The Cost-Effectiveness of 2nd and 3rd Line Treatment for Multiple Myeloma: Modeling Analysis Plan

Institute for Clinical and Economic Review

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Background

Multiple myeloma, also known as plasma cell myeloma, is the third most common blood cancer (after lymphoma and leukemia) in the United States, comprising approximately 1.4% of new cancer cases. Multiple myeloma incidence increases approximately 1% annually, although overall mortality rates have fallen in recent years. Approximately 24,000 individuals are diagnosed with multiple myeloma annually in the United States, and 11,000 will die each year.[1] Multiple myeloma primarily affects elderly individuals, with a median age at the time of diagnosis of ~70 years.[2] Standard treatments for multiple myeloma include chemotherapy, corticosteroid therapy, targeted therapy, high-dose chemotherapy with stem cell transplant, biological therapy, radiation therapy, surgery, and watchful waiting.[1] Several new targeted therapies have recently been approved for relapsed or refractory multiple myeloma (i.e., patients who have not responded to the most recent treatment or relapsed following such treatment) with the potential to improve progression-free survival and/or overall survival. There are uncertainties, however, regarding the comparative clinical effectiveness of these therapies as well as how their costs compare to the clinical value brought to patients.

Approach

The primary aim of this analysis will be 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). The model will analyze second- and third-line treatments separately. The analytic framework for this assessment is depicted in **Figure 1** below. The model will be developed in Microsoft Excel.

Key Model Choices and Assumptions

- The model will utilize a network meta-analysis of data from multiple trials to derive survival estimates for each drug regimen. This approach is necessary because head-to-head comparisons are not available for the majority of multiple regimens included in this study. Therefore, the model assumes that the trial populations used in the network are sufficiently homogeneous to allow for statistical pooling of the treatment effect.
- The baseline comparator will be lenalidomide + dexamethasone.
- Parametric curve functions will be fit for the baseline comparator in each treatment setting and used to extrapolate the data to a lifetime horizon.
- We will use the hazard ratios derived from network meta-analysis applied to the baseline curves to derive survival curves for all comparator interventions. Therefore, we assume proportional hazards hold for the relative survival curves.
- We will use PFS hazard ratios from 2 separate network meta-analyses performed in the 2nd and 3rd line patient subgroups applied to the lenalidomide + dexamethasone baseline curves to estimate regimen-specific PFS curves. There is insufficient data on the OS patient subgroups to utilize the same approach. Therefore, we will apply an estimate of the relationship between the PFS and OS curves derived from the Felix et al. study to estimate regimen-specific OS curves.[3]
- The model will assume that the trial-reported survival rates in baseline comparators, as well as the relative differences estimated from the network meta-analyses, will remain constant beyond trial-reported follow-up time in extrapolated survival estimates.
- Survival will be weighted by health state utilities to estimate quality-adjusted life years (QALYs). The model will include separate utilities for patients in the progression-free health state on treatment, progression-free health state off treatment, and progressed disease. The model will not include disutilities for individual adverse events.

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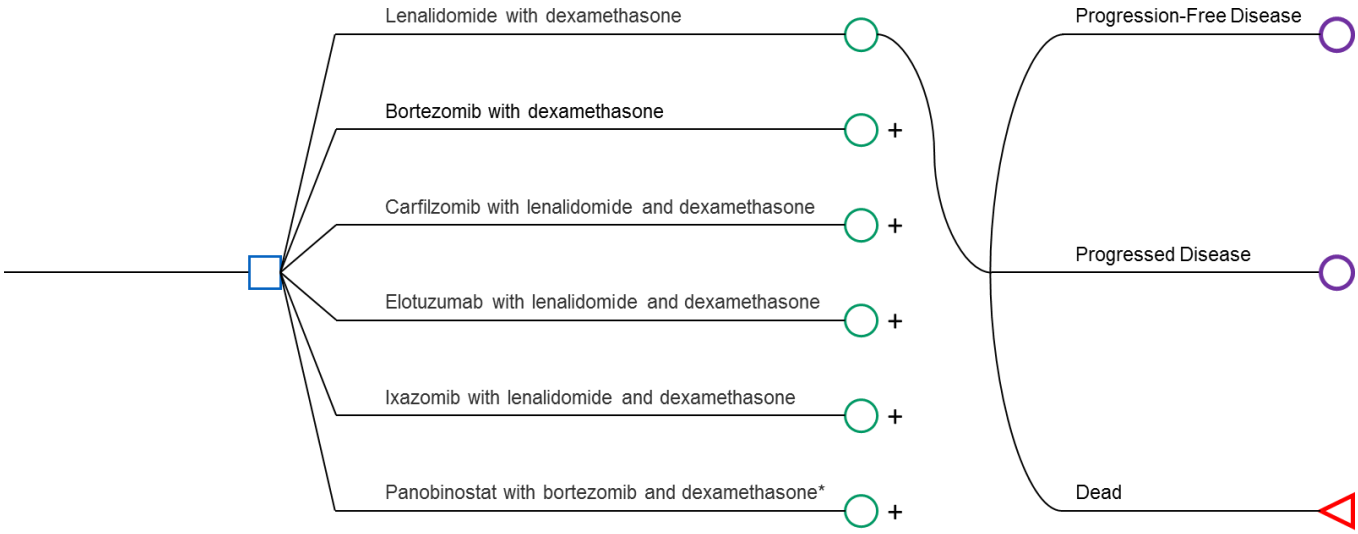
- The model will include grade 3/4 adverse events only, as less severe events are not expected to substantially impact patient health or costs. The models will include all grade 3/4 events that occur in at least 5% of patients in one or more of the included regimens.
- The model will include all treatment costs associated with each individual regimen, including drug acquisition costs (based on average patient characteristics, e.g., body surface area), drug administration costs (for intravenously administered drugs), supportive care costs (e.g. prophylaxis drugs and monitoring), costs of managing grade 3/4 events, and costs of disease progression.
- Disease progression costs will reflect a distribution of subsequent treatments and best supportive care. The distribution of treatments in disease progression will be consistent across comparators.
- All survival and health care costs will be discounted at 3% per year.

Figure 1: Analytic Framework: Management of Relapsed/Refractory Multiple Myeloma



Note: *Only evaluated in the 3rd line

For each treatment regimen, a hypothetical patient population will begin the model in the progression-free survival health state, where they remain until they either: (a) experience disease progression or (b) death from cancer or other causes. Patients who transition from the progression-free to the progressed disease state remain there until they either die from progressed cancer or from other causes. Patient survival, quality-adjusted survival, and health care costs will be estimated for each model cycle and then summarized over the entire time horizon for each treatment option. Model cycles will be 7 days each to: (a) allow for multiple dosing protocols, and (b) account for the high rates of disease progression in multiple myeloma.

Populations

The population of focus for the review will be adults with multiple myeloma 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.

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.

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 is lenalidomide in combination with dexamethasone (LEN-DEX). We recognize, however, that several recent trials have involved comparisons to bortezomib + dexamethasone, dexamethasone alone, and/or placebo. To account for the various trials and trial comparisons, a network meta-analysis will be conducted for each setting (i.e., 2nd and 3rd line).

Model Structure

Outcomes will be modeled using a partition survival approach and three health states: progression-free, progression, and death (see **Figure 2**).[4] The advantage of partition survival models is that they are less data intensive than more advanced modeling approaches. Statistical fitting methods allow the extrapolation of the survival results beyond the observed time frame, but rely on assumptions that may differ substantially between different parametric models. We will ensure that our assumptions do not lead to invalid models and nonsensical survival rates, such as the tail of the extrapolated progression-free survival curve crossing the tail of the overall survival curve.

We will fit parametric survival curves to progression-free survival (PFS) Kaplan-Meier data for the universal comparator (lenalidomide plus dexamethasone) in both the 2nd and 3rd line settings utilizing the approach described by Hoyle and Henley.[5] First we will extract data points from digitized copies of available survival curves, then use the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data. The potential model curves will include the distributional forms Weibull, exponential, log-normal, log-logistic, gamma, and Gompertz. The base case parametric function will be selected based on best model fit using AIC values and visual comparison.

We will then apply PFS hazard ratios, acquired from the network meta-analysis, to the universal comparator curves, to derive survival curves for the other interventions. This approach will allow us to model the relative efficacy of the interventions, model survival beyond available follow-up time, and facilitate probabilistic sensitivity analyses of survival.

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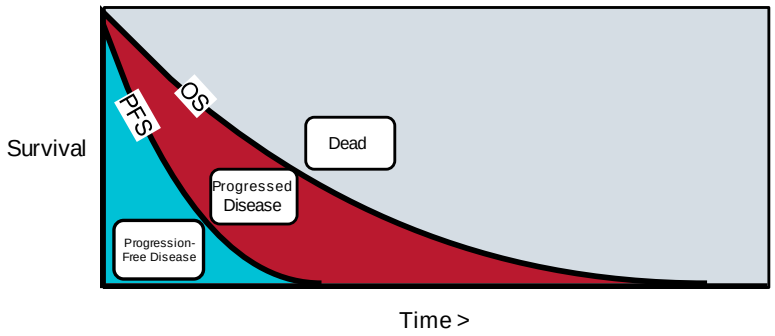
Figure 2: Partition survival model approach



Clinical Inputs

Base case progression-free survival will be derived from parametric fits to pooled Kaplan-Meier data from the MM-009 and MM-010 trials of LEN-DEX as described above.[6,7] We will then apply PFS hazard ratios from 2 separate network meta-analyses performed in the 2nd and 3rd line patient subgroups to the baseline LEN-DEX curves to estimate regimen-specific PFS curves. The PAN-BOR-DEX regimen has previously only been compared to bortezomib plus dexamethasone (BOR-DEX) and therefore could not be included in the network meta-analysis. We therefore used the PFS HR from the PANORAMA-1 trial of PAN-BOR-DEX vs. BOR-DEX. This assumption is supported by the fact that the PFS hazard ratio for BOR-DEX to LEN-DEX in the overall network meta-analysis (i.e., not the patient subgroup meta-analysis) is 1.07 (95% CI: 0.51 to 1.71), suggesting equivalence. There is insufficient data on OS for all regimens and for each patient subgroup (i.e., 2nd and 3rd line patients) to utilize the same approach for the regimen-specific OS curves. Therefore, we will apply an estimate of the relationship between the PFS and OS curves derived from the Felix et al. study to estimate regimen-specific OS curves.[3] Specifically, we will estimate a 2.5-month (95% confidence interval, 1.7–3.2) increase in median OS for each additional month of median PFS. The PFS hazard ratios versus LEN-DEX are shown in Table 1 below.

Table 1: Progression-Free Survival Hazard Ratios vs. LEN-DEX

Regimen	1 Prior Treatment			2 Prior Treatments		
	HR	Range: Low	Range: High	HR	Range: Low	Range: High
PAN-BOR-DEX*	0.66	0.50	0.86	0.64	0.50	0.83
CFZ-LEN-DEX	0.69	0.53	0.91	0.69	0.54	0.87
ELO-LEN-DEX	0.75	0.56	1.00	0.65	0.49	0.87
IX-LEN-DEX	0.88	0.65	1.19	0.58	0.40	0.84
LEN-DEX	---	---	---	---	---	---

*NOTE: Insufficient data to complete a network that includes BOR-DEX and PAN-BOR-DEX. Data for PAN-BOR-DEX taken directly from PANORAMA-1 trial of PAN-BOR-DEX vs. BOR-DEX.

Adverse Events

The model will include grade 3/4 adverse events derived from key clinical trials and/or the drug's prescribing information. The model will include any grade 3/4 adverse events that occur in >5% of patients in any of the treatment comparators, as listed in the table below.

Table 2: Adverse Event Inputs

	%	Reference
Bortezomib (Velcade) plus dexamethasone		
Diarrhea NOS	7.0%	Table 10 from Velcade PI (relapsed MM)
Fatigue	5.0%	(n=331 Vel only, 332 dex only)
Peripheral neuropathies	7.6%	
Thrombocytopenia	28.0%	
Anemia NOS	6.0%	
Neutropenia	13.6%	
Elotuzumab (Empliciti) in combination with lenalidomide (Revlimid) and dexamethasone		
Anemia	14.8%	Table 27 from FDA Medical Review
Neutropenia	24.8%	(from study CA204004, n=318 Erd, 317 Rd)
Thrombocytopenia	11.3%	
Lymphopenia	8.8%	
Cataract	6.3%	
Diarrhea	5.0%	
Fatigue	12.3%	
Pneumonia	13.8%	
Hyperglycemia	7.2%	
Back pain	5.0%	
Deep vein thrombosis	5.7%	
Lenalidomide plus dexamethasone		
Neutropenia	33.4%	Table 6 from Revlimid PI (at least 1 prior MM tx)
Thrombocytopenia	12.2%	
Anemia	9.9%	
Fatigue	6.5%	
Deep vein thrombosis	8.2%	
Pneumonia	8.5%	
Muscle weakness	5.7%	
Ixazomib (Ninlaro) plus Lenalidomide and dexamethasone		
Diarrhea	6.0%	Tables 4,5 from Ninlaro PI (n=360 NRd)
Thrombocytopenia	26.0%	
Neutropenia	26.0%	
Carfilzomib (Kyprolis) plus Lenalidomide and dexamethasone		
Anemia	14.0%	Table 8 from Kyprolis PI (all LOT)
Neutropenia	27.0%	(n=392 KRd)
Thrombocytopenia	15.0%	
Fatigue	5.0%	
Pneumonia	9.0%	
Hypokalemia	6.0%	
Hyperglycemia	5.0%	
Panobinostat (Farydak) plus Bortezomib and dexamethasone		
Diarrhea	25.0%	Table 4 from Farydak PI
Nausea	6.0%	AE's >=10% w/>=5% higher in Farydak arm
Vomiting	7.0%	
Fatigue	25.0%	

Drug utilization

The estimation of drug utilization and costs will be derived from the following data:

- Dosing schedule (see Table 3)
    - The dose may be fixed, by weight, or by body surface area (BSA)
- Dose intensity
- If a regimen is based on treat-to-progression, the treatment utilization and cost will be applied to all patients who remain in the PFS health state over time. If a finite number of cycles is used, patients may remain in the PFS state without active treatment.
- Whether or not vial sharing among patients is utilized
- Patient characteristics
- Drug unit costs (see **Table 4**)

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Table 3: 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	20 mg/m^2	to day 2	1,2	28	27 mg/m^2	day 8 to prog.	1,2,8,9,15,16
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

Cost Inputs[8]

Table 4: Drug unit costs

Drug	Formulation		Cost
Bortezomib	vial	3.5 mg	$1,612.00
Carfilzomib	vial	60 mg	$1,861.95
Dexamethasone	tab/vial	varied	
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

We will use the wholesale acquisition cost (WAC) for each drug, and note each available formulation. Based on the regimen dosage specified above, the model will utilize the lowest cost combination of tablets/vials for each regimen.

Adverse event costs will be derived from reasonable treatment assumptions used in previous analyses and the Centers for Medicare and Medicaid Services (CMS) list of Medicare severity diagnosis-related groups (MS-DRGs) relative weighting factors for the fiscal year 2015.[9]

To incorporate costs in the progression health state, we will use 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.[10] The model assumes that patients will receive one further line of treatment lasting 124 days followed by best supportive care. We will then calculate a mean cost per month weighted by the proportion of patients receiving each treatment.

Health State Utilities

Table 5: Health State Utilities

2nd Line	Base Case	Distribution	Source
Progression-free disease, on treatment	0.82	Beta	AMGEN/ASPIRE[11]
Progression-free disease, off treatment	0.84	Beta	AMGEN/ASPIRE[11]
Progressed disease	0.65	Beta	AMGEN/ASPIRE[11]
3rd Line	Base Case	Distribution	Source
Progression-free disease, on treatment	0.65	Beta	MM-003/NICE[12]
Progression-free disease, off treatment	0.72	Beta	Acaster et al.[13]
Progressed disease	0.61	Beta	MM-003/NICE[12]

Health state utilities will be derived from publicly available literature and/or manufacturer submitted data and applied to the disease states of progression-free and progressed disease. We will use consistent health state utility values across treatments evaluated in the model. For the progression-free health state, different utilities will be applied depending on whether the patient is on or off treatment to represent decreased quality of life due to treatment.

Other Inputs and Assumptions

An average patient height and weight will be acquired from trial evidence. This will be necessary for accurately calculating drug dosage in each regimen. Patient height and weight will be fixed among regimens to enable direct comparisons. The base case assumes that the mean patient height is 170cm and the mean patient weight is 80kg.

We will utilize a health system perspective (i.e., focus on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death. We will use a 3% discount rate for both costs and QALYs, and employ a half-cycle correction.

Model Outcomes

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

Model outcomes of interest will include:

- By intervention:
    - 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)
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios for each intervention versus the standard comparators

Sensitivity Analysis

We will run one-way sensitivity analyses to identify the key drivers of model outcomes. We will also perform an analysis with Bor-Dex as the baseline comparator, leveraging the data from the overall network meta-analysis. In addition, probabilistic sensitivity analysis will also be performed by jointly varying all model parameters over 10,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses comparing changes in drug prices across a range of incremental cost-effectiveness ratios, from $0 to $300,000 per QALY.

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References

1. A Snapshot of Myeloma. 2016; http://www.cancer.gov/research/progress/snapshots/myeloma.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012. 2015; http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site April 2015.
3. Felix J, Aragao F, Almeida JM, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. *BMC Cancer.* 2013;13:122.
4. Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Stat Med.* 1990;9(11):1259-1276.
5. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol.* 2011;11:139.
6. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med.* 2007;357(21):2123-2132.
7. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007;357(21):2133-2142.
8. Truven Health Analytics. RedBook Online. 2016; http://www.redbook.com/redbook/online/.
9. Roy A, Kish JK, Bloudek L, et al. Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework. *Am Health Drug Benefits.* 2015;8(4):204-215.
10. Farr AM, Stott-Miller M, Varker H, Spencer D, Shah M, Chen C. Treatment Sequencing Patterns Associated with Elderly Patients with Relapsed/Refractory Multiple Myeloma (MM) in the US Community Setting. *Blood.* 2016;126(23):5392.
11. Amgen. Data provided in response to ICER data request. QOL/Utility Data from ASPIRE Cost Effectiveness Model. Data on file.
12. NICE. Technology appraisal guidance: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. . http://www.nice.org.uk/guidance/ta338.
13. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer.* 2013;21(2):599-607.