pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Bortezomib (Velcade) for Multiple Myeloma

March 25, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by the CCO Hematology Disease Site Group** compared bortezomib to vincristine, doxorubicin and dexamethasone (VAD) in induction, and several different comparators for maintenance therapy, among patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). Bortezomib is used in combination with dexamethasone or other agents prior to ASCT (induction therapy) and used as monotherapy post-ASCT (maintenance therapy).

According to the pCODR Clinical Guidance Panel (CGP), appropriate comparators for induction therapy in Canada are high dose dexamethasone (HDD), or, less frequently, VAD. The Submitter did not include comparison to induction with HDD in modifications to the main economic analysis, acknowledging that there are no head-to-head trials with this comparator. According to the Submitter, VAD is associated with an increased incidence in adverse events related to two of the components vincristine and doxorubicin, without increased response rates compared to dexamethasone alone (Section 4.3.1 of submitted Pharmacoeconomic Report). This suggests no difference in the effectiveness of VAD compared to HDD except for additional toxicities. There is also additional cost with VAD compared to HDD.

The standard of care for maintenance in Canada is observation only, as maintenance therapy is not currently funded (including thalidomide, the comparator used in the main analysis). The Submitter did include a comparison to observation-only maintenance, but without head-to-head clinical trial evidence.

Bortezomib and vincristine are administered intravenously, doxorubicin is administered through continuous infusion, and dexamethasone and thalidomide are oral. Bortezomib can also be administered subcutaneously, which the Submitter suggests is the preferred route of administration over IV because it results in lower incidence of peripheral neuropathy and requires shorter chemotherapy administration time (Moreau et al 2011). The Submitter assumes that subcutaneous bortezomib would be used in clinical practice, and the submitted model assumes no difference between subcutaneous and IV bortezomib, except in rates of toxicities and chemotherapy administration costs.

Patients considered the following factors important in the review of bortezomib, which are relevant to the economic analysis: quality of life and disease symptom control; access to less toxic and more targeted regimens; and choice in available treatments, particularly to avoid side-effects of other treatments (e.g. infections with VAD).

The **Provincial Advisory Group (PAG)** considered several factors that would be important to consider if implementing a funding recommendation for bortezomib, and which are relevant to the economic analysis. PAG noted that the induction regimen of bortezomib in combination with dexamethasone and with or without cyclophosphamide is funded in some jurisdictions, while maintenance therapy would be a new indication. PAG expressed concern about increased chemotherapy administration/clinic time with maintenance bortezomib, as well as the burden and accessibility for the schedule of administration (once every two weeks for two years). PAG noted wastage could be an issue in smaller jurisdictions or those where extended stability of bortezomib is not permitted.

Bortezomib costs $1,869.89 per 3.5 mg vial. At the recommended dose of 1.3mg/m^2 and using body surface area of 1.75 m^2, the cost of bortezomib per dose is $1,215.43, and the cost per cycle in induction is $4,861.71.

1.2 Summary of Results

Overview

The Clinical Guidance Panel (CGP) has identified a net clinical benefit to the use of upfront bortezomib as part of first-line therapy with ASCT, although the exact gain is difficult to quantify. According to the CGP, there is evidence of a statistically significant benefit in progression-free survival (PFS) with up-front bortezomib. The studies that have demonstrated PFS gain involved some bortezomib post-transplant, although the studies have not provided sufficient evidence to clarify the optimal timing and duration for the addition of upfront bortezomib.

The Submitter included 4 main analyses to address the addition of bortezomib therapy to front line treatment in patients with multiple myeloma receiving high dose chemotherapy and ASCT. Given that the submitter was the CCO Hematology Disease Site Group, only published studies were used to populate the economic models. There are few studies that have examined bortezomib usage upfront with ASCT against a comparator appropriate to Canada. Thus, the submitted models have some limitations with respect to their validity for evaluating the drug in this context and the reliability of the results.

Two of the submitted analyses were not based on suitable clinical evidence: the first analysis was based on a study that examined the benefit of maintenance using thalidomide and prednisone (Stewart et al 2011), which is not relevant to this review because it does not involve bortezomib; the second analysis was based on a meta-analysis of trials for bortezomib pre- and post-ASCT, but was reported in abstract form only (Nooka et al 2011). The third submitted analysis used survival data from the IFM-2005-01 trial (Harousseau et al 2010) that may be compromised by subsequent treatment, given that following induction (with bortezomib and dexamethasone or VAD) and ASCT, 60% of patients in each treatment arm were enrolled prior to progression to the follow-up study (IFM-2005-02) for consolidation and maintenance with lenalidomide. The EGP reanalyzed this model and report the results, but the results should be interpreted with caution because of the above noted limitation.

The EGP used the remaining model, based on the HOVON-65/GMMG trial (Sonneveld et al 2012) to assess the cost-effectiveness of bortezomib pre- and post-ASCT therapy. The HOVON-65/GMMG trial compared bortezomib, doxorubicin and dexamethasone in induction and bortezomib alone every two weeks for two years in maintenance to VAD in induction and thalidomide daily in maintenance (Sonneveld et al 2012). The model using these data was re-analyzed to better suit the Canadian context and to help address uncertainty around the cost-effectiveness of the therapeutic approach, given that the study did not use an appropriate comparator. As supplementary analyses, the EGP used the remaining analyses described above, along with other modifications to the main analysis.

Data Inputs and Model Validation

To incorporate the survival data from published sources, the Submitter chose the clinical inputs so that the model closely matched the survival data for the first 48 months (beyond which only 10% remained at risk). While the EGP would like to have seen further assessment to ensure the clinical data were accurately captured by the model, to check the validity the EGP compared the outcomes for the cohorts in each group to published information. For example, the 3 year PFS rates observed in each group in the main analysis were similar to the trial. Similarly, the 5 year OS rates from the trial were observed in both model treatment arms. The 10 year survival among patients under 60, which might be a similar patient population to those eligible for ASCT is 30% (Brenner et al 2008); in the model, about 33% of each cohort were alive at 10 years. Thus, while the clinical inputs

used in the model are not ideal, they do appear reasonable. Since there is no long-term data or full patient-level data to support the projections, the Submitter attempted to mitigate any long-term impact of the survival curve estimations by using equal values for the two groups beyond the four years of trial data, which they suggest is a conservative approach. In other words, after four years in the model, patients receiving bortezomib and patients receiving the comparator share the same risks of progression and death.

EGP Reanalysis Results

The EGP modified the main analysis based on clinical opinion and a National Institute for Health and Clinical Excellence (NICE) review for this indication (NICE 2013, Final Scope) to reflect a shortened time horizon of 20 years and removed thalidomide maintenance comparator costs to reflect more accurately the incremental cost between upfront bortezomib pre- and post-ASCT and standard induction followed by observation only. The EGP also explored the implications of drug wastage.

The submitted model included the cost of maintenance for all patients except in instances of progression or death (as per trial design). However, the actual percentages of patients who begun and completed maintenance in the clinical trial were lower: less than 60% begun maintenance after ASCT, and less than 50% of those who begun maintenance completed 2 years (Sonneveld et al 2012). The EGP explored the cost implications of maintenance use similar to the trial, recognizing that some non-progressed patients did not receive the full course of maintenance therapy, perhaps because they were not suitable candidates following ASCT or may have refused or discontinued therapy.

When bortezomib combination induction and bortezomib maintenance is compared with standard induction and observation-only maintenance therapy, the EGP estimates that the incremental cost-effectiveness ratio is between $130,874 / QALY gained and $271,642 / QALY gained. The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $**182,619 / QALY gained**.

The incremental cost reported in our reanalysis should adequately reflect the correct comparison to observation in the maintenance period and includes costs according to protocol. The range is based on costs that reflect wastage on the high end, and on the low end, use of maintenance following induction and ASCT similar to the clinical trial. The incremental clinical benefit is based on the clinical trial and may be an underestimate of the true gain for bortezomib compared to observation only. As such, we expect these results to be conservative, notwithstanding the caveats of no long-term data or full patient-level data to support the projections.

For induction and maintenance, the incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost (ΔC) of bortezomib is between $47,843 and $99,303. The incremental cost is affected by wastage and percentage of patients who begin and complete maintenance therapy.
- the extra clinical effect (ΔE) of bortezomib is estimated to be 0.366 QALYs. The clinical effect is based on the clinical trial of bortezomib compared to thalidomide maintenance therapy, and may be an underestimate of the true gain for bortezomib compared to observation only.

The EGP based these estimates on the model submitted and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model for induction and maintenance showed that when:

- bortezomib is compared to observation-only maintenance costs (removal of thalidomide costs) the extra cost of bortezomib is \$66,759 (ΔC_{main}).
- the percentage of patients who begin and complete maintenance therapy is similar to the clinical trial, the extra cost of bortezomib without any wastage is \$47,843 (ΔC_{low}).
- wastage is included, the extra cost of bortezomib could be as high as \$99,303 (ΔC_{high}).
- the time horizon is shortened to 20 years, a more relevant time horizon for multiple myeloma, the extra clinical effect of bortezomib is 0.366 (ΔE_{main}), which has only a small impact on the estimated incremental effect and the incremental cost-effectiveness ratio.

For **bortezomib induction therapy only** compared to VAD, the EGP's best estimate of the incremental cost effectiveness ratio (ΔC / ΔE) of **\$101,761/ QALY gained** without wastage, and \$150,856 / QALY gained with wastage. As mentioned, caution should be taken when interpreting these results because of limitations in the survival data.

For induction and maintenance with bortezomib, the EGPs estimates differed from the submitted estimates. For induction alone, the EGP's estimated incremental cost-effectiveness ratio is similar to that estimated by the Submitter.

According to the Submitter, when bortezomib combination induction and bortezomib maintenance is compared with VAD induction followed by thalidomide maintenance:

- the extra cost (ΔC) of bortezomib is \$50,500. Costs considered in the analysis included costs of trial regimens from HOVON-65/GMMG, which includes the cost of thalidomide, which is not an option for maintenance in Canada. This analysis does not include wastage and has a lifetime, (50 year) time horizon.
- the extra clinical effect (ΔE) of bortezomib is 0.37 quality-adjusted life years gained. The clinical effect considered in the analysis was based on a lifetime (50 year) time horizon.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was \$131,100/ QALY gained. The submitter also provided a range of estimates based on less rigorous evidence from \$99,200 - \$225,700 / QALY gained for induction and for induction and maintenance with bortezomib.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The submitted analyses were not based on the studies involving the correct therapies or on fully reported and peer-reviewed evidence. The EGP estimates use the most suitable clinical data available, with modifications to the model intended to more closely represent

the Canadian setting (observation only maintenance, inclusion of wastage) and minimize any bias in favour of bortezomib.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Quality of life (QoL) was considered by patients to be the most important outcome. The model does not incorporate differences in QoL due to chemotherapy or due to toxicities, but does include QoL difference due to disease control from progression-free to progressed disease states. According to the Clinical Guidance Report, bortezomib in induction is associated with similar or improved rates of most grade 3/4 toxicities except peripheral neuropathy. None of the trials of bortezomib in maintenance reported statistically significant differences in Grade 3/4 adverse events (see CGR Section 6.3.2.2, Harms). Thus, the impact of chemotherapy-related toxicities to the quality of life should be small. The impact, if any, of the bortezomib maintenance therapy schedule for two years is not known. Quality of life measures specific to upfront bortezomib therapy with ASCT could be incorporated into future research.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Given the available data, the design and structure of the submitted analysis was adequate to address the use of bortezomib both pre- and post-ASCT for multiple myeloma. A three-state model may be simplistic for a relapsing/remitting disease; however, the difference in time spent in the progressed disease state between treatments in the model is negligible (0.009 QALYs), which means more detailed modelling in this area would not likely make a difference. The model did not factor in response or tolerance to induction or include the ASCT itself, which limits the use of the primary outcome from some of the clinical trials. However, the rates of ASCT and subsequent maintenance therapy were also generally similar between treatment groups in most trials.

As some Provincial jurisdictions already fund bortezomib as part of induction therapy, an ideal approach would include multiple treatment arms to address the use of bortezomib in induction alone, induction and maintenance, or neither (Figure 1). Although it may be possible using more sophisticated methodology to synthesize evidence from separate trials, it is not clear whether the available data are suitable for this approach. Based on their assessment of the available evidence, the Submitter did not attempt this approach. Without independently assessing all the evidence and creating the new model, we cannot know whether this would have made a substantially altered estimate for bortezomib use in induction and maintenance (the main analysis). The submitted models are not capable of assessing 1, and only assess 2 (supplemental analysis) and 3 (main analysis).

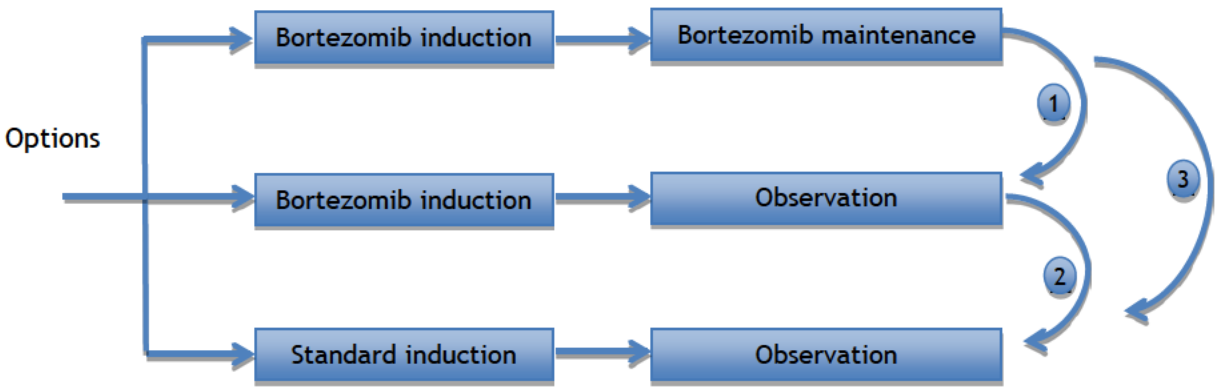

Figure 1. Schematic of comparators in the ideal analysis, for comparison to the included analyses.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The comparator used in the model is not appropriate to the setting in Canada, and the additional models aiming to address an appropriate comparator were based on evidence from abstract reports instead of fully published RCT data. Since the comparator in the HOVON-65/GMMG trial was a novel agent, its benefits may be offset by considerable cost. The inclusion of the inappropriate comparator's cost underestimates the incremental costs of bortezomib for the current Canadian setting, which may be misleading. In the absence of data with a more appropriate comparator, we removed the comparator cost from the main analysis so that the model does not make the extra cost of bortezomib look artificially favourable. Thus, the cost-effectiveness estimates from the EGP reanalysis for bortezomib induction and maintenance may be conservative.

The major assumptions made in the Submitter's analysis were that the hazards for progression or death were constant for the duration of the clinical trial. There was no formal testing to ensure the inputs used were the best fit for the clinical data. However, the Submitter attempted to mitigate long-term impact of this assumption by assigning equal risk of progression and death for each treatment group beyond the trial period, and the model results do reasonably align with long-term outcomes expected for patients with multiple myeloma.

Finally, the Submitter assumed no wastage would occur, given results of a long-term drug stability study. Since extended stability may not be common practice or policy in Canadian jurisdictions, and is not supported by the product monograph, the exclusion of wastage may lead to substantially underestimated costs for bortezomib.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Within the confines of the structure (assuming an indirect comparison is not possible), most of the inputs were similar to what the EGP would use. The EGP would have preferred to see a more thorough handling of the survival data to ensure that the model adequately reflects the clinical pathway. However, no better data were identified in the review to inform the research question, and the Submitter made a reasonable attempt to limit the long-term impact of their assumptions. The clinical data neither directly address relevant questions nor uses the appropriate comparator, and thus the EGP re-analysis was conducted to best inform the decision with the data available.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact is influenced by the number of patients with multiple myeloma eligible for ASCT, drug cost per course, market share for induction and maintenance, and assumptions around the percentage of patients who begin and complete maintenance therapy.

What are the key limitations in the submitted budget impact analysis?

The drug costs per course appear reasonable, but only include the administered dose. The model does not take wastage into account. The inclusion of wastage from unused portions of bortezomib vials would increase the total budget impact. Funding would also influence chemotherapy clinic costs, which are not captured.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The economic evaluation could be improved by obtaining primary clinical data with patient-level survival, using a comparator that is suitable for Canada in both the induction and maintenance setting, and fitting various mathematical curves to ensure good fit to the clinical data. Additionally, bortezomib-specific and induction/maintenance therapy quality-of-life utility estimates and would be valuable, especially because the estimates of cost-effectiveness are quite sensitive to changes in PFS quality-of-life measures.

Is there economic research that could be conducted in the future that would provide valuable information related to the addition of bortezomib to upfront therapy with ASCT for multiple myeloma?

The estimate of cost-effectiveness for bortezomib in this setting would be improved with proper head-to-head clinical data comparing bortezomib and dexamethasone in induction, bortezomib in maintenance therapy, and the current standard of care in Canada. In the absence of any such trials, the model could be improved by using additional methodology (e.g. indirect comparison, network meta-analysis) to synthesize data among relevant trials with different comparators in order to obtain a more comprehensive clinical picture.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the pCODR *Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Myeloma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of bortezomib (Velcade) for multiple myeloma. A full assessment of the clinical evidence of bortezomib (Velcade) for multiple myeloma] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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