

# CANADIAN COST ANALYSIS COMPARING MAINTENANCE THERAPY WITH BORTEZOMIB VERSUS LENALIDOMIDE FOR PATIENTS WITH MULTIPLE MYELOMA POST AUTOLOGOUS STEM CELL TRANSPLANT

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## ABSTRACT

### Background

Multiple myeloma (MM) is a cancer caused by malignant plasma cells that accumulate mostly in the bone marrow. In Canada, the most common maintenance therapy options after autologous stem cell transplant (ASCT) are bortezomib and lenalidomide.

### Objective

To determine the incremental cost between bortezomib and lenalidomide maintenance therapies for patients with MM post ASCT.

### Methods

Analyses were conducted to compare the annual costs of bortezomib and lenalidomide maintenance treatments for patients with MM post ASCT in Canada. The base case analysis included the acquisition costs of the drugs and administration costs. Additional analyses were conducted which considered the cost of adverse events (AEs) and the cost of treating second primary malignancies (SPMs).

### Results

In the Canadian healthcare system, the total annual per patient cost was \$33,967 for bortezomib maintenance therapy versus \$131,765 for lenalidomide maintenance therapy. One-way sensitivity analyses demonstrated that both AEs and SPMs had little impact on the incremental cost, and that differences between the two maintenance therapies were mainly due to the acquisition costs of the drugs.

### Conclusions

Bortezomib is significantly less costly than lenalidomide, and is an economically reasonable maintenance treatment option for patients with MM post ASCT.

**Key Words:** *Bortezomib, VELCADE<sup>®</sup>, multiple myeloma, lenalidomide, REVLIMID<sup>®</sup>, cost impact analysis*

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**M**ultiple myeloma (MM) results from the accumulation of malignant plasma cells mostly in the bone marrow. In Canada, MM is the third most prevalent hematological malignancy (after non-Hodgkin lymphoma and leukemia), and

is responsible for 1.8% of all cancer deaths.<sup>1</sup> According to the Canadian Cancer Society's Advisory Committee on Cancer Statistics, in 2015 there will be an estimated 2,700 new cases of MM.<sup>1</sup> With standard therapies, there is no cure for

MM; although, treatment options exist to extend progression free survival and overall survival as well as minimize disease-related symptoms that can significantly reduce quality of life, including pain, fatigue, and bone fractures.<sup>2-4</sup>

National Comprehensive Cancer Network (NCCN) guidelines suggest that younger and fit patients with limited comorbidities who present with symptomatic MM should first be treated with primary induction therapy, followed by high dose chemotherapy and autologous stem cell transplant (ASCT).<sup>5</sup> Post ASCT, patients may be placed on maintenance therapy. The NCCN recommends bortezomib (Velcade<sup>®</sup>), lenalidomide (Revlimid<sup>®</sup>), or thalidomide (Thalomid<sup>®</sup>) regimens as maintenance therapies for patients post ASCT.<sup>5</sup> Although Canadian guidelines for maintenance therapy are not available, treatment patterns are generally aligned with the NCCN recommendations. That is, in Canada, lenalidomide or bortezomib regimens can be used as post ASCT maintenance therapies; however, clinical practice varies by province.<sup>6-9</sup> Thalidomide is not commonly used as maintenance therapy post ASCT in Canadian practice.<sup>9</sup>

Lenalidomide as maintenance therapy for MM post ASCT has been evaluated in two randomized prospective clinical trials.<sup>6,7</sup> Additionally, results from a recent phase III clinical trial reported similar findings in patients eligible for ASCT, however only approximately half of the patients had received ASCT.<sup>10</sup>

Attal and colleagues (IFM 05-02 trial) reported on 614 post ASCT patients, randomized to receive maintenance treatment with either lenalidomide or placebo.<sup>6</sup> Results at a median follow-up time of 30 months demonstrated that lenalidomide improved progression free survival (PFS) when compared with placebo (41 vs. 23 months;  $p < 0.001$ ).<sup>6</sup> In the CALGB 100104 trial, 406 MM patients were randomized to receive maintenance therapy with either lenalidomide or placebo post ASCT.<sup>7</sup> Results at a median follow-up of 34 months demonstrated time to progression was 46 months in the lenalidomide group versus 27 months in the placebo group ( $p < 0.001$ ).<sup>7</sup>

Bortezomib was also evaluated in a randomized prospective trial as maintenance therapy post ASCT. In the phase III HOVON-

65/GMMG-HD4 trial, 827 patients with MM were randomized to receive induction therapy with PAD<sup>i</sup> followed by ASCT and maintenance therapy with bortezomib or induction therapy with VAD<sup>ii</sup>, followed by ASCT and maintenance therapy with thalidomide.<sup>8</sup> Although the study was not randomized specifically for maintenance therapy, an analysis of PFS calculated from the time of last high dose melphalan (HDM) showed a significant difference in favor of the PAD<sup>i</sup> induction and bortezomib maintenance therapy arm versus the VAD<sup>ii</sup> induction and thalidomide maintenance therapy arm (26 vs. 31 months, respectively).<sup>8</sup> Therefore, as reported by Sonneveld and colleagues, although post-transplantation bortezomib and thalidomide both achieved response upgrades, bortezomib contributed more to improvement of PFS.<sup>8</sup>

Lenalidomide and bortezomib are options for the maintenance treatment post ASCT for patients with MM; however, there are no comparative effectiveness studies (i.e., head-to-head RCTs) comparing these treatments in this context. In clinical practice, the choice between treatment options is based on a number of factors including patient characteristics, clinical evidence, and the physician's discretion. In an era of cost containment, it is also important to consider the economic implications of both choices. There are no published data on the relative difference in cost between these two maintenance therapies in this patient population. Therefore, this analysis was conducted to examine the incremental cost difference between bortezomib and lenalidomide maintenance therapies post ASCT for Canadian patients with MM.

## METHODS

An overview of the approach taken to conduct these analyses is presented in Figure 1. This figure depicts the design of the analyses, the inputs used to inform the analyses, and the desired outcomes.

<sup>i</sup>PAD induction therapy included bortezomib, doxorubicin, and dexamethasone. Patient then received high-dose melphalan (HDM) prior to ASCT.

<sup>ii</sup>VAD induction therapy included vincristine, doxorubicin, and dexamethasone. Patient then received HDM prior to ASCT.

**FIG. 1** Analytical Approach: The cost impact analysis was designed for a time horizon of 1 year, from the perspective of the Canadian healthcare system. The different analyses conducted, as well as the inputs and outputs of these analyses, are illustrated.

| Design                                                                                                                                                                                                                                                                                                                                                                                                                                      | Analyses                                                                                                                                                                                                                                               | Inputs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Outcomes                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Perspective</b></p> <ul style="list-style-type: none"> <li>Canadian Healthcare</li> </ul> <p><b>Time Horizon</b></p> <ul style="list-style-type: none"> <li>1 year</li> </ul> <p><b>Population</b></p> <ul style="list-style-type: none"> <li>Patients with Multiple Myeloma who are eligible for ASCT</li> </ul> <p><b>Treatments for MT:</b></p> <ul style="list-style-type: none"> <li>Bortezomib</li> <li>Lenalidomide</li> </ul> | <p><b>Base Case</b></p> <ul style="list-style-type: none"> <li>Treatment costs only</li> </ul> <p><b>Additional Analyses</b></p> <ol style="list-style-type: none"> <li>Including AE treatment costs</li> <li>Including SPM treatment costs</li> </ol> | <p><b>Base Case</b></p> <ul style="list-style-type: none"> <li>Dosing regimen</li> <li>Administration requirements</li> </ul> <p><b>Additional Analyses</b></p> <ol style="list-style-type: none"> <li><b>Including AEs</b> <ul style="list-style-type: none"> <li>Dose adjustments (i.e., RDI)</li> <li>Probability of experiencing an AE</li> <li>Probability of being hospitalized</li> <li>Hospitalization costs</li> <li>Outpatient treatment costs</li> </ul> </li> <li><b>Including SPMs</b> <ul style="list-style-type: none"> <li>Probability of developing an SPM</li> <li>SPM treatment costs</li> </ul> </li> </ol> | <p><b>Incremental Cost Differences per Patient</b></p> <ul style="list-style-type: none"> <li>Drug costs</li> <li>Total treatment costs</li> <li>AE treatment costs</li> <li>SPM treatment costs</li> </ul> <p><b>Net Cost Impact per Patient</b></p> <ul style="list-style-type: none"> <li>MTs only (base case)</li> <li>MTs + AEs</li> <li>MTs + AEs + SPMs</li> </ul> |

AE: Adverse event; ASCT: autologous stem cell transplant; MT: maintenance therapy; RDI: relative dose intensity; SPM: second primary malignancy

## Analyses

In the base case analysis, acquisition costs and the administration costs for each regimen were considered. Additional analyses were conducted to consider the economic impact of also including the cost of:

- managing adverse events (AEs) associated with each regimen; and
- managing AEs and treating second primary malignancies (SPMs) associated with each regimen.

## Parameters

Clinical inputs including dosing, AEs and SPM rates were derived from published trials that evaluated bortezomib<sup>8</sup> or lenalidomide<sup>6,7</sup> maintenance therapy in post ASCT MM patients. Canadian clinical expert opinion further informed the clinical inputs to ensure assumptions reflected Canadian practice (Table 1). Cost inputs (e.g., drug unit costs, labour costs) were obtained from public Canadian sources (Table 1).

## Maintenance Therapies

### *Dose Regimen*

The lenalidomide dose utilized in these analyses was an oral administration of 10 mg daily. The dose chosen for the analysis was within the range (10 – 15 mg per day) reported within the two trials evaluating lenalidomide as maintenance therapy post ASCT.<sup>6,7</sup> The lower end of the range was selected after consultation with clinicians who suggested this was more reflective of Canadian clinical practice. (*opinion of clinical authors*)

The bortezomib dose utilized in these analyses was a 1.3 mg/m<sup>2</sup> intravenous (IV) administration every two weeks, which was the recommended dose in the HOVON-65/GMMG-HD4 trial.<sup>8</sup> However, in Canadian practice, subcutaneous (SC) administration is the preferred route of administration.<sup>11</sup> The IV administration use was considered conservative as the AEs and subsequent costs may be higher than for SC administration, and was therefore selected in these analyses.<sup>11</sup>

Nevertheless, further research is required comparing SC and IV bortezomib for maintenance therapy in post ASCT patients. The economic impact of SC administration was assessed in sensitivity analyses. The bortezomib dose regimen utilized in these analyses was also validated by Canadian experts.

### **Acquisition Costs**

The acquisition costs of bortezomib and lenalidomide were estimated based on the Pan-Canadian Oncology Drug Review Final Recommendations. The unit costs reported were \$1,869.89 per 3.5 mg vial for bortezomib<sup>12</sup> and \$361.00 per 10 mg tablet for lenalidomide<sup>13</sup> (Table 1). The application of mark-up and dispensing fees to the acquisition costs of oral drugs is variable in Canada, and influenced by several factors including provincial regulation differences. For these analyses, pharmacy fees were not added to the acquisition cost of lenalidomide. This was because it was assumed that lenalidomide may be obtained from a hospital pharmacy, and would not be subjected to a pharmacy mark-up or dispensing fees.

### **Administration Costs**

In these analyses, bortezomib was considered to be administered intravenously. The per-hour administration unit cost was estimated by Tam and colleagues and included the preparation of the regimen, chemotherapy chair time, hourly wage for the pharmacist, hourly wage for the chemotherapy nurse, and overhead costs for the hospital.<sup>14</sup> The \$178 per hour 2010 cost was inflated to 2014 dollars (\$182 per hour) using the health care component of the Consumer Price Index for Canada.

The administration time for bortezomib was estimated based on the administration information provided in the Cancer Care Ontario BORT Regimen (1.3 mg/m<sup>2</sup> bortezomib every two weeks).<sup>15</sup> The approximate time for a patient visit was cited as 0.5 hours. Although in practice bortezomib may be administered quickly, within a few seconds, the cost of a 30 minute visit was considered for costing purposes. Therefore, based on the cost of \$182 per hour, bortezomib would cost \$91 per half-hour administration. This

translates into \$2,366 for one year of treatment. No administration costs were applied for lenalidomide as it is administered orally.

### **Adverse Events**

#### ***Probability of Experiencing AEs***

For the purpose of these analyses, included AEs were  $\geq$  grade 3 and broadly classified into three groups. Firstly, hematological events included neutropenia, thrombocytopenia, anemia, and febrile neutropenia. Secondly, gastrointestinal (GI) symptoms included nausea/vomiting, and diarrhea. Finally, the group termed ‘other non-hematological events’ included pain/peripheral neuropathy, infections, venous thrombotic events/pulmonary embolisms, rash, fatigue, and cardiac events. The probability of experiencing AEs was derived from the clinical trials evaluating bortezomib<sup>8</sup> or lenalidomide<sup>6,7</sup> and validated based on Canadian expert opinion. For bortezomib, the probability of experiencing an AE was derived from the number of patients experiencing AEs reported in the HOVON-65/GMMG-HD4 trial. For lenalidomide, the probability of experiencing an AE was the weighted average of the AEs reported in the CALGB 100104 and the IFM 05-02 trials.<sup>6,7</sup>

#### ***AE Management Costs***

AE management costs were applied as a onetime tariff in these analyses to reflect the fact that treatment-emergent AEs generally occur during the initial cycles of treatment. The costs of managing each AE was dependent on if hospitalization was required, or if the patient could be treated as an outpatient.

The estimated proportion of patients that would be hospitalized for each AE was informed by expert opinion. Febrile neutropenia was the only AE that required hospitalization in 100% of patients. Cardiac events were also expected to have a majority of patients requiring hospitalization (75%). In contrast, patients experiencing a number of AEs (e.g., fatigue, neutropenia, anemia, and pain) were not expected to be hospitalized. The remaining AEs were expected to include a combination of patients who required either hospitalization (5-30%) or outpatient care (70-95%) (Table 1).

**TABLE 1** Key Parameter Inputs and Unit Costs for Bortezomib and Lenalidomide

| Parameters                                              | Bortezomib                               | Lenalidomide                            |                                                     |
|---------------------------------------------------------|------------------------------------------|-----------------------------------------|-----------------------------------------------------|
| <b>MT</b>                                               |                                          |                                         |                                                     |
| Dosing Regimen                                          | 1.3 mg/m <sup>2</sup> every 2 weeks      | 10 mg daily                             |                                                     |
| Cost of Therapy                                         | \$1,869.89 per 3.5 mg vial <sup>12</sup> | \$361.00 per 10 mg tablet <sup>13</sup> |                                                     |
| <b>Clinical Parameters and Cost Inputs</b>              |                                          |                                         |                                                     |
| Grade 3/4 AEs<br>(% patients requiring hospitalization) | Bortezomib <sup>a</sup>                  | Lenalidomide <sup>b</sup>               | Treatment Costs<br>Per Patient <sup>c (16-18)</sup> |
| <b>Hematological AEs</b>                                |                                          |                                         |                                                     |
| Neutropenia (0%)                                        | 0%                                       | 49%                                     | \$61                                                |
| Thrombocytopenia (10%)                                  | 4%                                       | 14%                                     | \$915                                               |
| Anemia (0%)                                             | 1%                                       | 4%                                      | \$259                                               |
| Febrile neutropenia (100%)                              | n/r                                      | 3%                                      | \$6,921                                             |
| <b>GI Symptoms</b>                                      |                                          |                                         |                                                     |
| Nausea/Vomiting (20%)                                   | n/r                                      | 1%                                      | \$997                                               |
| Diarrhea <sup>d</sup> (20%)                             | 5%                                       | 3%                                      | \$2,006                                             |
| <b>Other Non-Hematological AEs</b>                      |                                          |                                         |                                                     |
| Cardiac Events <sup>e</sup> (75%)                       | 3%                                       | 0%                                      | \$6,433                                             |
| Pain/Neuropathy peripheral <sup>f</sup> (0%)            | 5%                                       | 2%                                      | \$67                                                |
| Infections <sup>g</sup> (30%)                           | 24%                                      | 14%                                     | \$2,474                                             |
| VTE/pulmonary embolism <sup>h</sup> (15%)               | n/r                                      | 3%                                      | \$3,357                                             |
| Rash <sup>e</sup> (5%)                                  | n/r                                      | 4%                                      | \$503                                               |
| Fatigue (0%)                                            | 1%                                       | 5%                                      | \$61                                                |
| <b>SPMs<sup>i</sup></b>                                 |                                          |                                         |                                                     |
|                                                         | 0.6%                                     | 2.5%                                    | \$68,035 <sup>21</sup>                              |

a. Grade 3 and 4 AEs as reported by Sonneveld (2012)

b. Grade 3 and 4 AEs taken as a weighted average of Attal (2012) and McCarthy (2012).

c. Treatment costs per AE per patient include weighted hospitalization and outpatient costs. All costs were inflated to 2014 CAD. Treatment costs for SMPs reflect an average cost per course of oncology treatment per patient.

d. For Sonneveld (2012), GI symptoms were reported as a single group and therefore for comparability, the rate has been included under the category of diarrhea, the most common grade 3 or 4 GI symptom.

e. Cardiac events and rash were not specifically described and therefore the exact type is unclear across trials.

f. For Attal (2012), pain included peripheral neuropathy (4/306) and back pain (4/306). For Sonneveld (2012), pain included peripheral neuropathy.

g. For Attal (2012), infections included upper respiratory infection (7/306), pneumonia (11/306), herpes zoster (7/306). For McCarthy (2012), infection included 'infection with normal ANC or Gr 1/2 neutropenia' (13/231) and infection, clinical or microbiological (14/231), and pneumonitis (6/231). For Sonneveld (2012), infections were classified broadly and there were no descriptions provided, except for herpes zoster, which was reported separately (0/229).

h. For Attal (2012), vascular events included deep-vein thrombosis (7/306), and pulmonary embolism (4/306), however in McCarthy (2012) the data was only for thrombosis (3/231). For Sonneveld (2012), thrombosis was broadly classified.

i. Only hematologic and solid second primary cancers were included in this tabulation. For Attal (2012), the second primary cancers were reported at a median follow-up of 45 months from the time of randomization. For McCarthy, the second primary cancer was reported and the median time from randomization was 28 months. For Sonneveld (2012), an SPM value was not reported.

AE: Adverse event; GI: gastrointestinal; MT: maintenance therapy; SPM: second primary malignancy

Hospitalization costs were obtained from the Ontario Case Costing Initiative.<sup>16</sup> Outpatient resource use was informed by clinical opinion and included oncologist visits, laboratory tests, drug treatments, and potential nurse care. Unit costs were obtained from the Ontario Schedule of Benefits,<sup>17</sup> the Ontario Drug Benefits Formulary,<sup>18</sup> and other Canadian public sources. The total costs assigned to each AE are depicted in Table 1.

Chemotherapy dose reductions as a result of AEs were assumed to occur, and therefore an estimated relative dose intensity (RDI) of 0.8 was applied to both lenalidomide and bortezomib maintenance therapies. This RDI value is consistent with the trial reported by Attal and colleagues;<sup>6</sup> however, published data were unavailable for the other trials.<sup>7,8</sup> The application of an RDI of 0.8 was considered appropriate by clinical experts.

## Second Primary Malignancies

### *Probability of Developing SPMs*

The probability of developing a SPM over the course of one year was derived from the clinical trial data.

For bortezomib treatment, the HOVON-65/GMMG-HD4 publication did not report SPMs;<sup>8</sup> however, extended follow-up data was presented in an abstract by Sonneveld and colleagues in 2013 which reported the actuarial probability to develop SPM to be 3% at 5 years.<sup>19</sup> These data were used to estimate the probability of developing an SPM at one year for bortezomib (0.6%) using the methodology described by Fleurence and colleagues and the following equations (where  $p$  is the probability,  $r$  is the rate,  $t$  is the unit of time):<sup>20</sup>

$$p = 1 - e^{-rt}$$
$$r = -\frac{1}{t} \ln(1 - p)$$

IFM 05-02 trial reported that 23 patients out of 306 who received lenalidomide developed at least one SPM (excluding non-melanoma skin cancers); the median follow-up in trial was 45 months.<sup>7</sup> It was observed in the CALGB 100104 trial that 18 patients out of 231 who received lenalidomide developed a SPM (excluding non-

melanoma skin cancers); the median follow-up in the trial was 34 months.<sup>6</sup> Therefore the one-year probability of developing a SPM was estimated for each trial to be 2.3% and 2.8%, respectively, based on the previously described methodology. The weighted average of the two estimates (2.5%) was utilized in these analyses.

### *SPM Treatment Costs*

The cost to treat SPMs utilized in these analyses was estimated as an average cost of an oncology treatment per patient.<sup>21</sup> This value was derived from the Cancer Care Society report estimating \$65,000 as the average cost per oncology treatment per patient, and inflated to \$68,035 in 2014 Canadian dollars, as shown in Table 1.

### **Deterministic Sensitivity Analyses**

One-way sensitivity analyses were conducted on key inputs including drug acquisition cost, administration cost, AE management cost, and SPM treatment cost. Each parameter was varied independently by  $\pm 20\%$ .

In addition, several sensitivity analyses were conducted to evaluate alternate assumptions. First, an alternative value of 1.0 for RDI was evaluated to assess the effect of not including chemotherapy dose adjustments. Second, an alternate assumption for the route of bortezomib was considered. A randomized phase III trial comparing SC and IV administration of bortezomib demonstrated both routes of administration conferred similar efficacy; however, SC administration had a better safety profile.<sup>11</sup> Peripheral neuropathy was significantly lower in patients who received SC bortezomib compared with IV bortezomib (i.e., grade 3 or worse was 6% vs. 16%;  $p=0.026$ ).<sup>11</sup> Therefore a sensitivity analysis was conducted to evaluate the impact of SC administration with a lower probability of grade 3 or greater peripheral neuropathy. Finally, the impact of potential drug wastage was considered for bortezomib. Based on a body surface area of 1.75 m<sup>2</sup>, the amount of bortezomib required per patient per administration would be 2.275 mg. Given that bortezomib is available in a 3.5 mg vial, if there was only one patient treated at a single center, the potential drug waste could be up to 35%. Although this is

assumed to be uncommon in Canadian practice, this scenario was evaluated to assess the impact of drug wastage on the incremental differences in costs between maintenance treatments.

## RESULTS

For the base case (considering only the drug acquisition costs and administration costs) the

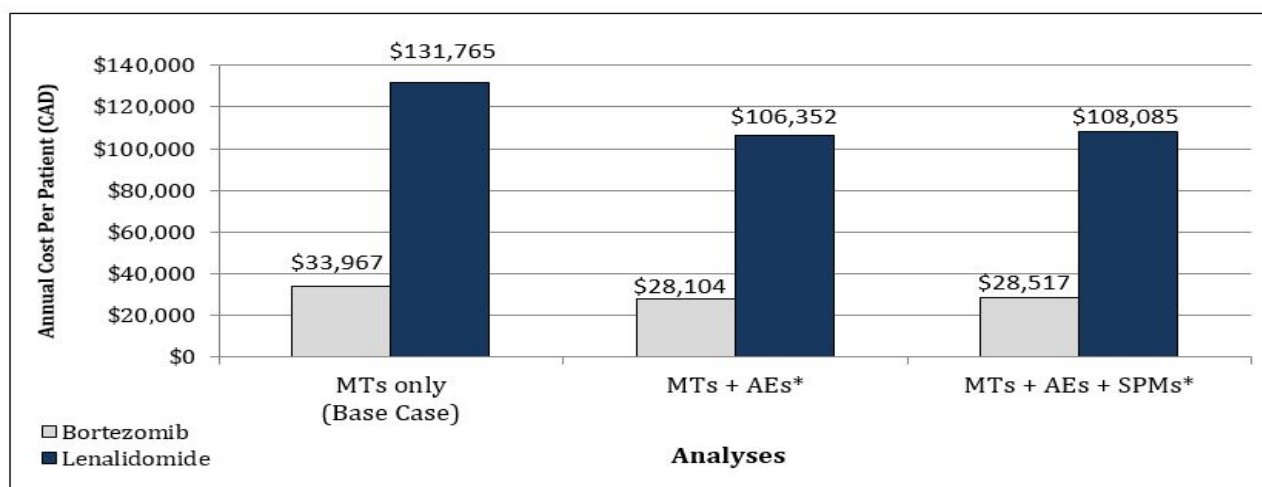
total annual costs of treatment per patient was \$33,967 for bortezomib maintenance therapy and \$131,765 for lenalidomide maintenance therapy (see Table 2 and Figure 2). Therefore, the base case analysis demonstrates that, from a Canadian public payer perspective, bortezomib maintenance therapy is significantly less costly when compared with lenalidomide maintenance therapy post ASCT.

**TABLE 2** Total Annual Patient Costs per Maintenance Treatment and Incremental Cost Differences

|                                                               | Bortezomib      | Lenalidomide     | Incremental Cost Difference for Bortezomib vs. Lenalidomide |
|---------------------------------------------------------------|-----------------|------------------|-------------------------------------------------------------|
| <b>MTs only (Base Case)</b>                                   |                 |                  |                                                             |
| Drug costs                                                    | \$31,601        | \$131,765        | -\$100,164                                                  |
| Administration/pharmacy costs                                 | \$2,366         | \$0              | \$2,366                                                     |
| <b>Total</b>                                                  | <b>\$33,967</b> | <b>\$131,765</b> | <b>-\$97,798</b>                                            |
| <b>MTs + AEs</b>                                              |                 |                  |                                                             |
| MTs                                                           | \$33,967        | \$131,765        | -\$97,798                                                   |
| Adverse Events treatment costs                                | \$930           | \$940            | -\$10                                                       |
| Dose adjustments (i.e., lower RDI leading to cost reductions) | -\$6,793        | -\$26,353        | \$19,560                                                    |
| <b>Total</b>                                                  | <b>\$28,104</b> | <b>\$106,352</b> | <b>-\$78,248</b>                                            |
| <b>MTs + AEs + SPMs</b>                                       |                 |                  |                                                             |
| MTs + AEs                                                     | \$28,104        | \$106,352        | -\$78,248                                                   |
| SPM treatment costs                                           | \$413           | \$1,733          | -\$1,320                                                    |
| <b>Total</b>                                                  | <b>\$28,517</b> | <b>\$108,085</b> | <b>-\$79,568</b>                                            |

AE: adverse event; MT: maintenance therapy; RDI: relative dose intensity; SPM: second primary malignancy

**FIG. 2** Results of Analyses for the Total Annual Patient Costs by Maintenance Therapy

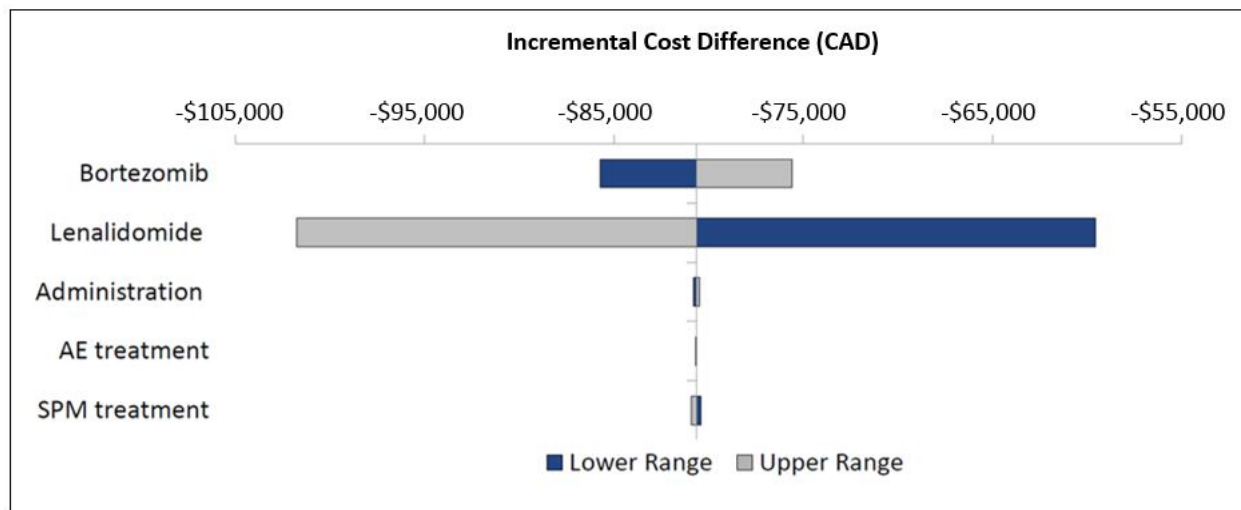


\*An RDI of 0.8 was applied to account for dose adjustments due to AEs which resulted in cost reductions. AE: adverse event; CAD: Canadian dollars; MT: maintenance therapy; RDI: relative dose intensity; SPM: second primary malignancy

Further analyses considering the additional costs of managing AEs (including hospitalization, outpatient care, and chemotherapy dose adjustments) also demonstrated cost savings (\$78,248 per-patient-per-year) associated with bortezomib maintenance therapy. Further still, when also including the costs associated with the treatment of SPMs, the incremental savings associated with bortezomib maintenance therapy was \$79,568. Therefore in all three analyses including treatment related costs, bortezomib maintenance therapy was the far less costly option than lenalidomide maintenance (Table 2 and Figure 2). For all of the cost inputs tested in the one-way sensitivity analyses, the incremental

difference in cost between bortezomib and lenalidomide ranged between approximately -\$60,000 to -\$100,000 per patient per year of treatment (Figure 3), illustrating that the findings were fairly robust to changes in the key cost inputs. The difference in overall costs between the two maintenance therapies was mainly due to the acquisition costs of the drugs, and, to a much lesser extent, administration fees. These one-way sensitivity analyses demonstrated that both AEs and SPMs had little impact on the incremental difference in cost between bortezomib and lenalidomide maintenance therapy post ASCT (Figure 3).

**FIG. 3** One-way Sensitivity Analyses of  $\pm 20\%$  for the Key Cost Inputs (Tornado Diagram)



AE: Adverse event; CAD: Canadian dollars; SPM: second primary malignancy

The results of the additional sensitivity analyses testing alternate assumptions for RDI and SC administration demonstrated that the cost savings associated with bortezomib increased. For example, when the RDI was assumed to be equal to 1.0 the cost savings associated with bortezomib maintenance therapy increased from \$79,568 to \$99,128.

Further, adjustment for SC administration compared with IV administration for bortezomib resulted in almost no change in the costs associated with managing AEs (from \$930 to

\$928). This is because the probability of developing peripheral neuropathy was the only parameter that was adjusted (from 5% to 2%), and the management cost was very low.

Conversely, when the potential maximum wastage was considered in the analyses (including drug acquisition, RDI, administration, AE, and SPM costs), the cost savings associated with bortezomib decreased from \$79,568 to \$65,956. However the overall conclusion is the same; bortezomib is a lower cost alternative when



compared with lenalidomide as maintenance therapy for patients with MM post ASCT.

## DISCUSSION

The economic implications of treatment decisions are of high importance in the current healthcare landscape. This analysis sought to compare the cost of two treatments, bortezomib and lenalidomide, as maintenance therapy options for patients with MM following ASCT. The results suggest that, overall, bortezomib is much less costly than lenalidomide; this difference was driven primarily by the annual acquisition costs of the two therapies. Compared with lenalidomide, the savings associated with bortezomib ranged from \$65,956 to \$99,128 per year depending on the breadth of costs incorporated and variations in assumptions regarding treatment. These results provide another consideration in the already-complex decision making process of how best to approach treatment for patients with MM post ASCT.

In Canadian practice, both lenalidomide and bortezomib regimens can be used as maintenance therapies for patients with MM post ASCT; however, clinical practice varies by province.<sup>9</sup> For example, the Alberta Health Services clinical practice guidelines for MM indicate that lenalidomide or bortezomib may be used as maintenance therapy depending on the patient population.<sup>9</sup> While the level of evidence is higher for lenalidomide than that for bortezomib in this specific patient population, as noted by the NCCN, treatment guidelines recommend either therapy, and treating physicians may prescribe bortezomib, amongst other factors based on positive personal experiences with the drug or the apparent superiority in high risk patients.<sup>22</sup> However, despite the use of both treatments, differences in their annual costs may not be readily apparent.

On the basis of clinician feedback, the analysis considered not only the annual acquisition costs of each treatment but also costs associated with administration, AE management, and the treatment of SPMs. Estimates of the probability of developing AEs and SPMs and their associated treatment costs were derived from

clinical trials evaluating post ASCT maintenance therapy with lenalidomide or bortezomib, although head-to-head clinical data were unavailable. Importantly, while bortezomib is administered via IV/SC, the current analysis indicates that it is associated with a significant cost savings when compared with lenalidomide given that lenalidomide is administered daily.

To estimate the magnitude of the economic impact of individual parameters, all of the cost inputs were tested in sensitivity analyses. For example, the results of a one-way sensitivity analysis indicated that the costs of managing AEs were not cost drivers. Therefore, even if there were differences in the AEs between the two maintenance therapies, the economic impact of these events would be minimal. Similarly, sensitivity analysis indicated that the costs associated with the treatment of SPMs had a minimal economic impact. Although these results suggest that the analysis was robust to changes in key parameters, the analysis should be re-evaluated if head-to-head clinical data become available.

A limitation of this costing analysis is that there is heterogeneity in the study design and reporting methods across the trials that were used to inform this cost comparison. It is therefore important to note the potential impact of such heterogeneity on the current analysis. Firstly, SPM rates were inconsistently reported in the clinical trials evaluating bortezomib and lenalidomide, with median follow-up durations that ranged from 34 to 60 months.<sup>6,7</sup> Calculations were conducted to adjust all of the data to a one-year probability assuming a linear relationship; however, given that the SPM rates in the trials were captured over varying time periods, it is possible that over or underestimation occurred (i.e., trials with a shorter follow-up time may not capture as many SPMs and therefore the annual probability may be underestimated). Secondly, heterogeneity was also noted in that heavier consolidation treatment was reported in the IFM 05-02 trial<sup>6</sup> compared with either the CALGB 100104 trial<sup>7</sup> or the HOVON-65/GMMG-HD4 trial.<sup>8</sup> This may have contributed to the higher discontinuation rates in the maintenance therapy phase observed in the study reported by Attal and

colleagues,<sup>6</sup> and potentially contributed to higher rates of AEs. Another limitation of this analysis is that indirect costs such as productivity, social services, and other costs outside the health care system were not included and therefore the impact of these parameters have not been quantified. However this costing analysis was considered from the Canadian public payer perspective and therefore the focus was only on the impact of direct costs to the health care system. Future analyses may be conducted to elucidate the incremental costs associated with maintenance therapies from a societal perspective.

In Canada, both bortezomib and lenalidomide may be used as maintenance therapies post ASCT in patients with MM. Clinical practice may depend on many factors (e.g., patient characteristics, clinical evidence, and the physician's discretion). It is also important to consider the relative cost of the treatment options. These analyses demonstrated that bortezomib maintenance therapy post ASCT was much less costly than lenalidomide. While further research is needed, from an economic perspective, bortezomib is clearly a reasonable treatment option for maintenance therapy of Canadian patients with MM post ASCT.

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