/L • CrCL > 30 mL/min • Corrected serum calcium ≤ 3.5 mmol/L • Haemoglobin ≥ 8 g/dL • Aspartate aminotransferase or Alanine aminotransferase < 3 times ULM • Serum total bilirubin < 17 µmol/l • Age ≥18	Primary • PFS (72 months) Secondary • Max. overall response • Response to tx • Clinical benefit rate • Time to max. response • DOR • OS • Compliance • AEs	September 2020

Source: www.ClinicalTrials.gov (Note: studies listed on site include both clinical trials and observational studies)