# Estimating the Economic Impact of Adding Panobinostat to a U.S. Formulary for Relapsed and/or Refractory Multiple Myeloma: A Budget Impact and Cost-Benefit Model

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## ABSTRACT

**BACKGROUND:** Multiple myeloma is an incurable B-cell malignancy with a natural history that involves alternating periods of remission and subsequent relapse. For relapsed and/or refractory multiple myeloma (RRMM), the typical patient currently receives more lines of therapy than has been feasible in the past, translating into longer progression-free survival (PFS). Consequently, cost issues have become more prominent because patients may be offered newer and more expensive therapies during a more prolonged overall treatment course.

**OBJECTIVE:** To estimate the economic impact of adding panobinostat to a U.S. health plan formulary as a treatment option with bortezomib and dexamethasone for patients with RRMM previously treated with a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), using a budget impact and cost-benefit model.

**METHODS:** Total costs of commonly used salvage therapy regimens were combined with market share data and population prevalence estimates of RRMM to yield the total cost of treatment, from the perspective of a U.S. third-party payer (commercial or Medicare) with a time horizon of 1 year. Comparator treatment regimens included bortezomib-dexamethasone, lenalidomide-dexamethasone, lenalidomide-bortezomib-dexamethasone, carfilzomib monotherapy, carfilzomib-lenalidomide-dexamethasone, and pomalidomide-dexamethasone. Costs (2015 U.S. dollars) included drug costs for oral oncology agents, medical and administration costs for injectable oncology agents, costs of adverse event (AE) prophylaxis and monitoring, and costs of grade 3/4 AEs.

**RESULTS:** In a hypothetical health plan with 1 million members, the annual number of RRMM patients with previous PI and IMiD treatments was estimated at 16 and 118 for a commercial and Medicare plan, respectively. Introduction of panobinostat as part of the panobinostat-bortezomib-dexamethasone regimen was not expected to result in a substantial budget impact to either commercial or Medicare plans, with an incremental cost <$0.01 per member per month. Panobinostat-bortezomib-dexamethasone had a low cost per treated patient per month without progression, owing to the minimal increase in expenditure over existing bortezomib-based regimens and long median PFS, compared with median duration of treatment.

**CONCLUSIONS:** Adding panobinostat to a plan formulary as a treatment option is expected to be cost neutral (and potentially cost saving in the context of new and more expensive treatment regimens). With a low cost per month without progression, panobinostat-bortezomib-dexamethasone represents good value for the money.

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### What is already known about this subject

- The introduction of second-generation therapies has significantly lengthened progression-free and overall survival for relapsed and/or refractory multiple myeloma (RRMM) patients.
- Literature searches show only estimates of the costs of therapies before introduction of the second-generation proteasome inhibitor carfilzomib or the immunomodulatory drugs lenalidomide or pomalidomide.

### What this study adds

- This budget impact model estimates the incremental cost after the introduction of panobinostat, including comparison with the recommended and most widely used treatments for patients suffering from RRMM.
- Results suggest that the addition of panobinostat to the formulary is cost neutral or cost saving in comparison with other currently used therapies.
- The driving factor in the costs of treating patients with RRMM rests on the difference between the duration of treatment and the duration of progression-free survival.

Multiple myeloma is an incurable B-cell malignancy resulting in the accumulation of terminally differentiated plasma cells that not only infiltrate the bone marrow but also have a propensity for damaging adjacent bone and marrow.[1,2] It accounts for 10% of all blood cancers and has a natural history that typically involves alternating periods of remission and subsequent relapse.[1,3] For relapsed and/or refractory multiple myeloma (RRMM)—with *relapsed* defined as response to therapy with subsequent progression beyond 60 days of the last therapy; *refractory* defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy; and *relapsed/refractory* defined as progression of disease while on or within 60 days of discontinuing therapy[4]—therapeutic advances have conferred prolonged overall survival from a median of 4.6 years in 2001-2005 to 6.1 years in 2006-2010.[5] The typical RRMM patient receives more lines of therapy than has been feasible in the

past, translating into longer progression-free survival (PFS), a primary goal of therapy. Consequently, cost concerns have become more prominent, since patients may be offered newer and more expensive therapies during a more prolonged overall treatment course.[6] However, it is also appreciated that disease complications characteristic of multiple myeloma are significant in the context of myeloma-related health care costs, requiring inpatient hospitalizations, readmissions, and procedures and a particularly long duration of hospitalization.[7-10] Prolonging PFS, that is, delaying progression, may therefore lead to reduced hospitalizations and costs savings, depending in part on the cost of therapy required for such PFS prolongation.[11]

There are several approved novel agents (proteasome inhibitors [PI] bortezomib and carfilzomib [second-generation], immunomodulatory drugs [IMiDs] lenalidomide and pomalidomide, and, most recently, the histone deacetylase [HDAC] inhibitor panobinostat) but no formal standard of care, since the National Comprehensive Cancer Network (NCCN) clinical practice guidelines assign multiple regimens a category 1 recommendation.[2] This lack of a formal standard of care results in various real-world practices regarding treatment regimens and their sequencing. Strategies for prolonging PFS in RRMM include retreatment with bortezomib or an IMiD after initial relapse and the addition of new drugs to these established agents.[11-13] Overall, lower clinical response rates and shorter PFS are anticipated with each subsequent relapse.[5,11]

Results from the pivotal placebo-controlled phase 3 study of the HDAC inhibitor panobinostat plus bortezomib and dexamethasone for the treatment of patients who received previous treatment with up to 3 previous lines of therapy demonstrated significantly longer PFS compared with bortezomib and dexamethasone alone.[2,14,15] Panobinostat increased median PFS from 8.1 months in the control arm to 12 months (hazard ratio [HR] = 0.63; 95% confidence interval [CI] = 0.52-0.76) in the panobinostat arm for the overall study population (N = 768) and from 5.8 months to 10.6 months (HR = 0.52; 95% CI = 0.36-0.76) in the subset of patients who had previously received bortezomib plus an iMiD and a median of 2 previous therapies.[15,16] Accelerated approval from the U.S. Food and Drug Administration (FDA) was based on this latter subset,[14] and panobinostat has since been incorporated into the NCCN clinical practice guidelines as a category 1 option for this same population.[2] As highlighted in the FDA-approved product labeling, panobinostat has the propensity to increase the rates of certain grade 3/4 adverse events (AEs), most notably diarrhea and cardiac events over bortezomib and dexamethasone alone.[14]

As with any new drug under consideration for formulary placement, the addition of panobinostat is expected to add certain costs while offsetting other costs. Therefore, a Microsoft Excel-based budget impact and cost-effectiveness model was constructed to estimate the economic impact of adding panobinostat to the formulary as a treatment option for these patients and to estimate the value for the money, both from the perspective of a U.S. third-party payer.

## Methods

### Model Structure Overview

The budget impact model structure is illustrated in Figure 1. The model was developed to assess the pharmacy and medical budget impact of panobinostat over a 1-year time horizon, while also assessing value for the money spent in terms of cost per patient for 1 month without progression. The target patient population was composed of adults aged ≥ 18 years who were initiating salvage therapy for RRMM, having previously been treated with ≥ 2 regimens that must have included a PI and an IMiD.

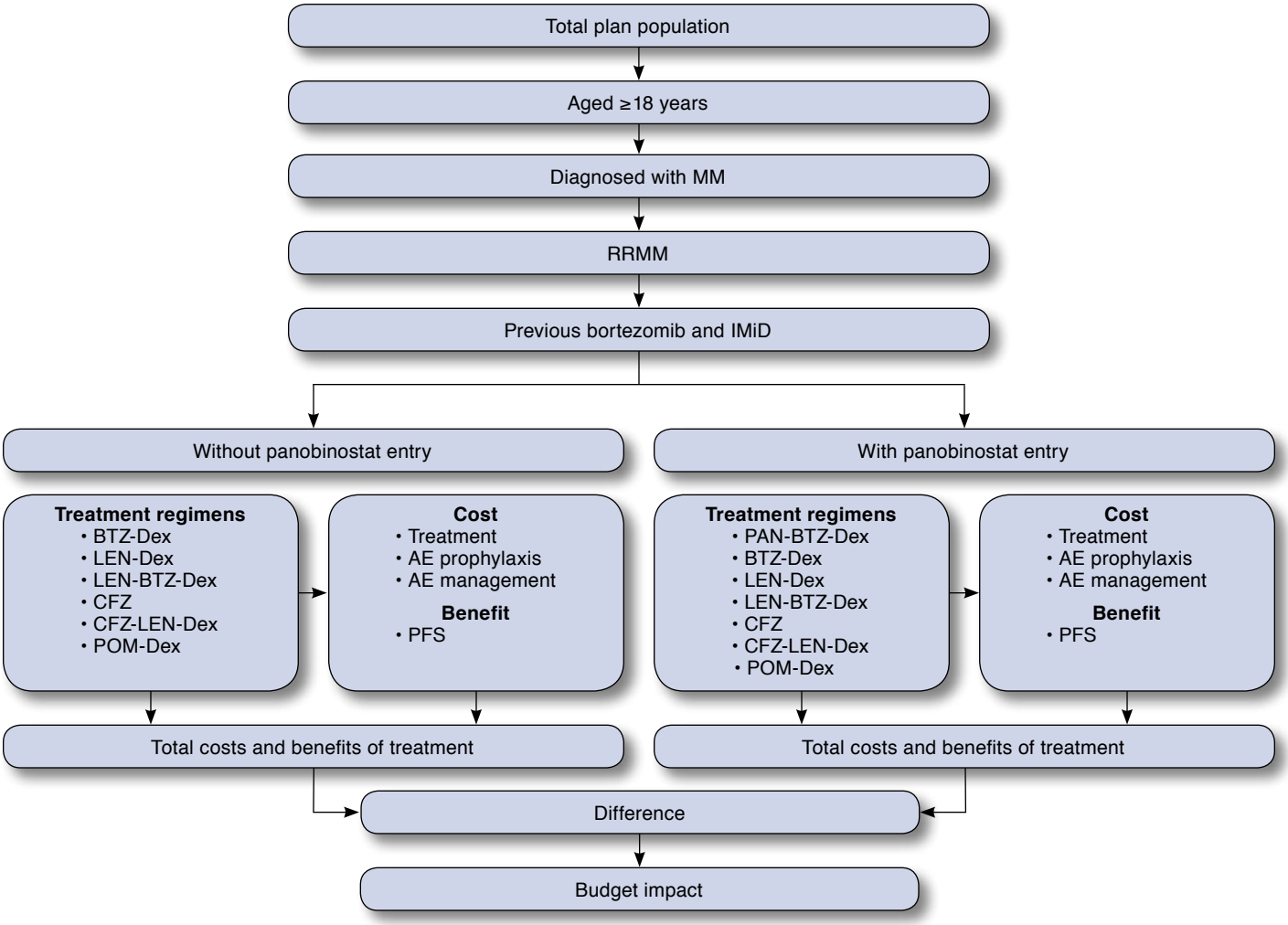
### Modeling Technique

Inputs for disease prevalence were used to estimate the size of the target population in a hypothetical health plan of 1,000,000 members, using default values derived from the 2012 U.S. Census data, Medicare demographic data, information from the Surveillance, Epidemiology, and End Results (SEER) database, and published literature.

Comparator treatment regimens, based on NCCN-recommended regimens for salvage therapy for RRMM and FDA-approved product labeling, included bortezomib-dexamethasone, lenalidomide-dexamethasone, lenalidomide-bortezomib-dexamethasone, carfilzomib monotherapy, carfilzomib-lenalidomide-dexamethasone, and pomalidomide-dexamethasone.

Total costs to a third-party payer (commercial or Medicare) were compared in the scenario before the introduction of panobinostat versus after the introduction of panobinostat. Cost per patient for each treatment regimen was calculated based on the drug price and cost of administration, AE prophylaxis and monitoring, and grade 3/4 AEs. All patients were assumed to be treated for the median duration of treatment (DOT) reported in product labeling or clinical trials. PFS for each regimen was based on the median PFS observed in product labeling or clinical trials, corresponding to the median DOT in the model. Detailed descriptions of the costs per treatment component have been previously published.[17] These data were combined with market share estimates to simulate the cost of treating RRMM patients with previous bortezomib and IMiD exposure. Current market shares were assumptions derived from Novartis market research. Total cost of RRMM treatment to the plan was calculated by multiplying the cost per treatment regimen by the size of the target patient population and respective proportion of patients. The total, per-member-per-year (PMPY), and per-member-per-month (PMPM) costs to the plan in the scenario after the introduction of panobinostat were subtracted from the total cost in the scenario before panobinostat to

**FIGURE 1** Budget Impact Model Structure




*AE = adverse event; BTZ = bortezomib; CFZ = carfilzomib; Dex = dexamethasone; IMiD = immunomodulatory drug; LEN = lenolidomide; MM = multiple myeloma; PAN = panobinostat; PFS = progression-free survival; POM = pomalidomide; RRMM = relapsed and/or refractory multiple myeloma.*

estimate the incremental costs resulting from adding panobinostat to the plan formulary.

The cost-effectiveness of each treatment regimen was calculated by considering the cost per month without progression, with low cost per month without progression indicative of good value for the money. Since PFS was an outcome reported across all comparator regimens, cost per month of PFS was deemed to be a representative way of comparing outcomes and assessing value.[18] To assess the relative impact of key parameters on the model results, a one-way sensitivity analysis was performed, whereby each model parameter was lowered or raised (default of ± 10%). Model results after each iteration of low and high value for each parameter were tested in the model were recorded and presented in tabular format and as a tornado chart in order to assess which parameters had the greatest impact on model results of incremental cost, as well as cost per month of PFS for each regimen.

## Model Inputs

**Target Population.** In a hypothetical commercial plan (1,000,000 covered lives), 72.3% of the population were estimated to be aged ≥ 18 years, and 0% were aged ≥ 65 years.[19] In a hypothetical Medicare plan, 17.0% of the population were estimated to be aged ≥ 18 years, and 83% were aged ≥ 65 years.[20] Prevalence of multiple myeloma (MM) in people aged < 65 and ≥ 65 years was derived from age-specific prevalence rates in the SEER database and weighted by age groups reported in

**TABLE 1** Cost per Treatment Regimen per Year in Commercial and Medicare Plans[a]

| | Drug and Administration ($) | | | Prophylaxis and Monitoring ($) | | | | | Total ($) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pharmacy | Medical | Hydration | CBC | Oral prophy[b] | DVT/PE | ECG | Grade 3/4 AEs ($) | Pharmacy[c] | Medical[d] | Total |
| **Commercial plan** | | | | | | | | | | | |
| PAN-BTZ-Dex | 50,704 | 46,226 | 536 | 1,308 | 117 | 0 | 155 | 10,118 | 51,362 | 57,804 | 109,166 |
| BTZ-Dex | 6 | 64,717 | 751 | 2,319 | 208 | 0 | 0 | 7,081 | 764 | 74,317 | 75,081 |
| LEN-Dex | 120,617 | 0 | 0 | 931 | 0 | 259 | 0 | 7,893 | 121,075 | 8,625 | 129,701 |
| LEN-BTZ-Dex | 100,510 | 70,880 | 823 | 2,616 | 235 | 242 | 0 | 2,246 | 101,199 | 76,353 | 177,552 |
| CFZ | 0 | 113,913 | 4,578 | 832 | 324 | 0 | 222 | 15,631 | 1,379 | 129,544 | 130,923 |
| CFZ-LEN-Dex | 103,866 | 120,516 | 4,435 | 812 | 309 | 226 | 217 | 1,783 | 104,517 | 127,647 | 232,164 |
| POM-Dex | 151,540 | 0 | 0 | 1,086 | 0 | 286 | 0 | 26,055 | 152,699 | 26,268 | 178,967 |
| **Medicare plan** | | | | | | | | | | | |
| PAN-BTZ-Dex | 50,704 | 45,351 | 434 | 1,059 | 117 | 0 | 126 | 10,118 | 51,362 | 56,549 | 107,911 |
| BTZ-Dex | 6 | 63,492 | 608 | 1,877 | 208 | 0 | 0 | 7,081 | 764 | 72,508 | 73,272 |
| LEN-Dex | 120,617 | 0 | 0 | 754 | 0 | 259 | 0 | 7,893 | 121,075 | 8,448 | 129,523 |
| LEN-BTZ-Dex | 100,510 | 69,539 | 666 | 2,118 | 235 | 242 | 0 | 2,246 | 101,199 | 74,357 | 175,556 |
| CFZ | 0 | 107,468 | 3,707 | 674 | 324 | 0 | 180 | 15,631 | 1,379 | 126,606 | 127,985 |
| CFZ-LEN-Dex | 103,866 | 120,516 | 3,591 | 658 | 309 | 226 | 176 | 1,783 | 104,517 | 126,607 | 231,124 |
| POM-Dex | 151,540 | 0 | 0 | 879 | 0 | 286 | 0 | 26,055 | 152,699 | 26,061 | 178,760 |

[a]*Assuming a duration on therapy needed to yield 12 months of PFS using the ratio of median duration of treatment to median PFS.*

[b]*Includes acyclovir for herpes zoster prophylaxis, dexamethasone for infusion reaction prophylaxis, and allopurinol for prophylaxis of renal toxicity and tumor lysis syndrome.*

[c]*Pharmacy costs include oral chemotherapy agents; DVT/PE prophylaxis; herpes zoster prophylaxis; renal toxicity and tumor lysis syndrome prophylaxis; and grade 3/4 anemia, hyponatremia, hypophosphatemia, leukopenia, thrombocytopenia, neutropenia, and lymphopenia.*

[d]*Medical costs include intravenous chemotherapy agents; intravenous hydration; CBC laboratory tests; ECGs, and all grade 3/4 AEs except those listed in pharmacy costs.*

*AE = adverse event; BTZ = bortezomib; CBC = complete blood count; CFZ = carfilzomib; Dex = dexamethasone; DVT = deep vein thrombosis; ECG = electrocardiogram; HZ = herpes zoster; LEN = lenalidomide; PAN = panobinostat; PE = pumonary embolism; PFS = progression-free survival; POM = pomalidomide; prophy = prophylaxis.*

the 2012 U.S. Census.[19,21] Because the SEER database does not present prevalence data using cutoffs of ≥ 18 years or ≥ 65 years (as would be relevant to a Medicare plan), age groups of 20-59 and 60+ were used as a proxy for 18-64 and 65+ years. Among patients with MM, 56.5% were assumed to be relapsed or relapsed/refractory at any given time, an input derived from approximating the area under the PFS survival curve for the pooled study population of nonbortezomib-based and bortezomib-based treatment arms of a meta-analysis of phase 3 trials.[22] Patients entered the model at any point in MM treatment. By taking the average proportion of patients who progressed over each time point, the proportion of patients in a progressed (relapsed and/or refractory) state was estimated to be over 60 months.

Among RRMM patients, 25.1% were expected to have been pretreated with a PI and an IMiD based on the subgroup of 193 of 768 randomized patients in the PANORAMA-1 phase 3 trial of panobinostat.[14] According to these prevalence estimates, 16 and 118 patients in a commercial plan and Medicare plan, respectively, made up the target patient population of RRMM patients with previous use of a PI and IMiD who would receive treatment with any second-line regimen.

**Proportion of Patients Treated.** It was assumed that 10% of patients currently treated with existing regimens would be prescribed panobinostat-bortezomib-dexamethasone upon panobinostat availability, with gain taken from each comparator regimen in proportion to the current market share. An example calculation is as follows: lenalidomide-dexamethasone future proportion of patients (28%) = current proportion of patients (32%) – (panobinostat-bortezomib-dexamethasone proportion of patients [10%] × current proportion of patients [32%]).

**Drug Utilization and Cost Inputs.** The cost of each treatment regimen was calculated by the sum of each individual treatment component (cost of drug, administration, and AE prophylaxis) and cost of grade 3/4 AEs observed for that treatment regimen. The unit cost of each grade 3/4 AE was based on published literature and inflated to 2015 U.S. dollars using the medical care component of the Consumer Price Index.[23] Any AE occurring in ≥ 5% of the treatment arm in any regimen was included in the model; additionally, the cost of cardiac arrhythmias was included because of the black box warning for cardiac toxicity observed in patients treated with panobinostat. Cardiac arrhythmias have also been reported in trials of carfilzomib.[24] Methods used to standardize AE rates (to account for different median durations of exposures), and values used to estimate the pharmacy or medical net cost per dose of the individual components of each treatment regimen have been previously published.[17] Of note, the cost of intravenous

**TABLE 2** Budget Impact of Panobinostat in Commercial and Medicare Plans: Base-Case Analysis

| | Total Annual Cost ($) | | PMPY ($) | | PMPM ($) | |
|---|---|---|---|---|---|---|
| | Current | Future | Current | Future | Current | Future |
| **Commercial plan** | | | | | | |
| PAN-BTZ-Dex | 0 | 174,921 | 0.00 | 0.17 | 0.00 | 0.01 |
| BTZ-Dex | 281,514 | 253,363 | 0.28 | 0.25 | 0.02 | 0.02 |
| LEN-Dex | 556,967 | 501,270 | 0.56 | 0.50 | 0.05 | 0.04 |
| LEN-BTZ-Dex | 406,832 | 366,149 | 0.41 | 0.37 | 0.03 | 0.03 |
| CFZ | 282,253 | 254,028 | 0.28 | 0.25 | 0.02 | 0.02 |
| CFZ-LEN-Dex | 178,562 | 160,706 | 0.18 | 0.16 | 0.01 | 0.01 |
| POM-Dex | 507,573 | 456,816 | 0.51 | 0.46 | 0.04 | 0.04 |
| **Total** | **2,213,703** | **2,167,253** | **2.21** | **2.17** | **0.184** | **0.181** |
| **Incremental change** | | **-46,450** | | **-0.05** | | **-0.004** |
| **Medicare plan** | | | | | | |
| PAN-BTZ-Dex | 0 | 1,277,359 | 0.00 | 1.28 | 0.00 | 0.11 |
| BTZ-Dex | 2,029,570 | 1,826,613 | 2.03 | 1.83 | 0.17 | 0.15 |
| LEN-Dex | 4,108,955 | 3,698,060 | 4.11 | 3.70 | 0.34 | 0.31 |
| LEN-BTZ-Dex | 2,971,674 | 2,674,507 | 2.97 | 2.67 | 0.25 | 0.22 |
| CFZ | 2,026,515 | 1,823,864 | 2.03 | 1.82 | 0.17 | 0.15 |
| CFZ-LEN-Dex | 1,313,214 | 1,181,893 | 1.31 | 1.18 | 0.11 | 0.10 |
| POM-Dex | 3,745,354 | 3,370,818 | 3.75 | 3.37 | 0.31 | 0.28 |
| **Total** | **16,195,283** | **15,853,113** | **16.20** | **15.85** | **1.350** | **1.321** |
| **Incremental change** | | **-342,169** | | **-0.34** | | **-0.029** |

*BTZ = bortezomib; CFZ = carfilzomib; Dex = dexamethasone; LEN = lenalidomide; PAN = panobinostat; PMPM = per member per month; PMPY = per member per year; POM = pomalidomide.*

medications used in this model differ from those in the published table for intravenous medications. Intravenous drug cost for commercial and Medicare plans were based on average sales price plus 6% without inflation for commercial costs (whereas the previous model inflated commercial intravenous drug costs to 123.5% of the Medicare rate). Inflation of commercial cost of medical services, such as physician office visits for infusion, was maintained. Additionally, all costs included in the previous model were updated to the most recent Medicare average sales price (applicable to July 1, 2015-September 30, 2015) or RED BOOK pricing.[25,26]

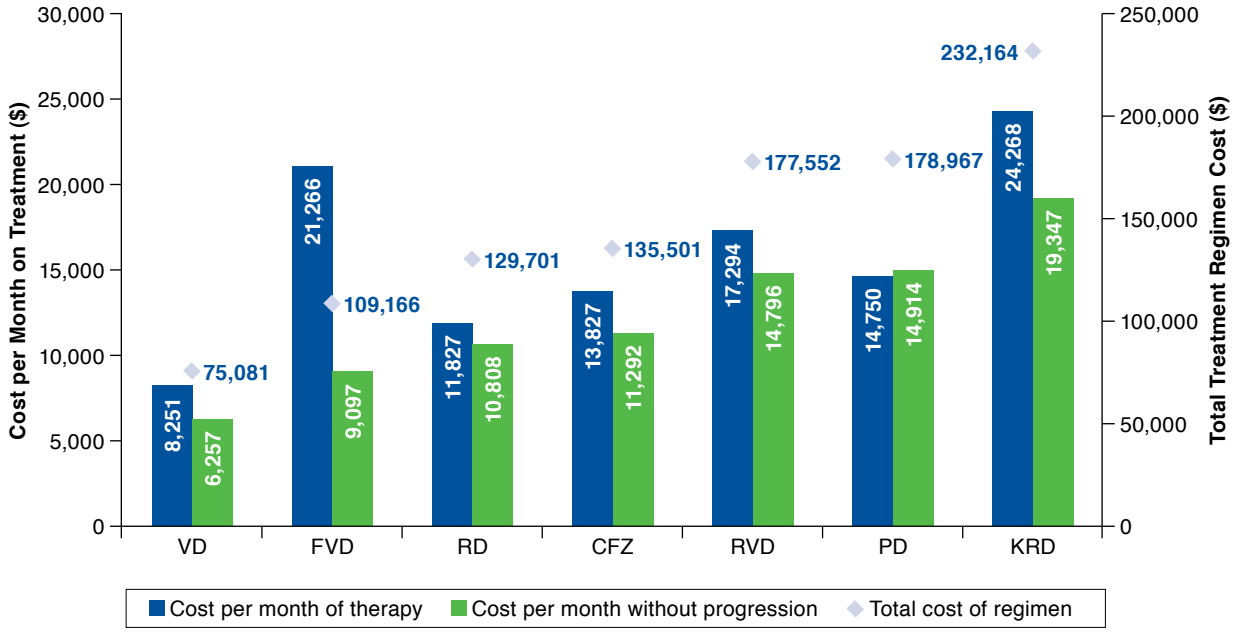
The model assumed perfect adherence to treatment, with no discontinuations or dose reductions.

**DOT and PFS.** According to the PANORAMA-1 phase 3 trial, the median PFS of panobinostat-bortezomib-dexamethasone in the overall study population was 12.0 months, with a median DOT of 5.8 months, compared with a median PFS of 8.1 months and a median DOT of 6.1 months for bortezomib-dexamethasone.[14,15] DOT and PFS data for comparator regimens were extracted from clinical trials in similar RRMM populations, although the median total number of previous regimens may have differed (range 1-4) from the PANORAMA-1 population. Based on these trials in a similar RRMM population, lenalidomide-dexamethasone had a median PFS of 11.1 months and median DOT of 10.1 months.[27] For lenalidomide-bortezomib-dexamethasone, median PFS and DOT were reportedly 9.5 and 8.0 months, respectively.[28] For carfilzomib-dexamethasone, median PFS and DOT were 3.7 months and 3.0 months, respectively, in a phase 2 trial in which 82% of patients had ≥ 4 lines of therapy, and 95% were refractory to their last line.[29] A similar phase 2 trial of carfilzomib-lenalidomide-dexamethasone in RRMM patients (median of 3 previous treatments) found a PFS of 15.4 months.[30] The median numbers of 28-day cycles in this study were 9.5 for carfilzomib, 8.5 for lenalidomide, and 9 for dexamethasone. For the model, this was approximated as nine 28-day cycles of carfilzomib-lenalidomide-dexamethasone (252 days or 8.4 months). Finally, pomalidomide-dexamethasone patients received a median of 4.7 months of treatment and obtained a median of 3.6 months of PFS among patients who had received a median of 5 previous therapies.[31] A scenario analysis was also undertaken to model the subpopulation of patients in the PANORAMA-1 phase 3 trial who had previouly used a PI and an IMiD, with a DOT and corresponding PFS of 4.6 months and 10.6 months for the panobinostat-bortezomib-dexamethasone arm versus 5.0 months and 5.8 months for the bortezomib-dexamethasone arm.

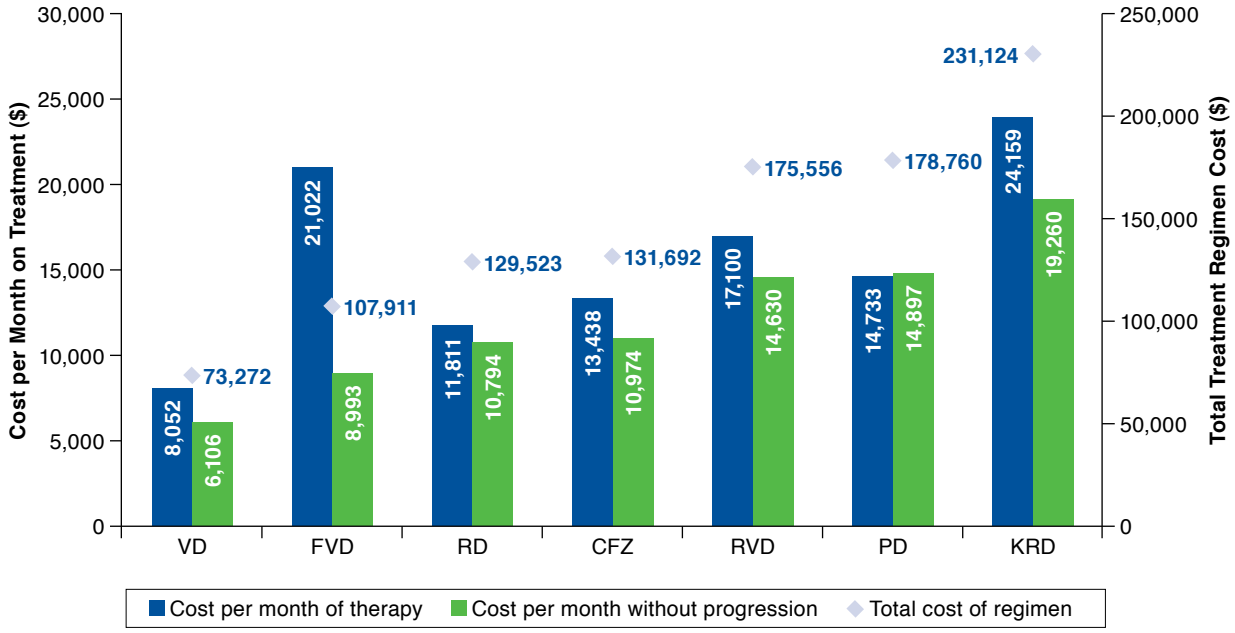
Under default settings for the base-case analysis, after completing a course of therapy, it was assumed that patients remained progression free for the median PFS reported in the literature and returned to therapy upon progression, with subsequent cycles of therapy assumed to provide equal PFS benefit. In any typical 12-month period, some patients would

**FIGURE 2** Total Cost of Treatment Regimen Over 1 Year, Cost per Month on Treatment,[a] and Cost per Month Without Progression[b] in Commercial and Medicare Plans

**A. Commercial Plan**




**B. Medicare Plan**




[a]*Calculated as the total cost of treatment regimen divided by the total months on treatment.*

[b]*Calculated as the total cost of the median duration of treatment divided by the median PFS.*

*CFZ = carfilzomib; FVD = panobinostat-bortezomib-dexamethasone; KRD = carfilzomib-lenalidomide-dexamethasone; PD = pomalidomide-dexamethasone; PFS = progression-free survival; RD = lenalidomide-dexamethasone; RVD = lenalidomide-bortezomib-dexamethasone; VD = bortezomib-dexamethasone.*

**TABLE 3** Budget Impact of Panobinostat in Commercial and Medicare Plans: Scenario Analysis (PANORAMA-1 Subset with Previous Treatment with PI and IMiD)

| | Total Annual Cost ($) | | PMPY ($) | | PMPM ($) | |
|---|---|---|---|---|---|---|
| | Current | Future | Current | Future | Current | Future |
| **Commercial plan** | | | | | | |
| PAN-BTZ-Dex | 0 | 186,184 | 0.00 | 0.19 | 0.00 | 0.02 |
| BTZ-Dex | 310,437 | 279,393 | 0.31 | 0.28 | 0.03 | 0.02 |
| LEN-Dex | 556,967 | 501,270 | 0.56 | 0.50 | 0.05 | 0.04 |
| LEN-BTZ-Dex | 406,832 | 366,149 | 0.41 | 0.37 | 0.03 | 0.03 |
| CFZ | 282,253 | 254,028 | 0.28 | 0.25 | 0.02 | 0.02 |
| CFZ-LEN-Dex | 178,562 | 160,706 | 0.18 | 0.16 | 0.01 | 0.01 |
| POM-Dex | 507,573 | 456,816 | 0.51 | 0.46 | 0.04 | 0.04 |
| **Total** | **2,242,625** | **2,204,547** | **2.24** | **2.20** | **0.187** | **0.184** |
| **Incremental change** | | **-38,078** | | **-0.04** | | **-0.003** |
| **Medicare plan** | | | | | | |
| PAN-BTZ-Dex | 0 | 1,359,649 | 0.00 | 1.36 | 0.00 | 0.11 |
| BTZ-Dex | 2,237,743 | 2,013,968 | 2.24 | 2.01 | 0.19 | 0.17 |
| LEN-Dex | 4,108,955 | 3,698,060 | 4.11 | 3.70 | 0.34 | 0.31 |
| LEN-BTZ-Dex | 2,971,674 | 2,674,507 | 2.97 | 2.67 | 0.25 | 0.22 |
| CFZ | 2,026,515 | 1,823,864 | 2.03 | 1.82 | 0.17 | 0.15 |
| CFZ-LEN-Dex | 1,313,214 | 1,181,893 | 1.31 | 1.18 | 0.11 | 0.10 |
| POM-Dex | 3,745,354 | 3,370,818 | 3.75 | 3.37 | 0.31 | 0.28 |
| **Total** | **16,403,456** | **16,122,759** | **16.40** | **16.12** | **1.367** | **1.344** |
| **Incremental change** | | **-280,697** | | **-0.28** | | **-0.023** |

*BTZ = bortezomib; CFZ = carfilzomib; Dex = dexamethasone; IMiD = immunomodulatory drug; LEN = lenalidomide; PAN = panobinostat; PI = proteasome inhibitor; PMPM = per member per month; PMPY = per member per year; POM = pomalidomide.*

be beginning therapy, while others would be mid-regimen or carried over from the previous year. To provide a fair comparison across regimens, median time on therapy corresponding to 12 months of PFS (using DOT/PFS) was calculated.

## Results

### Base-Case Analysis

The total costs per treatment regimen per year for a commercial plan and a Medicare plan are presented in Table 1. Over a 1-year time horizon, assuming patients resumed treatment upon progression to achieve 12 months of PFS using the DOT to PFS ratio, the bortezomib-dexamethasone regimen was associated with the lowest total cost to the plans (commercial and Medicare), and the panobinostat-bortezomib-dexamethasone regimen had increased overall monthly cost for therapy but not total cost over 1 year.

In a commercial hypothetical plan of 1,000,000 members, the introduction of panobinostat was not associated with substantial budget impact to the plan and is expected to be budget neutral (Table 2). Under default assumptions for proportion of patients who will receive panobinostat-bortezomib-dexamethasone in lieu of other used regimens, DOT, PFS, and rate of grade 3/4 AEs, addition of the panobinostat-bortezomib-dexamethasone was associated with a net savings of $46,450 (corresponding to -$0.05 PMPY or less than -$0.004 PMPM). In addition, panobinostat-bortezomib-dexamethasone demonstrated good value for the money, with a cost per month without progression under $10,000 per month (Figure 2A).

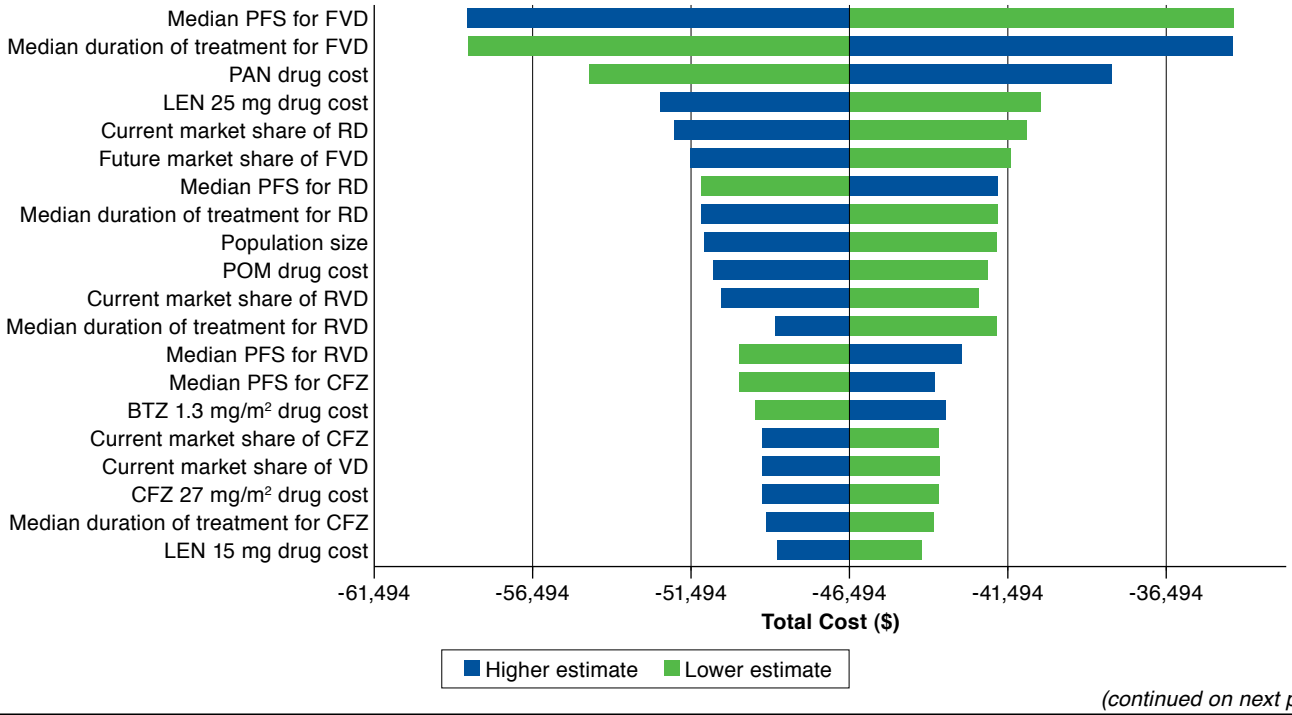
The addition of panobinostat-bortezomib-dexamethasone is also expected to be neutral or cost saving for a Medicare plan (Table 2). In a hypothetical Medicare plan of 1,000,000 members, the introduction of panobinostat is expected to result in cost savings of $342,169. This corresponds to a PMPY net savings of $0.34 ($0.029 PMPM). Cost per month without progression for panobinostat-bortezomib-dexamethasone was below $10,000 at $8,993 and lower than lenalidomide-dexamethasone ($10,794) and carfilzomib-dexamethasone but higher than bortezomib-dexamethasone ($6,106; Figure 2B).

### Scenario Analysis: Subpopulation of PANORAMA-1 Which Received Previous Treatment with a PI and an IMiD

Based on the subgroup of patients in PANORAMA-1 which had received previous PI and IMiD therapy, 5.2 treatment-months are expected to yield 12.0 months of PFS for the panobinostat-bortezomib-dexamethasone regimen, using the ratio of duration of treatment to PFS (4.6 months: 10.6 months). For bortezomib-dexamethasone, 10.3 treatment-months are expected to yield 12.0 months of PFS (5.0 months: 5.8 months). The DOT and PFS remained the same as those in the base-case analysis for all other regimens. The total costs per treatment

**FIGURE 3** One-Way Sensitivity Analysis Tornado Chart for the Outcomes of Total Incremental Cost and Cost Per Month of PFS for Each Regimen

**A. Total Incremental Cost**




(continued on next page)

regimen per year for panobinostat-bortezomib-dexamethasone were $116,196 and $114,862 for a commercial plan and a Medicare plan, respectively; corresponding values for bortezomib-dexamethasone were $82,795 and $80,788, respectively.

In assessing the incremental budget impact, panobinostat remained favorable in this scenario for commercial and Medicare plans (Table 3). In a commercial plan under this scenario, the total budget impact over 1 year is estimated at -$38,078 ($0.04 PMPY; $0.003 PMPM). For a Medicare plan, the anticipated budget impact is -$280,697 over 1 year ($0.28 PMPY; -$0.023 PMPM). The model predicts the introduction of the panobinostat-bortezomib-dexamethasone regimen to be potentially cost saving to the plan through the reduction in the proportion of patients treated with regimens more costly than panobinostat-bortezomib-dexamethasone for this subpopulation of patients.

## One-Way Sensitivity Analysis

For the outcome of total incremental budget impact (base-case model output = -$46,450 for a commercial plan), median PFS and median DOT for the panobinostat-bortezomib-dexamethasone regimen were the most influential parameters, varying the incremental budget from -$34,334 to -$58,565. The next most influential parameters were cost of panobinostat and lenalidomide 25 mg tablets. The most influential 20 parameters are displayed in Figure 3A. Under no scenario did the one-way sensitivity analysis show increased cost associated with the addition of panobinostat to the formulary.

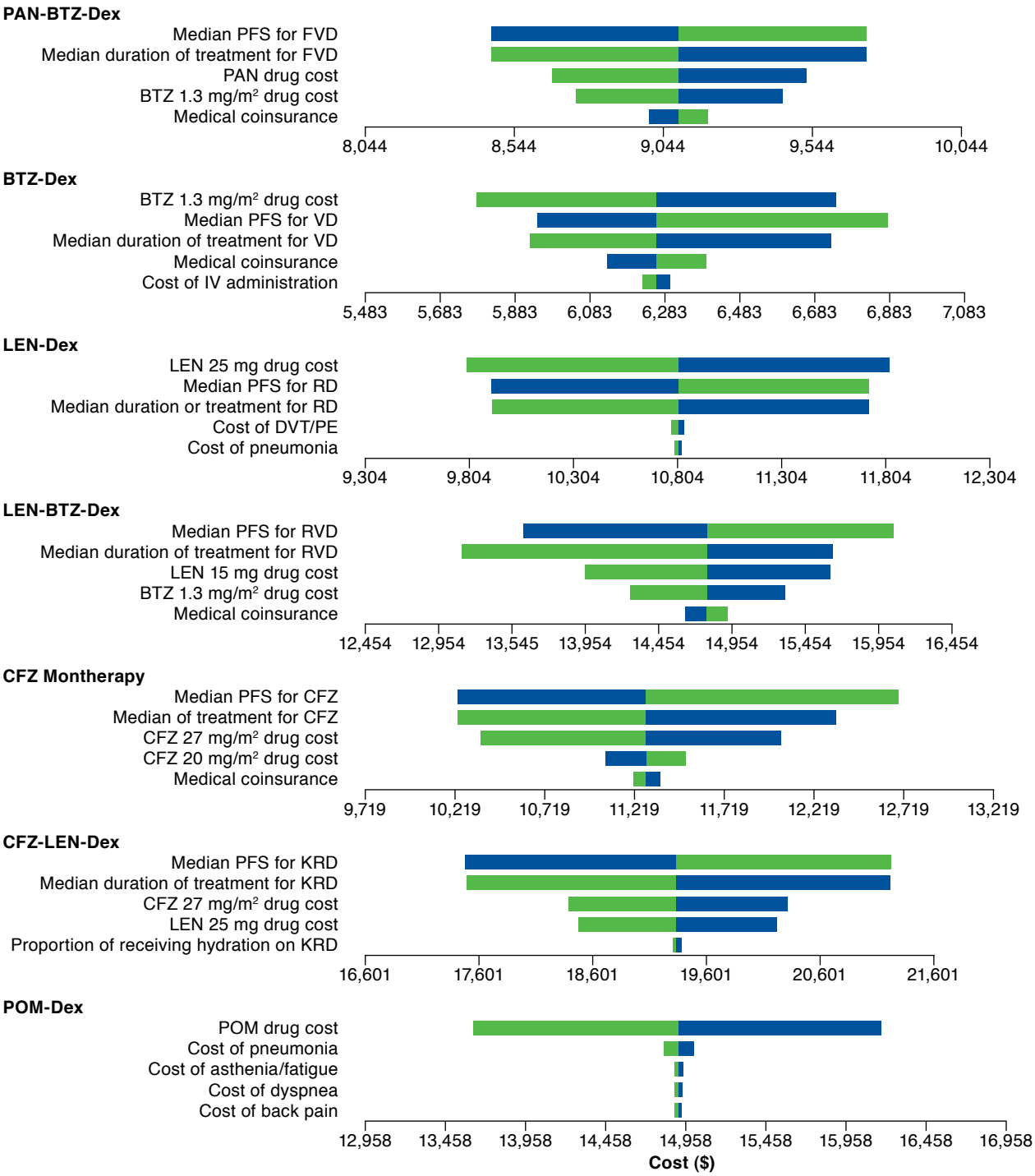
For the outcome of cost per month of PFS for each regimen, median PFS was the most influential factor on model results followed by median DOT (Figure 3B). After these 2 parameters, drug cost was typically the most influential.

## Discussion

Often, an immediate result of the introduction of new drugs into payer formularies is the associated budget impact. Therefore, an economic model was created to quantify the budget impact of the introduction of panobinostat into a typical payer formulary for patients experiencing their second or later relapse who have been previously treated with bortezomib and an IMiD. This model demonstrated that the incremental cost per month associated with the addition of panobinostat is balanced by the treatment benefit of months of PFS gained with panobinostat. In the PANORAMA-1 trial, although the median DOT was shorter with panobinostat versus placebo (5.0 vs. 6.1 months), it significantly extended the median PFS to 12 months (vs. 8.1 months for placebo).[15] Because of this ability to prolong

**FIGURE 3** One-Way Sensitivity Analysis Tornado Chart for the Outcomes of Total Incremental Cost and Cost Per Month of PFS for Each Regimen *(continued)*

**B. Cost Per Month of PFS**




*BTZ = bortezomib; CFZ = carfilzomib; Dex = dexamethasone; DVT = deep vein thrombosis; FVD = panobinostat-bortezomib-dexamethasone; IV = intravenous; KRD = carfilzomib-lenalidomide-dexamethasone; LEN = lenalidomide; PAN = panobinostat; PE = pulmonary embolism; PFS = progression-free survival; POM = pomalidomide; RD = lenalidomide-dexamethasone; RVD = lenalidomide-bortezomib-dexamethasone; VD = bortezomib-dexamethasone.*

PFS beyond the DOT (demonstrated in patients who had received previous treatment with a PI and an IMiD) and the low rates of cost-intensive AEs (e.g., venous thromboembolic events, included as black box warnings for lenalidomide and pomalidomide), panobinostat represents better value compared with other regimens indicated in the RRMM population (with the exception of bortezomib-dexamethasone). Additionally, panobinostat is associated with an acceptable budget impact from the perspective of a health plan formulary, with a projected small incremental PMPM cost of less than $0.01, and it may be cost saving overall because of the low cost per month of PFS gained on panobinostat-bortezomib-dexamethasone, compared with alternative regimens in this population.

RRMM exacts a heavy humanistic and economic burden on patients. Although RRMM remains an incurable disease at present, this population is benefiting from a growing list of approved agents with the ability to prolong PFS. When the PFS benefits extend beyond the DOT, this provides time off of therapy that not only brings about clinical benefit but also humanistic and economic benefit by reducing disease-related symptoms and exposure to treatment-related toxicity, which provides patients with a chance to return to a more normal daily experience.[18] While the availability of options is welcome for relapsing-remitting disease, clinical decision making is becoming increasingly complex, warranting not only further studies comparing the efficacy of various combinations and sequences but also cost-effectiveness analyses to guide choice of a given therapy at time of relapse and retreatment. There has been a paucity of published cost analyses for novel therapies in the RRMM setting, although data have been emerging in recent years.[6,32,33] More specifically, an economic model by Durie et al. (2013) compared total treatment costs along with cost per month without progression for lenalidomide-dexamethasone with bortezomib-dexamethasone, demonstrating substantially higher drug and medical costs (translating into an annual increase of $17,000) with the latter combination.[6] This analysis was limited by the comparison involving only 2 regimens and its consideration of only selected AEs, prompting the development of a more comprehensive treatment cost estimator, which established the framework on which this budget impact analysis is based.[17]

The current model focused on calculating the economic impact of adding panobinostat to the health plan formulary, including pharmacy and medical budget impacts. It was comprehensive, characterizing total annual incremental budget impact, incremental budget impact PMPY, incremental budget impact PMPM, and cost per month without progression. While the monthly cost of panobinostat-bortezomib-dexamethasone was relatively high compared with the alternative treatment regimens (other than carfilzomib-lenalidomide-dexamethasone), the total cost of treating an RRMM patient using the panobinostat-bortezomib-dexamethasone regimen was less expensive than the alternative regimens of lenalidomide-bortezomib-dexamethasone and carfilzomib-lenalidomide-dexamethasone (and lenalidomide-dexamethasone in a Medicare plan) because of the more favorable ratio of median DOT to PFS benefit over the entire year. While offering a competitively priced treatment option for RRMM patients, panobinostat-bortezomib-dexamethasone also offers superior value compared with alternative treatment regimens, with a PFS cost per month of $9,097 in a commercial plan and $8,993 in a Medicare plan.

### Limitations

We acknowledge that this modeling study and its results have limitations. The model took the perspective of a third-party payer, so it only included costs relevant to this audience. Patient out-of-pocket costs (copays and coinsurance) are only considered to the extent that they offset payer costs. Also, indirect costs of lost productivity are not considered in the model. There are other limitations inherent to modeling studies based on data from published sources of clinical trial data and pricing information. In real-world practice, the DOT, adherence to treatment, and dosing schedules may differ from clinical trial experiences. The model is highly sensitive to assumptions of baseline proportions of patients on alternative treatment regimens, which are based on the market share of these products derived from market research data. The budget impact of panobinostat-bortezomib-dexamethasone for any specific health plan will be highly dependent on the most common RRMM salvage therapy regimens used within that plan. Not all possible RRMM salvage therapies used in clinical practice were included in the model. To maintain simplicity and transparency, the model assumed that patients returned to their original treatment regimens upon disease progression, as is recommended by some physicians and some clinical practice guidelines.[11,34] This assumption may not reflect individualized real-world patient treatment pathways; however, the ability to model detailed treatment pathways is limited by data availability. Finally, it is important to emphasize that the purpose of the framework was to compare regimens with respect to cost per month of therapy and costs for 12 months of PFS—not to compare the efficacy of the different treatment regimens, which would be influenced by the variability of the study populations across the clinical trials and prescribing practices in the real-world setting.

## Conclusions

Adding panobinostat to the plan formulary for the treatment of PI- and IMiD-pretreated RRMM, in combination with bortezomib and dexamethasone, is not associated with significant budget impact for a health plan. The neutral or cost-saving budgetary impact is driven by the favorable DOT/PFS ratio in the panobinostat regimen, its comparatively low incidence of costly AEs, and the proportionate reduction in market share for costly alternative regimens.

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## DISCLOSURES

Funding for this study was sponsored by Novartis, East Hanover, New Jersey. Bloudek and Kish are employees of Xcenda, a consulting company contracted by Novartis to conduct this analysis. Roy, Globe, and Kuriakose are employees of Novartis. Siegel is on the advisory boards and speaker's bureau of Celgene, Onyx/Amgen, Millennium/Takeda, and Novartis and is on the advisory boards of Merck. Jagannath is a consultant to Sanofi, Bristol-Meyers Squibb, and Celgene. Orloski is a contractor to Xcenda and provided medical writing support, which was funded by Novartis.

Study design and concept were contributed by Bloudek, Roy, and Kish, assisted by Globe. Bloukek took the lead in data collection, along with Kish, and data interpretation was performed by Siegal, Jagannath, Globe, and Kuriakose. The manuscript was written primarily by Orloski, along with Roy and Kish, and revised by Roy, along with Siegal, Jagannath, Globe, Orloski, and Kuriakose.

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