Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness and Value

Draft Report

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Institute for Clinical and Economic Review

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Stakeholder Input

The following stakeholders provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these stakeholders is responsible for the final contents of this report, however, which is solely the responsibility of the ICER team and its affiliated researchers.

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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
CI	Confidence interval
CFZ	Carfilzomib
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
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

An executive summary will be provided as part of the full Evidence Report.

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 that emerge into the bloodstream. Ultimately, the proliferation of plasma cells can cause bone and skeletal damage, anemia, hypercalcemia, neutropenia, and renal failure.[1] 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 5 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 Millenium) as well as the second-generation IMiD lenalidomide (Revlimid®, Celgene), which has largely supplanted earlier use of thalidomide. These agents have been used following treatment with autologous stem cell transplant or as first-line treatment in those ineligible for transplant due to age, frailty, and/or organ dysfunction. 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.

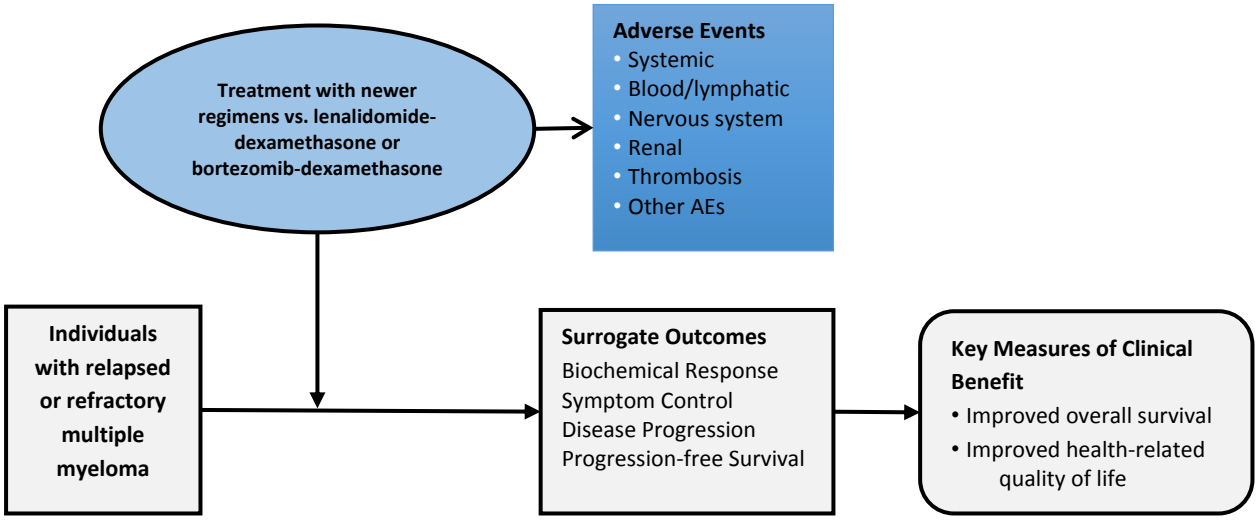
Scope of the Assessment

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.[3]

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[4]; among relapsed patients, survival has more than doubled (median of 2.5 vs. 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.[5] In the setting of relapsed and/or refractory disease, further treatment is guided by two major factors: (1) the presence of aggressive disease; and (2) the level and duration of response to prior treatment. 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. 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).[8]

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.[9] 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.[10]

With the development of multiple new therapies for MM, treatment options for clinicians have greatly expanded. However, in current practice the appropriate use and sequence of available agents is far from standardized. 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.[11,12]

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 triple therapy and "treat to progression" labeling for the newest agents.[13] 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.[14,15] 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.[16,17]

Definitions[18,19]

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; 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

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 eliminate 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. 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.[20] Key attributes of the drugs considered for this review can be found in Table 1.

Newer agents described below 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 a surrogate for overall survival in clinical practice, as they have not been shown to be universally predictive of 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 Strength	Treatment Duration	Unit Price (USD)
Carfilzomib (CFZ) (Kyprolis®; Onyx/Amgen)	Proteasome inhibitor	Intravenous *Powder for solution*	20-27 mg/m^2	18 cycles	$1,861.95 for 60 mg vial
Daratumumab (DARA) (Darzalex™; Janssen Biotech)	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 monoclonal 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 Millenium)	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	$502.69/cap
Bortezomib (BOR) (Velcade®; Takeda Millenium)	Proteasome inhibitor	Intravenous or subcutaneous *Powder for solution*	1.3 mg/m^2	8 cycles$^{\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)

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). 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

			Primary End Point		Secondary End Point	
Cancer Type	Patient Population	Current Baseline Median OS (months)	Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	Improvement in 1-Year Survival Rate (%)*	Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	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[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	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; 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.[21]

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.[22-24] Pre-clinical studies of bortezomib (Velcade®, Takeda Millenimum) showed a direct inhibition of MM cell lines that had shown resistance to other therapies; it was approved for use in both newly-diagnosed and relapsed MM patients in 2003. Carfilzomib (Kyprolis®, Onyx/Amgen) is a newer-generation PI that was first approved in 2012 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.[25] The most recent entrant to the class is ixazomib (Ninlaro®, Takeda Millenium), 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.[26-28] Thalidomide (Thalomid®, Celgene) and its analogue lenalidomide (Revlimid®, Celgene) were both FDA-approved in 2006 in combination with dexamethasone for newly-diagnosed patients

and those who had received one prior line of treatment, respectively. A second thalidomide analogue, pomalidomide (Pomalyst®, Celgene), was approved for use with 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.[29] 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.[30]

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.[31] 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.[32] 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.[33] 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 with at least three prior lines of treatment. Combination studies with PI and IMiD therapy are ongoing. Elotuzumab (Empliciti™, Bristol Myers-Squibb) is an immunostimulatory antibody to CS1, a signaling lymphocyte activating-molecule that is highly expressed on both normal and MM plasma cells.[34] Early studies of elotuzumab showed little to no clinical response when used as monotherapy,[35] 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[36]. We reviewed Express Scripts coverage policy recommendations as well, and found that ExpressScripts lists carfilzomib, daratumumab, ixazomib and pomalidomide on its plan preferred list, and lists elotuzumab and panobinostat as non-plan preferred.

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,[11] for each regimen within the scope, as well as guidelines from the National Institute for Health and Care Excellence (NICE)[37] and the International Myeloma Working Group (IMWG).[12] Specifically, NICE has published a myeloma pathway that recommends bortezemib monotherapy after a patient's first relapse, and subsequently treatment with lenalidomide with 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

The NICE guidance evaluating carfilzomib with lenalidomide and dexamethasone after prior therapy was suspended in January 2016. The manufacturer withdrew the submission.[38]

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 1 evidence and with a footnote specifying an indication for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent.

NICE Guidelines

NICE guidelines regarding daratumumab are currently in development.[39]

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 on the basis of category 1 evidence and with a footnote specifying an indication for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent.

NICE Guidelines

NICE guidelines regarding elotuzumab are currently in development.[40]

Ixazomib

NCCN Guidelines

The NCCN guideline update in January 2016, reflected in version 3.2016, added ixazomib with lenalidomide and dexamethasone to the 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.[41]

Panobinostat

NCCN Guidelines

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

NICE Guidelines

NICE guidelines state that panobinostat, in combination with bortezomib and dexamethasone, is recommended as a possible treatment for people with relapsed or refractory multiple myeloma and have already had at least two other treatments including bortezomib and an immunomodulatory drug.[37]

Pomalidomide

NCCN Guidelines

The NCCN guidelines include pomalidomide plus dexamethasone as a preferred regimen for patients who have received at least two prior therapies, including an immunomodulatory agent and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. NCCN designates this regimen as category 1.

NICE Guidelines

The NICE guidelines do not recommend treatment with pomalidomide plus dexamethasone for treating relapsed/refractory multiple myeloma patients who have had at least two prior therapies, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.[37]

IMWG Recommendations[12]

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

For first relapse:

- In patients who experience a high quality, prolonged response with minimal toxicity to initial therapy, re-treatment can be considered if they have obtained at least a 6–9 month treatment-free interval. The alternative is to change to a different class of drug and reserve the original treatment scheme for second relapse.
- Patients who experience suboptimal response or significant toxicity with initial therapy should receive a regimen that incorporates at least one agent to which the patient has not been previously exposed.
- There is no specific preference between regimens that contain lenalidomide, bortezomib, or both drugs; the choice of regimen should be based on response and tolerability to immediate prior therapy, current clinical status and co-morbidities of the patient, and access and availability of agents.
- Patients with poor prognosis disease characteristics at time of relapse should be considered for three- or four-drug regimens while those with indolent disease characteristics be considered for one- or two-drug combinations, recognizing that randomized studies are necessary to validate these recommendations.
- Patients with poor prognosis disease characteristics should be treated until disease progression recognizing the risk of rapid relapse in the absence of sustained exposure to chemotherapy. Treatment-free intervals can be considered in patients with indolent disease characteristics based on discretion of the treating physician and preferences of the patient.
- Carfilzomib and pomalidomide should be primarily used for patients refractory and/or intolerant to both bortezomib and lenalidomide.

For second relapse and beyond:

- Clinical trial participation should be offered if an appropriate study is available.
- Patients in second relapse or beyond should receive a salvage regimen incorporating at least one agent to which there has not been prior evidence of resistance or intolerability.

- Patients with aggressive disease characteristics at time of relapse should be considered for three- or four-drug regimens while those with indolent disease characteristics be considered for one-or two-drug regimens, and here in cytotoxic agents can be added to appropriate proteasome inhibitor and IMiD-based combinations.
- Patients in second relapse and beyond should receive ongoing therapy until the particular regimen is no longer tolerated or there is evidence of disease progression, at which time an alternative regimen should be chosen.

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 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 vs. 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.[42] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[3] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Figure B1.

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 Figure B1.

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.

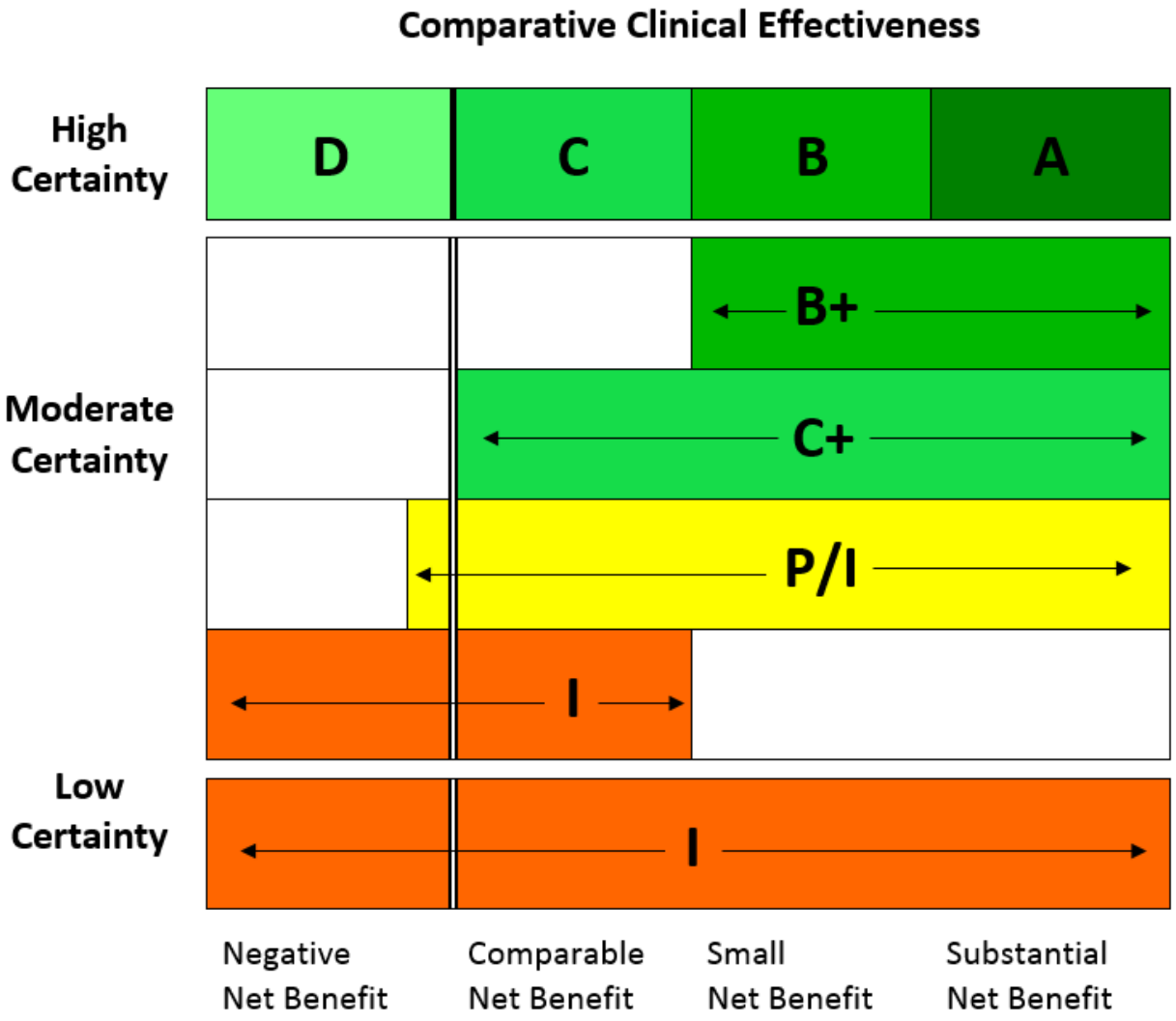
Further information on methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data can be found in the appendices.

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.[43]

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. We identified one published Phase III study each of CFZ+LEN+DEX and ELO+LEN+DEX, both compared to LEN+DEX alone.[44,45] IX+LEN+DEX was also compared to LEN+DEX in a Phase III trial (TOURMALINE-MM1), but this study has not yet been published; information was gleaned from available conference abstracts as well as FDA prescribing information and review materials.[46] 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.[47,48]

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.[49,50]

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.[51-53] 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

The six key studies of interest for this review 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[a] 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. Trial populations were similar with respect to

[a] 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

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.[44-47]

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.[48] 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.[48] Patients in the DARA trial also had a median of five previous treatments, and 88% were refractory to LEN.[49]

Quality of Individual Studies

Using criteria from U.S. Preventive Services Task Force (USPSTF), we rated two publications of one RCT to be of good quality.[47,54] 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.[44,45,48,51-53,55-58] 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.[49,50] 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[44] **Open-label RCT** **Phase 3** **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[49] **Open-label single-arm study** **Phase 2** **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 • 12 mo. OS: 64.8% (95% CI: 51.2-75.5) • Median PFS: 3.7 m • ORR: 29.2%		
ELOQUENT-2[45] **Open-label RCT** **Phase 3** **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: 0.71 (95% CI: 0.54-0.93) • 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[46] **Double-blind RCT** **Phase 3** **(unpublished)** **Ixazomib (IX)**	• Median age: 66 • ECOG=2: 6% • ISS Stage III: 13% • Previous SCT: 57% • High risk: 19% • Prior regimens (median): 2 • Prior BOR: 69% • Prior LEN: 12%	**IX+LEN+DEX** (n=360)	**Placebo+LEN+DEX** (n=362)	• D/C due to AEs: 13% • SAEs: 40% • 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=0.012)		
		• Median PFS: 20.6 m • ORR: 78%	• Median PFS: 14.7 m • ORR: 72%, p<0.001	
PANORAMA-1[47] **Double-blind RCT** **Phase 3** **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: 0.87 (95% CI: 0.69-1.10; p=0.26) • 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[48] **Open-label RCT** **Phase 3** **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.

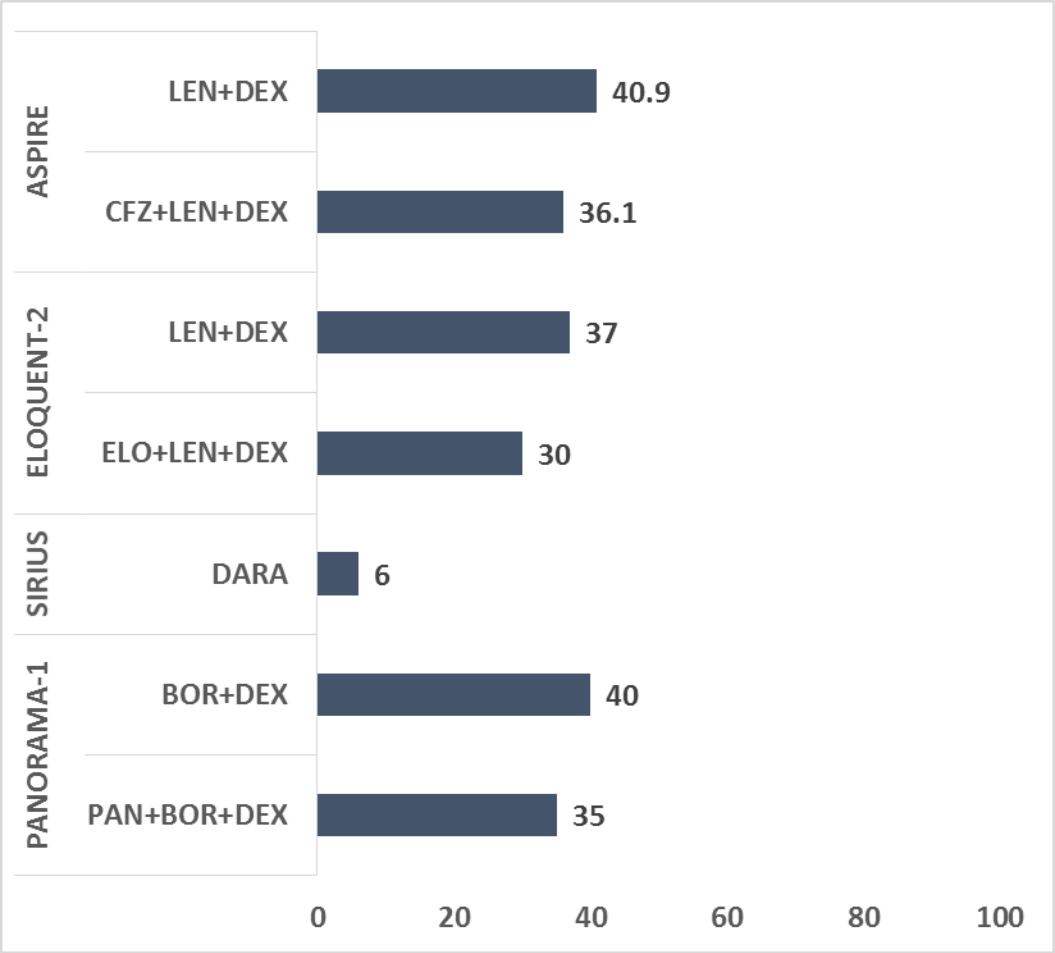
Overall Survival (OS)

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.[59] The current data for OS among the regimens of interest are relatively limited. Four of the six 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).[48] 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=0.5426).[60]

In an interim analysis of overall survival, ELO+LEN+DEX improved a 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).[61] 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).[44] No data on overall survival are currently available for DARA or IX+LEN+DEX.

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, PAN+BOR+DEX, and DARA. Similar absolute reductions in reported deaths (~5-7%) were noted in the trials of CFZ, ELO, and PAN, although differences were not tested statistically. The absolute rate of death (6%) was lower in the single-arm SIRIUS trial of DARA relative to these other trials (30-40%), in all likelihood due to the much shorter duration of follow-up (median of 9 months vs. 23-32 months for the other drugs).[44,45,47,49]

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 statistically-significantly improved among patients with ≥2 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.[61] Data from an ASH abstract of the trial of PAN+BOR+DEX focus only on the subset of patients with ≥2 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).[60]

Patients in the trial of POM+LoDEX had more advanced disease, and this subgroup analysis is presented for patients with ≤3 versus >3 prior lines of treatment. A statistically-significant improvement in OS was observed among patients with ≤3 prior lines of treatment (median 11.1 vs. 6.9 months; HR 0.56, 95% CI 0.33-0.96; p=0.02).[56,62] In contrast, the hazard ratio for patients with >3 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, improvements in OS were not statistically-significant for patients with either the del(17p) or t(14;16) high-risk mutations.[61] 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.[48] 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).[48]

Progression Free Survival (PFS)

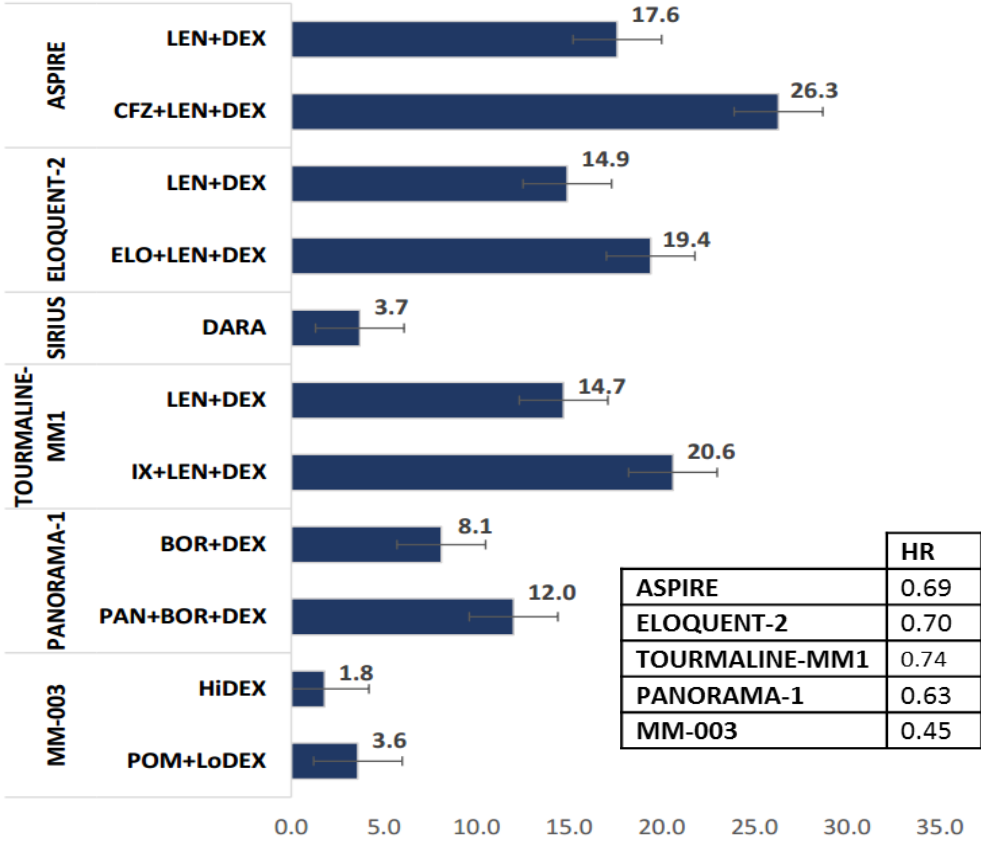
As is standard for regulatory submissions, all of the key trials other than the SIRIUS study of DARA used progression free survival (PFS) as the primary endpoint of the study. PFS is calculated from the time of the start of treatment to disease progression or death. It has been used as a surrogate marker for duration of overall survival, but evidence on its predictive power in relapsed and/or refractory disease is mixed (see "Topic in Context"). As is shown in Figure 4, all of the MM regimens evaluated with RCTs showed statistically-significant improvement in PFS relative to control treatment.[44-49] 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.[21] 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 censored observations. As described further in the "Controversies

and Uncertainties" section, the FDA Advisory Committee questioned the veracity of the PFS finding for the overall sample, due to censoring, drug discontinuation, and other concerns.[63]

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).[44,45,47] The one exception was the pivotal trial of IX+LEN+DEX, which showed a somewhat better HR vs. LEN+DEX alone (0.58) in patients with two or more prior treatments compared with those treated with one prior line (0.88).[64] We have no explanation for why this regimen would have better performance in more heavily-pretreated patients; this difference may be better understood when peer-reviewed publications of this trial are available.

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 Advisory Committee 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).[54] 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 ≤3 versus >3 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 vs. HiDEX treatment.[56,62] 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 vs. 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).[48,65,66] The trial of IX+LEN+DEX presented data only for the high-risk subgroup; risk reduction versus LEN+DEX was somewhat better in comparison to findings for the overall sample (0.54 vs. 0.74 respectively).[46,67]

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).[44,48,62] 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.

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[44]	All patients[44]	Patients with 1 prior line[68]	Patients with 1 prior line[68]	Patients with ≥2 prior lines[68]	Patients with ≥2 prior lines[68]
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[45]	All patients[45]	Patients with 1 prior line[45]	Patients with 1 prior line[45]	Patients with 2 or 3 prior lines[45]	Patients with 2 or 3 prior lines[45]
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[46]	All patients[46]	Patients with 1 prior line[64]	Patients with 1 prior line[64]	Patients with 2 or 3 prior lines[64]	Patients with 2 or 3 prior lines[64]
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[69]	All patients[69]	Patients with 1 prior line[69]	Patients with 1 prior line[69]	Patients with 2 or 3 prior lines[69]	Patients with 2 or 3 prior lines[69]
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[48]	All patients[48]	Patients with ≤3 prior lines[56,62]	Patients with ≤3 prior lines[56,62]	Patients with >3 prior lines[56,62]	Patients with >3 prior lines[56,62]
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 vs. 2-3). We also could not include DARA or POM+LoDEX in the network, the former because methods to incorporate single-arm data in a network meta-analysis are immature and unvalidated,[70,71] the latter because the trial population had more advanced disease than the patients in the trials of CFZ, ELO, and IX in combination with LEN+DEX, as well as PAN+BOR+DEX.

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 E).

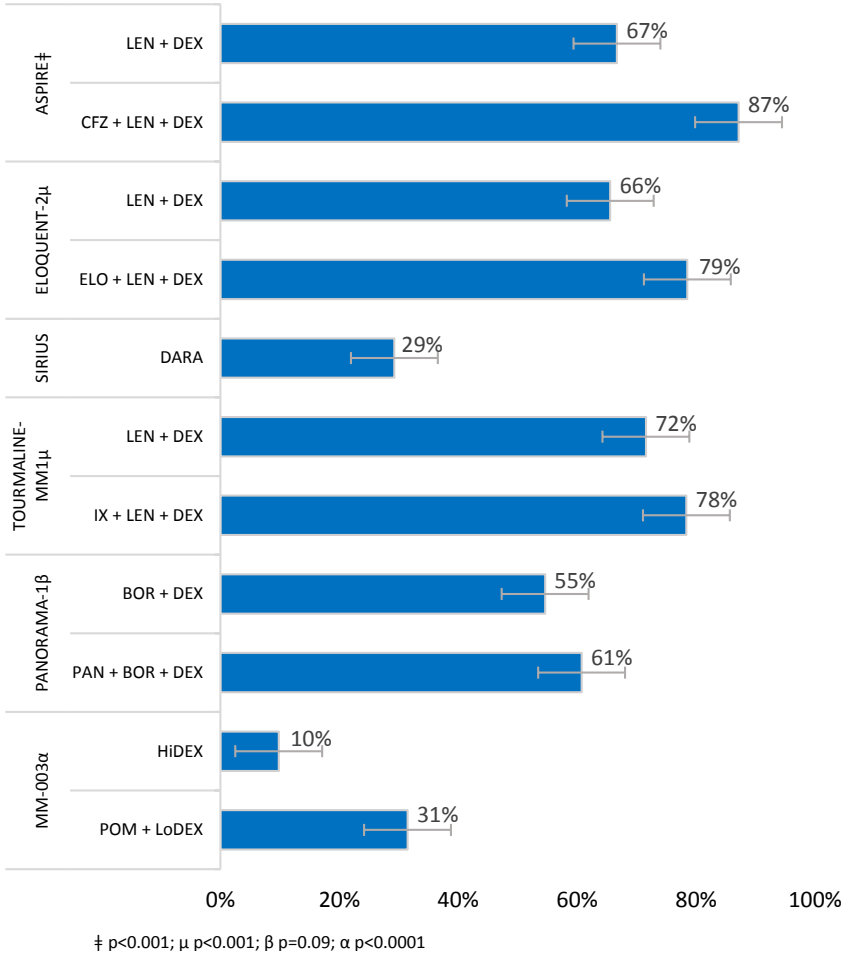
Overall Response Rate (ORR)

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).[44,45,47,48] 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).[54] 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<0.001; 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 three of our six regimens, all of which 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.[44] 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;[72] using this standard, the MID was met at both Cycle 12 and Cycle 18.

Patients randomized to POM+LoDEX did not have improved global health status relative to those receiving HiDEX therapy, but did have statistically-greater improvements in the physical functioning, emotional functioning, health utility, pain, fatigue, disease symptoms, and side effects of treatment domains.[55] 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.[b] No differences in HrQoL were reported in the ELOQUENT-2 trial of ELO+LEN+DEX versus LEN+DEX.[45] All three of these trials used open-label designs, raising concerns that gains in quality of life might have been overstated by patients who knew that they were receiving a newer regimen rather than historical standard treatment.

Data on HrQoL have not yet been presented or published for IX+LEN+DEX, 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,[c] although this was not reported for IX. Discontinuation of study therapy due to adverse events (AEs) ranged between 5 and 15% for all regimens except for PAN+BOR+DEX (36%).[47] As discussed in the

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

"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.[63]

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.[47] The label for PAN includes a black box warning that specifically mentions severe diarrhea.[73] 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. 13-22%).[47]

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.[74] However, differences in the incidence of DVT/PE (2% vs. 1% for POM+LoDEX vs. HiDEX) were similar to those seen with other regimens (3.1-3.6% of patients treated with ELO or CFZ in combination with LEN+DEX, compared to 2.3-2.5% for LEN+DEX).[44,45,48] 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.[75] 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.[44]

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.[44-48]

Table 5. Measures of Safety, Including Commonly Reported Grade 3-4 Adverse Events

	CFZ+LEN+DEX[44]	DARA[49]	ELO+LEN+DEX[45]	IX+LEN+DEX[46,67]	PAN+BOR+DEX[47]	POM+LoDEX[48]
Discontinuation due to AEs	15%	5%	13%	13%	36%	9%
All serious AEs	60%	30%$^{\alpha}$	65%	40%$^{\beta}$	60%	61%
Treatment-related Death	2%	0	2%‡	NR	3%	4%
Grade ≥3 AEs						
Fatigue	8%	3%	8%	NR	24%	5%
Diarrhea	4%	1%*	5%	6%	25%	1%
Peripheral neuropathy	3%	NR	4%	2%	18%	1%
Anemia	18%	24%	19%	9%	18%	33%
Thrombocytopenia	17%	19%	19%	13%	67%	22%
Neutropenia	30%	12%	34%	19%	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.[76,77] 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.[18,78,79] 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.[d,63,80,81]

The evidence base for DARA is less robust than that for other regimens given that it is currently limited to two single-arm Phase II studies. 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 and safety of IX is also hampered somewhat by the lack of published, peer-reviewed data from the Phase III trial. And, finally, the comparison of POM+LoDEX to HiDEX was justified as the standard salvage treatment for heavily pretreated patients at the time of trial design. 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.

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 even robust indirect comparisons of the regimens in our review. As noted in the "Topic in Context" section,

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

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).[2,63] 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%).[2,44-49]

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." Although concerns over toxicity and the limitations of the evidence remain, a subset analysis in patients who had received prior BOR and IMiD therapy revealed a more favorable risk/benefit profile for the drug. However, 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. This is because observed PFS benefits were modest (approximately two months), so questions remain as to whether its benefits outweigh the risks as a salvage treatment in those refractory to both prior LEN and BOR therapy. Certainty is also moderate because the incremental benefits are unknown relative to any salvage therapy other than high-dose dexamethasone. Because of these concerns, 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, we did not identify a single randomized or comparative study 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, and there is 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 require frequent office visits. Travel to a physician's office or clinic and the requirement for an injection may pose a burden to MM patients and caregivers at various stages of disease, so all-oral treatment may be an attractive option for some. Conversely, the monitoring and opportunity for patient education and counseling at these visits may offer additional benefits.

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 budgetary impact of different treatment regimens. Budgetary 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.

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

We did not identify any 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

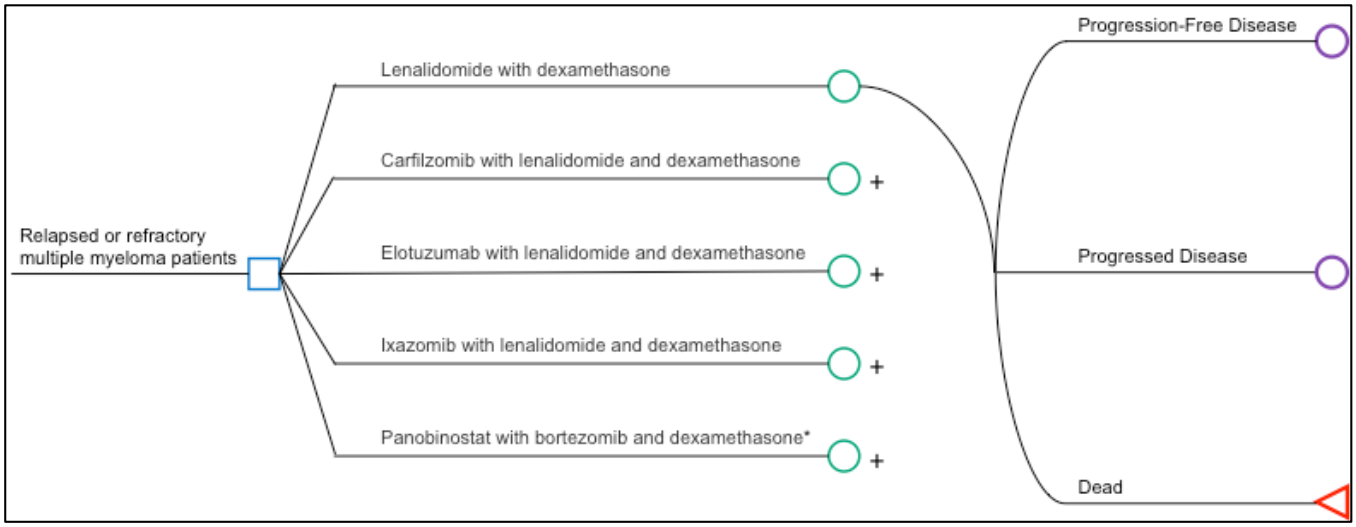
Cost-Effectiveness Model: Methods

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.

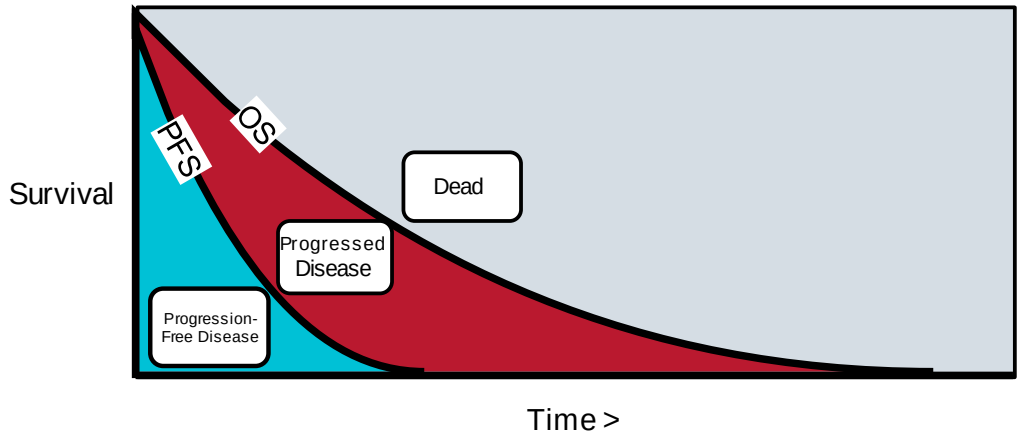
Outcomes were modeled using a partition survival approach and three health states: progression-free (PF), progression (PRO), and death (see Figure 7). Advantages of partition survival models are that they are less data intensive than other more complex modeling approaches, and that they leverage commonly 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.[82]
Mean height (m)	1.7	Talamo et al.[82]

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 vs. LEN+DEX could be estimated. POM+LoDEX was studied in a population with more advanced disease (i.e., refractory to BOR and/or LEN) and so its 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.[83] 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.[84,85] 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.[86] This analysis has been used widely, including for support of previous model submissions to HTA agencies.[87] 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 an unadjusted estimate of the PFS to OS relationship from the baseline comparator study of LEN+DEX (3.42-month increase in OS for each additional month of median PFS).[88]

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 >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

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).[89] 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[90]
Progression-free disease, off treatment	0.84	Beta	AMGEN/ASPIRE[90]
Progressed disease	0.65	Beta	AMGEN/ASPIRE[90]
Third-Line			
Progression-free disease, on treatment	0.65	Beta	MM-003/NICE[87]
Progression-free disease, off treatment	0.72	Beta	Acaster et al.[91]
Progressed disease	0.61	Beta	MM-003/NICE[87]
Disutility for any grade 3/4 adverse event	-0.076	Beta	MM-003/NICE[87]

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 two 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), and 2) using BOR+DEX as the comparator.

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 vs. 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 $211,000 for ELO+LEN+DEX to approximately $268,000 for IX+LEN+DEX versus LEN+DEX, nearly all of which were driven by increased drug costs rather than progression, supportive care, or adverse event costs. 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 $323,468, vs. $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 were estimated to be greater than $250,000 per QALY for each second-line regimen versus 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). In addition, adverse event costs are lower for each of the newer regimens vs. LEN+DEX as an artifact of more complete reporting of adverse events occurring with ≥5% frequency in the trial publications and prescribing information for LEN+DEX. Finally, our drug cost estimates 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 vs. Potluri: approximately $310,000).[92]

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 $195,000 for ELO+LEN+DEX to approximately $244,000 for IX+LEN+DEX versus LEN+DEX, nearly all of which were again driven by increased drug costs. Incremental cost effectiveness ratios were estimated as approximately $290,000 per QALY for ELO+LEN+DEX, $313,000 per QALY for CFZ+LEN+DEX, and $436,000 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) vs. 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 (vs. 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.

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	**$287,508**	**$518,819**	**$498,872**	**$555,888**
Drug Costs	$240,913	$461,843	$430,979	$508,247
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	$7,166	$2,614	$6,702	$2,087
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**	**4.70**	**4.65**	**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)	**--**	**$267,464**	**$255,498**	**$390,639**
Total Costs	**--**	**$231,311**	**$211,364**	**$268,380**
Drug Costs	--	$220,929	$190,065	$267,334
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	--	-$4,552	-$464	-$5,078
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	**$261,718**	**$482,576**	**$457,129**	**$506,041**	**$195,096**
Drug Costs	$216,151	$427,021	$391,837	$459,683	$136,366
Supportive Care Costs	$473	$1,779	$2,364	$2,255	$415
Administration Costs		$8,113	$13,394		$3,128
Progression Costs	$37,929	$43,048	$42,833	$42,015	$46,984
Adverse Event Costs	$7,166	$2,614	$6,702	$2,087	$8,203
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	2.67

Incremental Results vs. LEN-DEX

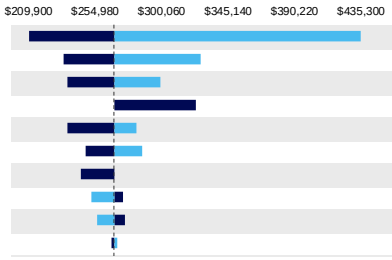
3rd Line	LEN-DEX	CFZ-LEN-DEX	ELO-LEN-DEX	IX-LEN-DEX	PAN-BOR-DEX
ICER (vs. L+Dex)	**--**	**$312,840**	**$289,425**	**$435,855**	**-$46,925**
Total Costs	**--**	**$220,858**	**$195,411**	**$244,324**	**-$66,622**
Drug Costs	--	$210,870	$175,686	$243,532	-$79,784
Supportive Care Costs	--	$1,307	$1,891	$1,783	-$58
Administration Costs	--	$8,113	$13,394		$3,128
Progression Costs	--	$5,120	$4,904	$4,087	$9,055
Adverse Event Costs	--	-$4,552	-$464	-$5,078	$1,038
Total QALYs	**--**	**0.71**	**0.67**	**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 X. 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 vs. 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.

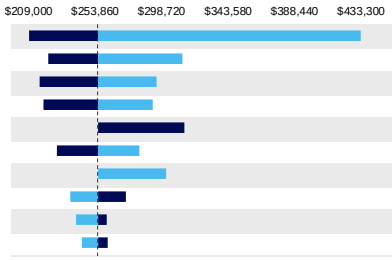
Figure 8. One-Way Sensitivity Analysis Results: Tornado Diagrams

2nd-line CFZ + LEN + DEX



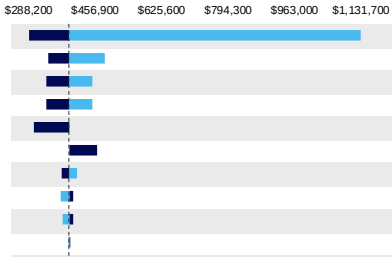
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, CL+Dex	0.57	0.83	$209,935	$435,250	$225,315
Felix Hazard Ratio	0.31	0.58	$233,392	$326,669	$93,277
Cost: Carfilzomib 60 mg vial	$1,489.56	$2,234.34	$236,354	$299,019	$62,665
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$323,312	$267,686	$55,626
Dose Intensity: CL+Dex Carfilzomib	72.8%	100.0%	$236,354	$283,180	$46,827
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$248,444	$286,929	$38,485
Cost: Carfilzomib vial sharing?	Yes	No	$245,178	$267,686	$22,508
2nd Line Utility, Progressed Disease	0.62	0.74	$273,742	$252,413	$21,329
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$274,841	$256,324	$18,517
Cost: Carfilzomib administration	$167.39	$251.09	$265,747	$269,625	$3,878

2nd-line ELO + LEN + DEX



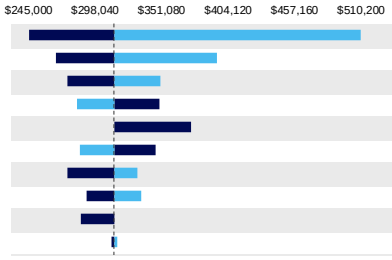
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, EL+Dex	0.57	0.86	$209,071	$433,253	$224,182
Felix Hazard Ratio	0.31	0.58	$222,381	$312,859	$90,479
Dose Intensity: EL+Dex Lenalidomide	40.8%	61.2%	$216,239	$295,152	$78,914
Cost: Elotuzumab 400 mg vial	$1,894.40	$2,841.60	$218,739	$292,652	$73,913
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$313,837	$255,696	$58,142
Cost: Elotuzumab 300 mg vial	$1,420.80	$2,131.20	$227,978	$283,413	$55,434
Dose Intensity: EL+Dex Elotuzumab	66.4%	99.6%	$255,696	$301,891	$46,195
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$274,381	$237,010	$37,370
2nd Line Utility, Progressed Disease	0.62	0.74	$261,489	$241,084	$20,405
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$262,524	$244,852	$17,672

2nd-line IX + LEN + DEX



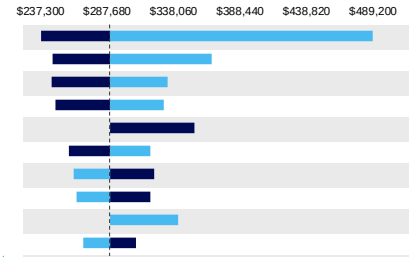
Parameter	Low Value	High Value	Low Result	High Result	Spread
2nd Line PFS HR, IL+Dex	0.59	0.93	$288,299	$1,131,627	$843,328
Felix Hazard Ratio	0.31	0.58	$338,300	$480,603	$142,303
Cost: Ixazomib 4 mg capsule	$2,312.00	$3,468.00	$332,338	$449,394	$117,056
Dose Intensity: IL+Dex Ixazomib	64.0%	96.0%	$332,338	$449,394	$117,056
Dose Intensity: IL+Dex Lenalidomide	80.0%	100.0%	$301,787	$390,866	$89,079
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$460,834	$390,866	$69,968
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$371,755	$409,976	$38,221
2nd Line Utility, Progressed Disease	0.62	0.74	$399,760	$368,442	$31,318
2nd Line Utility, Progression-free, on treatment	0.78	0.88	$401,240	$374,383	$26,857
Cost: Deep Vein Thrombosis	$25,316	$37,974	$391,622	$390,110	$1,512

3rd-line CFZ + LEN + DEX



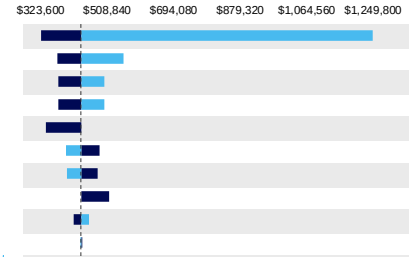
Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, CL+Dex	0.57	0.83	$245,024	$510,197	$265,173
Felix Hazard Ratio	0.31	0.58	$267,024	$395,405	$128,381
Cost: Carfilzomib 60 mg vial	$1,489.56	$2,234.34	$275,885	$350,220	$74,335
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$349,539	$283,463	$66,076
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$374,193	$313,052	$61,141
3rd Line Utility, Progressed Disease	0.49	0.73	$346,138	$285,740	$60,398
Dose Intensity: CL+Dex Carfilzomib	72.8%	100.0%	$275,885	$331,432	$55,547
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$291,100	$335,005	$43,905
Cost: Carfilzomib vial sharing?	Yes	No	$286,319	$313,052	$26,734
Cost: Carfilzomib administration	$167.39	$251.09	$310,752	$315,352	$4,600

3rd-line ELO + LEN + DEX



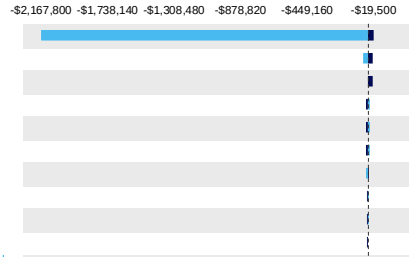
Parameter	Low Value	High Value	Low Result	High Result	Spread
3rd Line PFS HR, EL+Dex	0.57	0.86	$237,380	$489,156	$251,776
Felix Hazard Ratio	0.31	0.58	$246,490	$366,610	$120,120
Dose Intensity: EL+Dex Lenalidomide	40.8%	61.2%	$245,823	$333,392	$87,569
Cost: Elotuzumab 400 mg vial	$1,894.40	$2,841.60	$248,351	$330,864	$82,513
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$353,528	$289,607	$63,920
Cost: Elotuzumab 300 mg vial	$1,420.80	$2,131.20	$258,665	$320,549	$61,884
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$323,326	$262,257	$61,069
3rd Line Utility, Progressed Disease	0.49	0.73	$320,262	$264,309	$55,953
Dose Intensity: EL+Dex Elotuzumab	66.4%	99.6%	$289,607	$341,178	$51,570
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$309,743	$269,471	$40,272

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	$323,678	$1,249,789	$926,111
Felix Hazard Ratio	0.31	0.58	$369,322	$554,782	$185,460
Cost: Ixazomib 4 mg capsule	$2,312.00	$3,468.00	$371,212	$500,961	$129,750
Dose Intensity: IL+Dex Ixazomib	64.0%	96.0%	$371,212	$500,961	$129,750
Dose Intensity: IL+Dex Lenalidomide	80.0%	100.0%	$337,348	$436,087	$98,739
3rd Line Utility, Progression-free, on treatment	0.52	0.78	$486,498	$395,142	$91,356
3rd Line Utility, Progressed Disease	0.49	0.73	$482,390	$397,893	$84,497
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	$513,035	$436,087	$76,948
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	$414,296	$457,877	$43,581
Cost: Deep Vein Thrombosis	$25,316	$37,974	$437,013	$435,160	$1,853

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	-$19,598	-$2,167,763	$2,148,164
Cost: Lenalidomide 25 mg capsule	$402.15	$603.23	-$22,317	-$83,338	$61,021
Dose Intensity: L+Dex Lenalidomide	80.0%	100.0%	-$22,317	-$52,828	$30,511
Cost: Panobinostat 20 mg capsule	$977.78	$1,466.66	-$64,554	-$41,101	$23,453
Dose Intensity: PB+Dex Panobinostat	64.6%	96.8%	-$64,554	-$41,101	$23,453
3rd Line Utility, Progression-free, off treatment	0.58	0.86	-$66,788	-$43,694	$23,093
Felix Hazard Ratio	0.31	0.58	-$46,701	-$69,506	$22,805
Cost: Bortezomib 3.5 mg vial	$1,289.60	$1,934.40	-$60,222	-$45,434	$14,788
Dose Intensity: PB+Dex Bortezomib	60.6%	90.8%	-$60,222	-$45,434	$14,788
Cost: Bortezomib vial sharing?	Yes	No	-$63,496	-$52,828	$10,668

Results of our PSA analysis can be found in Appendix E. Our findings show substantial variability in model outcomes. However, incremental cost-effectiveness ratios never approached commonly-cited thresholds (i.e., $50,000 - $150,000 per QALY gained) for any regimen other than PAN+BOR+DEX.

We also ran a scenario analysis (see Appendix E) in which 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.

We also ran a 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.

6.4 Potential Budget Impact

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

Potential Budget Impact Model: Methods

Potential budgetary 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. 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 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[93], which equates to 0.0285% of the 2012 U.S. population[94]. Applying that rate to the projected 2016 U. S. population[95] 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[96]. 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 acknowledge that almost 50% 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."[93]

Given that "invasive cases" would generally exclude asymptomatic MM patients (as well as MGUS), 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 US 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 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. That is, we assumed that the three second-line regimens we examined would together achieve 75% uptake by year 5. 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 made this assumption because of the need for varied regimens beyond first- (or second-) line treatment, and the reported evidence of increased effectiveness over comparator regimens. 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, 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 US 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 15.

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 15. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US 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 16 presents the potential budgetary 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 budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $172,000 per patient receiving CFZ+LEN+DEX, $129,000 per patient receiving ELO+LEN+DEX, and $171,000 per patient receiving

IX+LEN+DEX. In this particular case, weighted potential budgetary impact is driven by a number of factors, including dosing frequency and dose intensity, dosing strategy (i.e., treat to progression vs. fixed-duration treatment), and the rate of progression for each regimen. For example, potential budget impact at one year is 50% greater for CFZ+LEN+DEX vs. IX+LEN+DEX, owing to higher costs and greater dose intensity for CFZ vs. IX. However, weighted potential budgetary impact at five years is nearly identical between the two regimens, as CFZ is given for a fixed duration (with LEN+DEX continuing as necessary), while the entire IX+LEN+DEX regimen is given until progression.

Over five years, the average potential budget impact per year is approximately $291.6 million for CFZ+LEN+DEX, or 32% of the budget impact threshold of $904 million for a new drug. Average potential budget impact per year is estimated to be approximately $218.2 million per year for ELO+LEN+DEX (24% of the threshold), and approximately $291.0 million for IX+LEN+DEX (32% of threshold).

Table 16. 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	$120,271	$204.1	8,485	$171,820	$291.6
ELO+LEN+DEX	33,941	1,697	$59,322	$100.7	8,485	$128,597	$218.2
IX+LEN+DEX	33,941	1,697	$79,903	$135.6	8,485	$171,498	$291.0
Total	33,941	5,091	$86,499	$440.4	25,455	$157,305	$800.8

*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 relative to LEN+DEX are shown in Table 17. We modeled the potential budgetary 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 budgetary impact is approximately $170,000 per patient receiving CFZ+LEN+DEX, $125,000 per patient receiving ELO+LEN+DEX, and $164,000 per patient receiving IX+LEN+DEX. Using PAN+BOR+DEX rather than LEN+DEX over the 5-year timeframe produces a negative potential budget impact of -$38,843, given its use for no more than 16 cycles (budget impact is positive for PAN+BOR+DEX in the first year given its higher acquisition costs).

Average potential budget impact per year is approximately $76 million for CFZ+LEN+DEX, approximately $56 million per year for ELO+LEN+DEX, approximately $73 million for IX+LEN+DEX,

and -$17.4 million for PAN+BOR+DEX. No regimen approached the potential budget impact threshold of $904 million for a new drug.

Table 17. 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	$124,375	$55.6	2,235	$169,511	$75.8
ELO+LEN+DEX	11,930	447	$65,390	$29.2	2,235	$125,469	$56.1
IX+LEN+DEX	11,930	447	$78,540	$35.1	2,235	$163,614	$73.1
PAN+BOR+DEX	11,930	447	$29,812	$13.3	2,235	-$38,843	-$17.4
Total	11,930	1,788	$74,529	$133.3	8,940	$104,938	$187.6

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

6.5 Value-Based Price Benchmarks

Value-based price benchmarks will be provided as part of the full Evidence Report.

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 $267,000/QALY for CFZ+LEN+DEX, $255,000/QALY for ELO+LEN+DEX, and approximately $391,000/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). 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.

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 budget impact for CFZ+LEN+DEX would go above an annual threshold of $904 million at an assumed uptake of 50%. Uptake of IX+LEN+DEX would need to approach 100% of eligible patients to exceed this annual threshold, while the budget impact of ELO+LEN+DEX would not exceed the threshold even at 100% 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.[86] 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.[97] 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 vs. LEN+DEX also found an incremental benefit for the former, albeit a smaller effect than that observed in our analysis.[98] 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 vs. 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.

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.

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

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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 labeling 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 US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[99,100]

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 ShowingResults of Literature Search for Multiple Myeloma

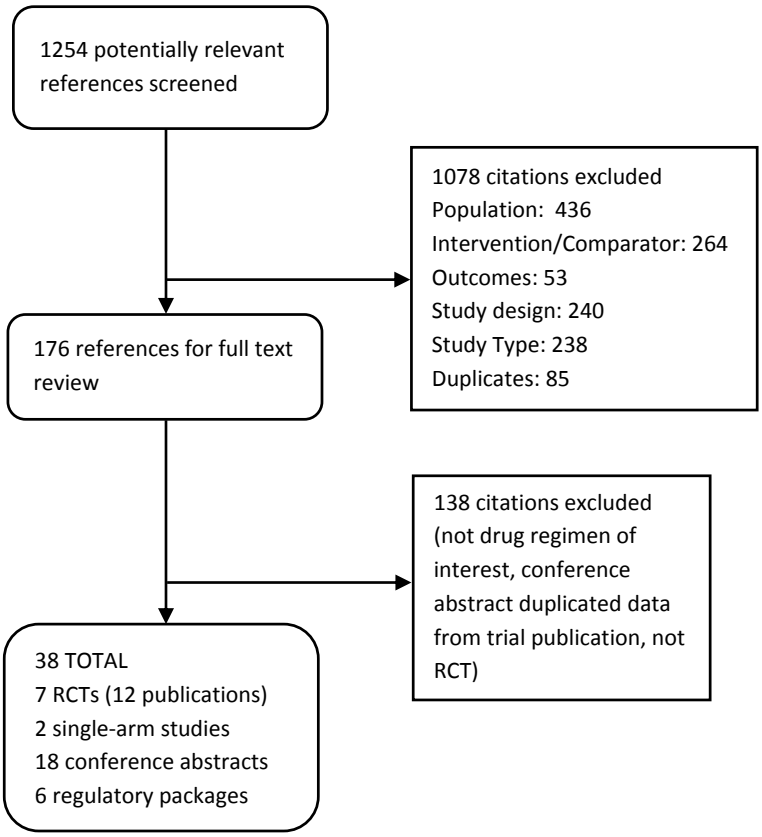


Table B1. Summary Evidence Table

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**[44] **(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)	Primary endpoint: 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 Secondary endpoints: 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**[65] **(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[68]** **(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 **Dimopolous MA Haematologica 2015[101]** **(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[102]** **(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**[49] **(SIRIUS)** ***poor***	Randomized Single-arm Multicenter Open-label Phase III Median f/u: 9.3 months; study is ongoing *Crossover permitted*	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): 64 (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) 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**[50] ***poor***	Nonrandomized Multicenter Open-label Phase II-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) c) (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% 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[45]

(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[103]** **(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**[53] **(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[104]

(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[105]

(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**[106] **(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)						
NCT01564537, unpub. **FDA Prescribing Information[46]** **(TOURMALINE-MM1)**	RCT Multicenter Double-blind Phase III *all oral triplet therapy	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 refractory MM s/p 1-3 prior lines not refractory to prior LEN or PI 18yr+ ECOG PS 0-2	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 (13) 2) 42 (12) High-risk, n (%) 1) 75 (21) 2) 62 (17)	Primary endpoint: PFS 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=0.012 Secondary endpoint: Overall response rate n (%) 1) 282 (78) 2) 259 (72) Complete response n (%) 1) 42 (12) 2) 24 (7) Partial response n (%) 1) 109 (30) 2) 118 (33) Median DOS months 1) 20.5 2) 15	Grade 3/4 AEs: marginally higher in intervention arm, d/t ↓plts. Rates of d/c were similar between arms. Intervention arm associated w/ low rates of peripheral neuropathy (common w/ BOR) and no cardiac or renal AEs.

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[67]** **(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% D/c 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[47]

(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[54]

(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>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[107]

(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[108]** **(PANORAMA-1)**	PANORAMA-1	*See PANORAMA-1* Subanalysis of patients who experienced diarrhea as AE	See *PANORAMA-1*	See *PANORAMA-1*	See *PANORAMA-1*	D/c 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[60]** **(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**[109] **(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**[69] **(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[48]

(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><td></td><td>1)</td><td>2)</td></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[57]

(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**[56] **(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[55]** **(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[58]

(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[62]

(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**[110] **(MM-003)**	*See MM-003* Subanalysis of patents 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**[111] **(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**[112] **(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[51]

(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)

D/c 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**[52] ***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[60]	All patients[60]			Patients with 2 or more prior lines, including BOR & IMiD[60]	Patients with 2 or more prior lines, including BOR & IMiD[60]
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[48]	All patients[48]	Patients with 3 or fewer lines[56,62]	Patients with 3 or fewer lines[62 56]	Patients with more than 3 lines[56,62]	Patients with more than 3 lines[62 56]
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 theray

	MM-003[48]			
	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

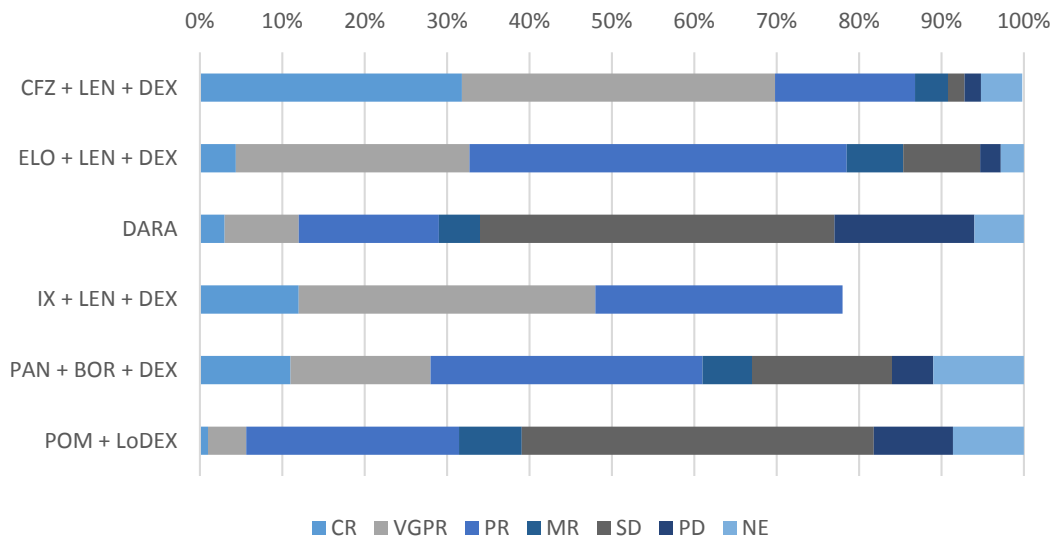
	ASPIRE					
	CFZ+LEN+DEX	**LEN+DEX**	**CFZ+LEN+DEX**	**LEN+DEX**	**CFZ+LEN+DEX**	**LEN+DEX**
	All patients[44]	**All patients[44]**	**Patients with high-risk cytogenetics[65]**	**Patients with high-risk cytogenetics[65]**	**Patients with standard-risk cytogenetics[65]**	**Patients with standard-risk cytogenetics[65]**
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[45]	**All patients[45]**	**Patients with high-risk cytogenetics[66]**	**Patients with high-risk cytogenetics[66]**	**Patients with standard-risk cytogenetics[66]**	**Patients with standard-risk cytogenetics[66]**
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[46]	**All patients[46]**	**Patients with high-risk cytogenetics[67]**	**Patients with high-risk cytogenetics[67]**		
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[48]					
	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[44]					
	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[482]	All patients[482]	Patients refractory to BOR & LEN[48,62]	Patients refractory to BOR & LEN[48,62,]		
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.[49,54,56,113] 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.[65]

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.[57]

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%[65]	79.2%[65]	87.0%[113]	87.3%[113]			
	LEN + DEX	73.5%[65]	59.6%[65]	70.1%[113]	64.4%[113]			
SIRIUS	DARA	29.4% (19.0-41.7)[49]	20.0% (5.7-43.7)[49]	≤3 prior Tx: 26.3% (9.1-51.2) >3 prior TX: 29.9% (20.5-40.6)[49]		28% (19.1-38.2)[49]	27.4% (18.7-37.5)[49]	26.4% (17.6-37.0)[49]
PANORAMA-1	PAN + BOR + DEX				58.9% (46.8- 70.3)[54]			
	BOR + DEX				39.2% (28.0-51.2)[54α]			
MM-003	POM + LoDEX	35.2%[57]	del(17p): 31.8% t(4;14): 15.9%[57]	≤3 prior Tx: 26% >3 prior TX: 34%[56]		30%[56]	31%[56]	29%[56]
	HiDEX	9.7%[57]	del(17p): 4.3%[57] 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	ISS I/II and absence of t(4;14), 17p13 del and þ 1q21 and age o55 years
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.[70] 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).[71]

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.

Results of Network Meta-Analysis

Table D1. Network Meta-Analysis: Overall Survival

ELO LEN DEX						
0.90 (0.63 to 1.28)	**CFZ LEN DEX**					
0.81 (0.36 to 1.82)	0.90 (0.41 to 2.00)	**PAN BOR DEX**				
0.71 (0.33 to 1.53)	0.78 (0.37 to 1.68)	0.87 (0.69 to 1.10)	**BOR DEX**			
0.71 (0.54 to 0.93)	0.79 (0.63 to 0.99)	0.88 (0.41 to 1.88)	1.01 (0.49 to 2.08)	**LEN DEX**		
0.67 (0.40 to 1.13)	0.75 (0.45 to 1.24)	0.83 (0.45 to 1.54)	0.96 (0.54 to 1.69)	0.95 (0.61 to 1.48)	**BOR**	
0.38 (0.26 to 0.56)	0.43 (0.30 to 0.61)	0.47 (0.23 to 0.96)	0.54 (0.28 to 1.06)	0.54 (0.41 to 0.71)	0.57 (0.40 to 0.81)	**DEX**

FE Model:
resdev, 8.164 vs. 7;
DIC = 2.081

Table D2. 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

Table D3. 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 D4. Network Meta-Analysis: Subgroup Analysis of PFS: 2-3 Prior Line of Therapies

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

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	9.9%	*	14.0%	14.8%	9.0%	*
Back Pain	2.3%	*	*	5.0%	0.6%	0.8%
Cataract	3.1%	*	*	6.3%	*	*
Deep Vein Thrombosis	8.2%	1.6%	*	5.7%	*	*
Diarrhea	3.1%	1.6%	2.0%	5.0%	6.0%	25.0%
Fatigue	6.5%	*	5.0%	12.3%	*	25.0%
Herpes Zoster/Simplex	*	6.3%	*	*	*	1.0%
Hyperglycemia	10.8%	*	5.0%	7.2%	*	*
Hypokalemia	6.2%	*	6.0%	4.7%	*	*
Infection	9.6%	32.8%	*	*	*	*
Lymphopenia	2.8%	*	*	8.8%	*	*
Motor Neuropathy	*	7.8%	*	*	*	*
Muscle Weakness	5.7%	*	*	1.9%	*	***
Nausea	1.7%	3.1%**	0.2%	0.9%	2.0%	6.0%
Neuropathic Pain	*	14.1%	*	*	*	*
Neutropenia	33.4%	17.2%	27.0%	24.8%	26.0%	*
Peripheral/Sensory Neuropathy	1.7%	18.8%	2.0%	3.8%	2.0%	17.6%
Pneumonia	8.5%	*	9.0%	13.8%	6.0%	12.6%
Psychiatric Reactions	*	7.8%	*	*	*	*
Thrombocytopenia	12.2%	34.4%	15.0%	11.3%	26.0%	*
Venous Thromboembolism	11.4%	*	4.0%	*	*	*
Vertigo	*	10.9%	*	*	*	*
Vomiting	*	**	*	0.3%	1.0%	7.0%

* Not reported
** Reported as "Nausea and vomiting"
*** Included in peripheral neuropathy

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[44]	
Carfilzomib	91.0%
Lenalidomide	80.5%
Dexamethasone	85.3%
ELO-LEN-DEX[66]	
Elotuzumab	83.0%
Lenalidomide	51.0%
Dexamethasone	45.0%
Dex (IV)	45.0%
IX-LEN-DEX[67]	
Ixazomib	80.0%
Lenalidomide	100.0%
Dexamethasone	100.0%
PAN-BOR-DEX[47]	
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	$1,038	Roy et al.[114]
Back Pain	$10,914	Roy et al.[114]
Cataract (DRG 125)	$3,669	CMS[115]
Deep Vein Thrombosis	$30,265	Roy et al.[114]
Diarrhea	$10,760	Roy et al.[114]
Fatigue	$6,946	Roy et al.[114]
Herpes Zoster/Simplex	$1,006	Roy et al.[114]
Hyperglycemia	$147	Roy et al.[114]
Hypokalemia	$1,773	Roy et al.[114]
Infection	$5,218	Roy et al.[114]
Lymphopenia	$172	Roy et al.[114]
Motor Neuropathy	$764	Roy et al.[114]
Muscle Weakness (DRG 566)	$3,577	CMS[115]
Nausea	$12,117	Roy et al.[114]
Neuropathic Pain	$730	Roy et al.[114]
Neutropenia	$165	Roy et al.[114]
Peripheral/Sensory Neuropathy	$825	Roy et al.[114]
Pneumonia	$16,249	Roy et al.[114]
Psychiatric Reactions (DRG 887)	$5,353	CMS[115]
Thrombocytopenia	$149	Roy et al.[114]
Venous Thromboembolism (DRG 299)	$7,712	CMS[115]
Vertigo (DRG 149)	$3,567	CMS[115]
Vomiting	$13,452	Roy et al.[114]

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	$488,294	$480,327	$731,122

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	$569,185	$546,825	$826,500	$7,206

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	$228,390	$218,227	$333,241

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	$262,660	$242,467	$363,403	Dominant

Figure E1. Second-Line Probabilistic Senstivity 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	**$287,509**	**$287,787**	**($223,135 - $363,671)**	**$518,817**	**$522,765**	**($412,890 - $649,625)**	**$498,871**	**$517,279**	**($388,394 - $685,374)**	**$555,888**	**$561,663**	**($409,437 - $757,113)**
Drug Costs	$240,913	$242,380	($182,210 - $311,459)	$461,843	$467,376	($363,811 - $587,502)	$430,979	$450,652	($330,238 - $608,691)	$508,247	$515,462	($369,356 - $705,784)
Supportive Care Costs	$528	$532	($438 - $644)	$1,882	$1,893	($1,685 - $2,125)	$2,607	$2,651	($2,032 - $3,457)	$2,491	$2,526	($1,931 - $3,340)
Administration Costs				$8,377	$8,379	($6,678 - $10,109)	$14,698	$14,962	($10,595 - $20,411)			
Progression Costs	$38,901	$37,703	($27,210 - $51,158)	$44,101	$42,509	($30,089 - $53,205)	$43,885	$42,320	($29,858 - $53,018)	$43,062	$41,589	($29,331 - $53,158)
Adverse Event Costs	$7,166	$7,172	($5,945 - $8,532)	$2,614	$2,607	($2,072 - $3,226)	$6,702	$6,695	($5,536 - $8,032)	$2,087	$2,087	($1,584 - $2,669)
Total QALYs	**2.59**	**2.65**	**(1.88 - 3.68)**	**3.45**	**3.56**	**(2.44 - 5.10)**	**3.41**	**3.52**	**(2.40 - 5.06)**	**3.27**	**3.37**	**(2.30 - 4.92)**
PFS QALYs	1.41	1.42	(1.17 - 1.72)	1.91	1.95	(1.49 - 2.52)	1.89	1.92	(1.46 - 2.53)	1.81	1.83	(1.39 - 2.44)
Progression QALYs	1.17	1.23	(0.62 - 2.07)	1.54	1.61	(0.81 - 2.72)	1.52	1.60	(0.80 - 2.72)	1.46	1.53	(0.77 - 2.65)
Total Life Years (OS)	**3.53**	**3.63**	**(2.53 - 5.11)**	**4.70**	**4.86**	**(3.26 - 6.97)**	**4.65**	**4.81**	**(3.20 - 6.98)**	**4.46**	**4.60**	**(3.07 - 6.79)**
PFS LYs	1.73	1.74	(1.44 - 2.08)	2.34	2.38	(1.84 - 3.08)	2.31	2.35	(1.80 - 3.08)	2.21	2.24	(1.71 - 2.97)
Progression LYs	1.80	1.89	(0.96 - 3.14)	2.37	2.48	(1.27 - 4.13)	2.34	2.46	(1.23 - 4.12)	2.25	2.36	(1.19 - 4.02)

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)	**--**	**--**	**--**	**$267,686**	**$281,911**	**($176,323 - $483,880)**	**$255,696**	**$304,139**	**($170,756 - $500,426)**	**$390,866**	**$469,189**	**($242,108 - $1,016,273)**
Total Costs	**--**	**--**	**--**	**$231,308**	**$234,979**	**($167,820 - $314,168)**	**$211,362**	**$229,493**	**($128,250 - $365,137)**	**$268,379**	**$273,877**	**($159,171 - $423,902)**
Drug Costs	--	--	--	$220,929	$224,997	($159,781 - $301,743)	$190,065	$208,272	($110,958 - $338,705)	$267,334	$273,082	($161,939 - $421,694)
Supportive Care Costs	--	--	--	$1,354	$1,361	($1,208 - $1,532)	$2,079	$2,119	($1,573 - $2,844)	$1,963	$1,994	($1,460 - $2,726)
Administration Costs	--	--	--	$8,377	$8,379	($6,678 - $10,109)	$14,698	$14,962	($10,595 - $20,411)			
Progression Costs	--	--	--	$5,200	$4,806	(-$554 - $8,875)	$4,983	$4,617	(-$363 - $8,771)	$4,161	$3,886	(-$290 - $8,279)
Adverse Event Costs	--	--	--	-$4,552	-$4,565	(-$5,963 - -$3,297)	-$464	-$477	(-$2,109 - $1,130)	-$5,078	-$5,085	(-$6,543 - -$3,782)
Total QALYs	**--**	**--**	**--**	**0.86**	**0.91**	**(0.39 - 1.61)**	**0.83**	**0.87**	**(0.32 - 1.63)**	**0.69**	**0.72**	**(0.16 - 1.50)**
PFS QALYs	--	--	--	0.50	0.52	(0.23 - 0.91)	0.48	0.50	(0.19 - 0.92)	0.39	0.41	(0.09 - 0.84)
Progression QALYs	--	--	--	0.37	0.39	(0.14 - 0.74)	0.35	0.37	(0.12 - 0.74)	0.29	0.31	(0.07 - 0.70)
Total Life Years (OS)	**--**	**--**	**--**	**1.17**	**1.23**	**(0.52 - 2.19)**	**1.12**	**1.18**	**(0.43 - 2.23)**	**0.93**	**0.97**	**(0.22 - 2.04)**
PFS LYs	--	--	--	0.61	0.64	(0.28 - 1.10)	0.58	0.61	(0.23 - 1.12)	0.48	0.50	(0.11 - 1.02)
Progression LYs	--	--	--	0.56	0.59	(0.22 - 1.13)	0.54	0.57	(0.19 - 1.14)	0.45	0.47	(0.11 - 1.05)

Figure E2. Third-Line Probabilistic Senstivity 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	**$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)[116]

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)[117]

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 (pCDOR) 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)[118]

The pCDOR 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)[119]

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[120]
- 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[121]

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)[122]
- 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)[123]

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 3 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 3 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 3 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 2 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 2 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 • QoI • Cost effectiveness	May 2017
Panobinostat/ Bortezomib/ Dexamethasone in Relapsed or Relapsed-and-refractory Multiple Myeloma (NCT02654990) **Sponsor** **Novartis Pharmaceuticals**	Phase 2 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 3 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 3 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 2 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)