

# Cost-effectiveness of bortezomib for multiple myeloma: a systematic review

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**Objectives:** To review published cost-effectiveness analyses (CEA) assessing bortezomib (BTZ) for multiple myeloma (MM) and explore possible bias affecting the cost-effectiveness of BTZ.

**Methods:** Literature was searched for published CEAs assessing BTZ or BTZ-containing regimens for MM from 2003 to 2015. The reported incremental cost-effectiveness ratios (ICER) were adjusted by 2014 country-specific gross domestic product per capita (GDPPC) to compare the cost-effectiveness threshold of the World Health Organization (3 GDPPC per gained quality-adjusted life year [QALY]).

**Results:** A total of 17 published CEAs were included in this review. When compared to non-BTZ treatments, BTZ-containing regimens were cost-effective for induction treatment prior to stem cell transplantation (SCT) in Canada, Poland, and Germany (ICER per QALY: 0.9299–2.254 GDPPC). BTZ/melphalan/prednisolone (VMP) was cost-effective for previously untreated and SCT-ineligible MM patients when compared to melphalan plus prednisolone (MP), melphalan/prednisone/lenalidomide with lenalidomide maintenance, and cyclophosphamide/thalidomide/dexamethasone (CTD) (ICER per QALY: dominant to 2.374 GDPPC) in Canada, UK, and USA. BTZ was cost-effective for relapsed/refractory MM when compared to best supportive care (ICER per life year: 0.9317–1.8210 GDPPC) in the UK and the USA, thalidomide in USA (0.5178 GDPPC/LY), and dexamethasone (DEX) in four Nordic countries (€54,451–€81,560/QALY). However, the cost-effectiveness for VMP versus MP plus thalidomide (MPT) and continuous lenalidomide (LEN) plus low-dose DEX (RD) for previously untreated and SCT-ineligible MM patients and BTZ versus LEN/DEX for relapsed/refractory MM patients could be unreliable because of the bias associated with model design and the indirect comparisons of treatment effects.

**Conclusion:** Published CEAs suggested that BTZ or BTZ-containing regimens were cost-effective when compared to most non-BTZ treatments for MM. However, the conflicting cost-effectiveness for VMP versus MPT for previously untreated and SCT-ineligible MM and BTZ versus LEN/DEX for relapsed/refractory MM needs more robust evidence for further clarification.

**Keywords:** cost-effectiveness, bortezomib, multiple myeloma, systematic review

## Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm characterized by proliferation of neoplastic plasma cells that impair hematopoiesis and activate osteoclastic bone resorption and also secrete a monoclonal paraprotein (M-protein) in serum and/or urine.<sup>1</sup> MM is ranked as the second most common hematological malignancy

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(12%–15% of all cases).<sup>2</sup> The 5-year survival rate of MM has substantially improved since the launch of bortezomib (BTZ),<sup>3</sup> a breakthrough in the treatment of MM. Two open-label, Phase II trials (SUMMIT<sup>4</sup> and CREST<sup>5</sup>) established the treatment efficacy of BTZ for overall survival (OS) in heavily pretreated patients with MM. The Phase III APEX trial proved the superiority of BTZ over high-dose dexamethasone (DEX) for any relapsed MM.<sup>6</sup> The VISTA trial, a large Phase III trial including 682 patients, observed significantly extended median OS (13.3 months) associated with BTZ/melphalan/prednisone (VMP) when compared to melphalan/prednisone (MP) (56.4 versus 43.1 months).<sup>7</sup> Another Phase III trial, the IFM 2005-01 trial, reported that BTZ plus DEX was superior to vincristine/doxorubicin/DEX regarding postinduction overall response rate (78.5% versus 62.8%) and median progression-free survival (PFS) (36.0 versus 29.7 months) when used for the treatment of MM as induction treatment prior to stem cell transplantation (SCT).<sup>8</sup> Thus, BTZ has been approved and recommended in all treatment settings for MM.

Even though BTZ treatments have been proven to be effective in randomized clinical trials (RCTs), the cost-effectiveness of BTZ is often required to support reimbursement decision-making in many countries where there are public health systems or third payers for health care. When compared to clinical efficacies that are usually associated with strong internal validity,<sup>9</sup> the cost-effectiveness could vary substantially because of heterogeneity and bias associated with study design, data sources, evidence synthesis methods, and country settings.<sup>10</sup> To guide the interpretation of the published cost-effectiveness of BTZ for MM patients, we conducted this systematic review to summarize the published cost-effectiveness analyses (CEA) assessing BTZ or BTZ-containing regimens for MM and to explore the potential bias affecting the cost-effectiveness of BTZ or BTZ-containing regimens.

## Study methods

This study was designed as a systematic review of published CEAs assessing BTZ or BTZ-containing regimens for MM by treatment settings.

## Literature search

A literature search was conducted in the electronic bibliographic databases, including MEDLINE, EMBASE, and Web of Science. The literature search strategy was developed by combining the keywords for disease (“myeloma”, “multiple myeloma”, “myelomatosis”, “Kahler’s disease”, and “MM”), treatment (“bortezomib” and “Velcade”), and cost-effectiveness (“cost-effectiveness”, “CEA”, “cost-utility”,

“CUA”, “cost-benefit”, “CBA”, “cost-minimization”, “CMA”, “incremental cost-effectiveness ratio”, “ICER”, “incremental cost-utility ratio”, and “ICUR”). The literature search time was defined from May 2003 to September 2015, the first market authorization of BTZ for MM. Additionally, conference proceedings and presentations from MM-related medical conferences (ASH annual meeting, Congress of EHA, and ASCO annual meeting) and health economics conferences (ISPOR, HTAi, and SMDM) in 2013 and 2014 were searched to include any eligible CEAs that had not been fully published prior to our literature search.

## Identifying qualified CEA

The identified references from literature search were pooled together to delete duplicated records. Two reviewers independently screened the cleaned references for relevance to the cost-effectiveness of BTZ for MM by reading titles and abstracts. The full publications of the relevant references were retrieved and reviewed for further assessment according to the following inclusion and exclusion criteria. The inclusion criteria were 1) original CEA assessing the cost-effectiveness of BTZ or BTZ-containing regimens for MM; 2) containing sufficient information to assess the cost-effectiveness of BTZ or BTZ-containing regimens for MM; 3) using life years (LY) and/or quality-adjusted life years (QALY) as health benefit measurements in CEA; and 4) published in English. The exclusion criteria were: 1) studies in patients with hematological malignancies other than MM; 2) the study only assessing the treatment effects or costs associated with BTZ or BTZ-containing regimens for MM; and 3) reviews, letters, or commentaries citing the cost-effectiveness of BTZ or BTZ-containing regimens for MM.

## Data extraction

A data extraction form was developed in Microsoft Excel according to ISPOR health economic evaluation publication guideline and clinical practices guidelines for MM. Two reviewers independently reviewed the publications of the included studies to extract study characteristics (publication type, publication year, country setting, study patients, and treatment strategies assessed in CEA), the design of the CEA (time horizon, health benefit measurement, cost perspective, currency, currency year, and annual discounting rate for health benefits and costs), CEA model information (model design, model structure, health states, model variables, and model assumption), data sources and evidence synthesis methods for model variables, and the results of base case analysis and sensitivity analysis, such as one-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

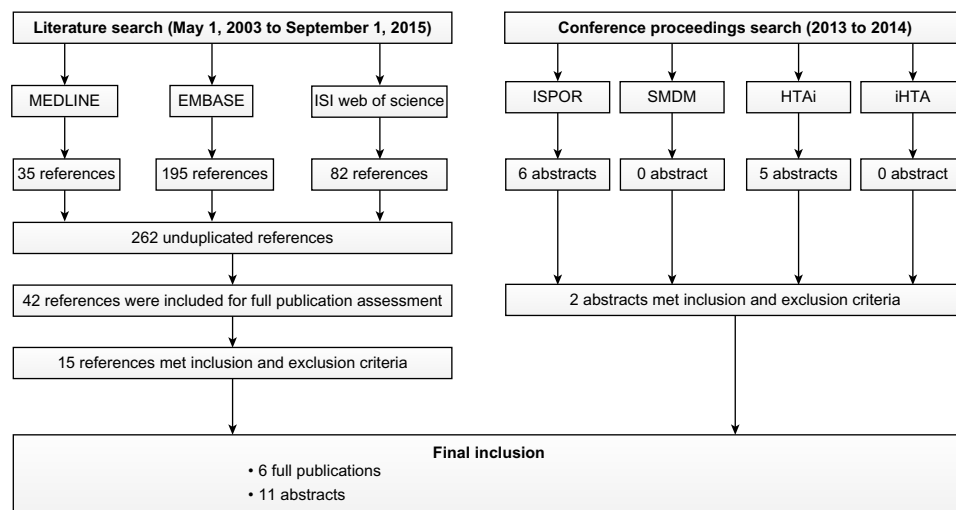
## Data analysis

The included CEAs were summarized by treatment settings, including induction treatment prior to SCT, treatment for previously untreated and SCT-ineligible MM patients, and treatment for patients with refractory/relapsed MM. A narrative review approach was used to describe the study characteristics, CEA design, CEA model characteristics, data sources, and evidence synthesis methods used to estimate model variables. The reported base case incremental cost-effectiveness ratios (ICER) in the included CEAs were adjusted to the 2014 currency value according to the country-specific annual inflation rates in the past and further divided by 2014 country-specific gross domestic product per capita (GDPPC) to compare with the cost-effectiveness threshold defined by the World Health Organization (WHO) (3 GDPPC per gained QALY).<sup>11</sup> The reported key factors affecting the cost-effectiveness of BTZ treatments in one-way sensitivity analysis and the results of the PSA were summarized to confirm the robustness of base case analysis. The key model assumptions in the included CEAs were also reviewed for their impacts on the cost-effectiveness of BTZ treatments for MM. Finally, potential bias associated with study design, model structure, data sources, and evidence synthesis methods in the included CEAs were explored to guide the interpretation of the reported cost-effectiveness of BTZ.

## Results

Our literature searches of MEDLINE, EMBASE, and Web of Sciences identified 312 references. After the deletion of the duplicate references, 262 references were included for further assessment of the relevance of the cost-effectiveness of BTZ or BTZ-containing regimens for MM by reading

their titles and abstracts. The full publications of 42 relevant references were retrieved for final eligibility assessment using the defined inclusion and exclusion criteria. After the exclusion of 27 references (6 abstracts which were fully published, 4 CEAs without assessing BTZ or BTZ-containing regimens for MM, 4 studies not qualified for CEA, 4 studies without sufficient information for cost-effectiveness assessment, 2 CEAs without using LY or QALY as health benefit measurement, 2 reviews, 1 letter to editor, 1 published in Italian, 1 assessing BTZ for follicular lymphoma, 1 assessing budget impact, and 1 without control strategy for the calculation of ICER), 15 references met both inclusion and exclusion criteria, and so their full publications were reviewed for data extraction. An additional search of the conferences proceedings and presentations identified eleven relevant abstracts. Of these eleven abstracts, only two abstracts were qualified for inclusion. Thus, this systematic review included 17 CEAs, including 3 CEAs (Kouroukis et al,<sup>12</sup> Mucha et al,<sup>13</sup> and Van Beurden-Tan et al<sup>14</sup>) assessing BTZ-containing regimens as induction treatment prior to SCT, 6 CEAs (Rickert et al,<sup>15</sup> Garrison et al,<sup>16</sup> Oster et al,<sup>17</sup> Picot et al,<sup>18</sup> Yoong et al,<sup>19</sup> and Cavenagh et al<sup>20</sup>) assessing VMP for previously untreated and SCT-ineligible MM, and 8 CEAs (Bagust et al,<sup>21</sup> Mehta et al,<sup>22</sup> Felix et al,<sup>23</sup> Fragoulakis et al,<sup>24</sup> Hornberger et al,<sup>25</sup> Jiang et al,<sup>26</sup> Liwing et al,<sup>27</sup> and Moller et al<sup>28</sup>) assessing BTZ for relapsed/refractory MM. The literature search process is illustrated in Figure 1, and the excluded references from the final assessment of study eligibility are summarized in Table S1. The study characteristics, data sources of model variables, and the base case ICER adjusted by 2014 country-specific GDPPC of the included CEAs are summarized in Tables 1–3, respectively.



**Figure 1** Flow chart to illustrate the literature search process for identification of articles eligible for the cost-effectiveness analyses assessing bortezomib or bortezomib-contained regimens for multiple myeloma.

**Table 1** Summary of study characteristics of the included cost-effectiveness analyses assessing bortezomib or bortezomib-contained regimens for multiple myeloma

Included study	Publication type	Country	Study design	Model design	Model cycle length	Time horizon	Cost perspective	Annual discount rate for health benefits (%)	Annual discount rate for costs (%)	Model health state
Kouroukis et al <sup>12</sup>	Abstract	Canada	Cost-utility	Markov	Not reported	50 years	Public health system	5	5	Progress free Progressive disease Death
Mucha et al <sup>13</sup>	Abstract	Poland	Cost-utility	Markov	Not reported	Lifetime	National Health Foundation	4	5	First-line Second-line Third-line Subsequent line Death
Van Beurden-Tan et al <sup>14</sup>	Abstract	Germany	Cost-effectiveness/ utility	Markov	1 month	Lifetime	Third payer	3	3	First-line Second-line Third-line Fourth-line Death
Rickert et al <sup>15</sup>	Abstract	Sweden	Cost-utility	Partitioned survival model	Not reported	30 years	Public health system	Not reported	Not reported	Progress free Progressive disease Death
Garrison et al <sup>16</sup>	Full publication	USA	Cost-effectiveness/ utility	Markov	1 month	20 years	Third payer	3	3	Stable disease Minor response Partial response Complete response Treatment free Progressive disease Second-line Death
Oster et al <sup>17</sup>	Abstract	USA	Cost-effectiveness/ utility	Partitioned survival model	Not reported	Lifetime	Third payer	3	3	Progress free Progressive disease Death
Picot et al <sup>18</sup>	Full publication	UK	Cost-utility	Partitioned survival model	6 weeks	30 years	National health system	4	4	Treatment Posttreatment Progressive disease Not reported
Yoong et al <sup>19</sup>	Abstract	Canada	Cost-utility	Not reported	Not reported	10 years	Public health system	Not reported	Not reported	Not reported
Cavenagh et al <sup>20</sup>	Abstract	USA	Cost-effectiveness/ utility	Partitioned survival model	Not reported	Lifetime	US payer	3	3	Not reported
Bagust et al <sup>21</sup>	Abstract	UK	Cost-utility	Partitioned survival model	Not reported	Lifetime	National health system	0	0	Not reported
Mehta et al <sup>22</sup>	Full publication	USA	Cost-utility	Decision making tree	Not reported	Lifetime	Third payer	0	0	Not reported
Felix et al <sup>23</sup>	Abstract	Portugal	Cost-effectiveness/ utility	Markov	Not reported	Lifetime	Public health system	5	5	Not reported

Fragoulakis et al <sup>24</sup>	Full publication	Greece	Cost-effectiveness/ utility	Discrete event simulation	Not reported	Lifetime	Public health system	4	4	Partial response Complete response Stable disease Progressive disease Progress free Progressive disease Death
Hornberger et al <sup>25</sup>	Full publication	Sweden	Cost-effectiveness/ utility	Partitioned survival model	3 weeks	10 years	Public health system	3	3	Progressive disease Progress free Progressive disease Death
Jiang et al <sup>26</sup>	Abstract	UK	Cost-effectiveness/ utility	Partitioned survival model	Not reported	Lifetime	National health system	4	4	Progressive free Progressive disease Death
Liwing et al <sup>27</sup>	Abstract	Nordic four countries (Finland, Norway, Sweden, Denmark)	Cost-effectiveness/ utility	Partitioned survival model	Not reported	Lifetime	Public health system	Not reported	Not reported	Progress free Progressive disease Death
Moller et al <sup>28</sup>	Full publication	Norway	Cost-effectiveness/ utility	Discrete event simulation	Not reported	2 years	Public health system	4	4	Partial response Complete response Stable disease Progressive disease

## BTZ-containing regimens as induction treatment prior to SCT

Three included CEAs<sup>12-14</sup> assessing the cost-effectiveness of BTZ-containing regimens as induction treatment prior to SCT in Canada, Poland, and Germany were published in abstracts and had similar study characteristics. The base case ICER per gained QALY for BTZ-containing regimens versus non-BTZ treatments in the Canadian CEA based on IFM 2005-01 phase III trial<sup>29</sup> was 2.2544 GDPPC. The Polish CEA<sup>13</sup> compared bortezomib/dexamethasone (VD) versus vincristine/adriamycin/dexamethasone (VAD) and cyclophosphamide/thalidomide/DEX (CTD) likely using an indirect comparison method to estimate treatment efficacies associated with the two treatments from two trials.<sup>29,30</sup> The reported base case ICERs per gained QALY for VD versus VAD and CTD were 1.0083 and 1.2584 GDPPC, respectively. Two CEAs compared BTZ/thalidomide/DEX (VTD) versus CTD and thalidomide/DEX (TD) in Poland and Germany, respectively.<sup>13,14</sup> The base case ICERs per gained QALY for VTD versus CTD and TD were 0.5588 and 0.9864 GDPPC, respectively in Poland. However, the base case ICER per gained QALY for VTD versus TD in Germany (0.9299 GDPPC) was only half that of the ICER in Poland. The key factors affecting the cost-effectiveness of VTD included the induction cost and transplant percentage. The cost-effectiveness proportion for VTD versus TD was 57.1% in Germany at the cost-effectiveness threshold of €35,000 per gained QALY.

## VMP for previously untreated and SCT-ineligible MM

Five included CEAs assessed the cost-effectiveness of BTZ-containing regimens for previously untreated MM patients who were ineligible for SCT due to old age. These five CEAs compared VMP versus melphalan plus prednisone (MP),<sup>15-17,19</sup> MP plus thalidomide (MPT),<sup>15,16,18,19</sup> lenalidomide (LEN) maintenance (MPR-R),<sup>16,17</sup> and continuous LEN plus low-dose DEX (RD).<sup>20</sup>

### VMP versus MP

Five included CEAs compared VMP versus MP for previously untreated and SCT-ineligible MM patients in USA, Sweden, UK, and Canada. Three of these CEAs used a partitioned survival model that decomposed survival by disease progression status. One CEA used a Markov model with seven health states for simulation. One included CEA did not report the model design. The VISTA trial<sup>31</sup> was the data source for the treatment effects of VMP. However, the methods comparing VMP versus MP for survival outcomes in these CEAs were

**Table 2** Summary of the data sources of treatment effects, costs, and utility in the included cost-effectiveness analyses assessing bortezomib or bortezomib-contained regimens for multiple myeloma

Treatment setting	Comparison	Included studies	Data source for treatment effects	Data sources for costs	Data source for utility
Induction treatment prior to SCT	BTZ treatment versus non-BTZ treatment	Kouroukis et al <sup>12</sup>	IFM2005-01 trial	Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events	Van Agthoven et al <sup>42</sup>
	VD versus CTD	Mucha et al <sup>13</sup>	IFM2005-01 trial	Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events	Van Agthoven et al <sup>42</sup>
	VD versus VAD	Mucha et al <sup>13</sup>	IFM2005-01 trial	Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events	Van Agthoven et al <sup>42</sup>
	VTD versus CTD	Mucha et al <sup>13</sup>	PETHEMA trial	Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events	Van Agthoven et al <sup>42</sup>
	VTD versus TD	Mucha et al <sup>13</sup>	PETHEMA trial	Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events	Van Agthoven et al <sup>42</sup>
Previously untreated MM but ineligible for SCT	VMP versus MP	Van Beurden-Tan et al <sup>14</sup>		Medical costs for treatment, SCT, and adverse events	Not reported
		Rickert et al <sup>15</sup>	VISTA trial	Medical costs for treatment, adverse events, disease relapse, and palliative care	Not reported
		Garrison et al <sup>16</sup>	VISTA trial	Medical costs for treatments, adverse events, and second-line treatment	VISTA trial
		Oster et al <sup>17</sup>	Palumbo et al, <sup>46</sup> San Miguel et al, <sup>32</sup> Facon et al, <sup>34</sup> Hulin et al, <sup>33</sup> Palumbo et al, <sup>35</sup> any VISTA trial	Medical costs for treatment and adverse events	Not reported
		Yoong et al <sup>19</sup>	VISTA trial	Medical costs for treatment and adverse events, maintenance therapy, and second-line treatment	Not reported
	VMP versus MPT	Picot et al <sup>18</sup>	VISTA trial and Palumbo et al, <sup>46</sup> San Miguel et al, <sup>32</sup> Facon et al, <sup>34</sup> Hulin et al, <sup>33</sup> and Palumbo et al <sup>35</sup>	Medical costs for treatment and adverse events, maintenance therapy, and second-line treatment	Study mapping EORTC QLQ-C30 to EQ-5D <sup>43</sup>
		Rickert et al <sup>15</sup>	VISTA trial and Palumbo et al, <sup>46</sup> San Miguel et al, <sup>32</sup> Facon et al, <sup>34</sup> Hulin et al, <sup>33</sup> and Palumbo et al <sup>35</sup>	Medical costs for treatment, adverse events, relapse, and palliative care	Not reported
		Garrison et al <sup>16</sup>	VISTA trial and IFM99-06 trial	Medical costs for treatment, adverse events, and second-line treatment	VISTA trial
		Yoong et al <sup>19</sup>	VISTA trial	Medical costs for treatment, adverse events, and second-line treatment	Not reported
		Picot et al <sup>18</sup>	VISTA trial and Palumbo et al, <sup>46</sup> San Miguel et al, <sup>32</sup> Facon et al, <sup>34</sup> Hulin et al, <sup>33</sup> and Palumbo et al <sup>35</sup>	Medical costs for treatment, adverse events, and second-line treatment	Study mapping EORTC QLQ-C30 to EQ-5D <sup>43</sup>
VMP versus MPR-R	Garrison et al <sup>16</sup>	VISTA trial and MM-015 trial	Medical costs for treatment, adverse events, and second-line treatment	VISTA trial	
	Oster et al <sup>17</sup>	Palumbo et al, <sup>46</sup> San Miguel et al, <sup>32</sup> Facon et al, <sup>34</sup> Hulin et al, <sup>33</sup> and Palumbo et al, <sup>35</sup> MM-015, and VISTA trial	Medical costs for treatment, adverse events	Not reported	

(Continued)

**Table 2** (Continued)

Treatment setting	Comparison	Included studies	Data source for treatment effects	Data sources for costs	Data source for utility
	VMP versus RD	Cavenagh et al <sup>20</sup>	FIRST trial and VISTA trial	Medical costs for drugs, administration, medical care, second- and third-line antimyeloma regimens, and management of toxicity	Not reported
Relapsed/refractory MM	BTZ versus BSC	Bagust et al <sup>21</sup>	SUMMIT I trial	Medical costs for treatment and adverse events	Not reported
		Mehta et al <sup>22</sup>	SUMMIT I trial	Medical costs for treatment and adverse events	Not reported
	BTZ versus THD	Mehta et al <sup>22</sup>	SUMMIT I trial	Medical costs for treatment and adverse events	Not reported
	BTZ versus DEX	Hornberger et al <sup>25</sup>	APEX trial, MM-009 trial, and MM-10 trial	Medical costs for treatment and adverse events	Van Agthoven et al <sup>42</sup>
		Liwing et al <sup>27</sup>	APEX trial, MM-009 trial, and MM-10 trial	Medical costs for treatment, adverse events, and palliative care	Not reported
	BTZ versus LEN/DEX	Felix et al <sup>23</sup>	APEX trial, MM-009 trial, and MM-10 trial	Not reported	Not reported
		Fragoulakis et al <sup>24</sup>	APEX trial, MM-009 trial, and MM-10 trial	Medical costs for treatment, adverse events, and palliative care	Van Agthoven et al <sup>42</sup>
		Hornberger et al <sup>25</sup>	APEX trial, MM-009 trial, and MM-10 trial	Medical costs for treatment, adverse events, and palliative care	Van Agthoven et al <sup>42</sup>
		Jiang et al <sup>26</sup>	APEX trial, MM-009 trial, and MM-10 trial	Not reported	Not reported
Liwing et al <sup>27</sup>		APEX trial, MM-009 trial, and MM-10 trial	Not reported	Not reported	
		Moller et al <sup>28</sup>	APEX trial, MM-009 trial, and MM-10 trial	Medical costs for treatment, adverse events, and palliative care	Van Agthoven et al <sup>42</sup>

**Abbreviations:** BSC, best supportive care; BTZ, bortezomib; CTD, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; LEN, lenalidomide; MM, multiple myeloma; MP, melphalan/prednisone; MPR-R, melphalan/prednisone/lenalidomide with lenalidomide maintenance; MPT, melphalan/prednisone/thalidomide; RD, lenalidomide plus low-dose dexamethasone; SCT, stem cell transplantation; THD, thalidomide; TD, thalidomide/dexamethasone; VD, bortezomib/dexamethasone; VAD, vincristine/adriamycin/dexamethasone; VMP, bortezomib/melphalan/prednisone; VTD, bortezomib/thalidomide/dexamethasone.

not exactly the same. Three included CEAs<sup>15,16,19</sup> directly used the VISTA trial to estimate hazard ratio associated with VMP versus MP for PFS (0.48) and OS (0.695). However, the other two studies<sup>17,18</sup> estimated the baseline hazard rate associated with MP for PFS and OS from five RCTs (VISTA trial,<sup>32</sup> IFM 01/01 trial,<sup>33</sup> IFM 99/06,<sup>34</sup> the GIMEMA trial,<sup>35</sup> and MMIX02 trial<sup>36</sup>) and projected higher hazard ratio associated with VMP versus MP for PFS (0.578). The reported base case ICER per gained QALY for VMP versus MP in these five studies ranged from 1.1060 to 2.3744 GDPPC. Four of the included CEAs reported that the survival differences between VMP and MP had the strongest impact on the cost-effectiveness of VMP. The reported cost-effective proportion for VMP versus MP in PSA was 20.4% at the cost-effectiveness threshold of US\$50,000 per QALY, but it increased to 100% at the cost-effectiveness threshold of US\$100,000 per QALY.

### VMP versus MPT

Four included CEAs compared VMP versus MPT for previously untreated and SCT-ineligible MM patients in Sweden,<sup>15</sup>

USA,<sup>16</sup> UK,<sup>18</sup> and Canada.<sup>19</sup> Due to the lack of trials directly comparing VMP versus MPT for previously untreated MM, indirect comparison methods were used in these four studies to estimate the impact of VMP versus MPT on survival in the CEAs. Even though the indirect comparisons used the same data sources (VISTA trial for VMP and published RCTs comparing MPT versus MP for MPT), the indirect comparisons generated conflicting results for OS associated with the two treatments. For example, a mixed treatment comparison meta-analysis in one CEA<sup>16</sup> estimated longer OS associated with VMP (61 versus 50.2 months), whereas another CEA<sup>18</sup> projected slightly shorter OS associated with VMP (6.64 versus 6.66 years) according to the extracted survival probabilities from Kaplan–Meier plots in the five RCTs. Thus, the two CEAs reported conflicting data on cost-effectiveness of VMP by reporting dominance of VMP over MPT and dominance of VMP by MPT. The other two included CEAs<sup>15,19</sup> reported that the base case ICERs per gained QALY for VMP versus MPT were 2.0248 and 0.7323 GDPPC, respectively. The reported key factors affecting the cost-effectiveness of

**Table 3** Summary of the published base case cost-effectiveness studies of bortezomib or bortezomib-contained regimens for multiple myeloma (ICER was adjusted by 2014 country-specific GDPPC)

Treatment setting	Comparison	Included studies	Country	Adjusted ICER by 2014 GDPPC
Induction treatment prior to SCT	BTZ-containing regimen versus non-BTZ treatment	Kouroukis et al <sup>12</sup>	Canada	2.2544/QALY
	VD versus CTD	Mucha et al <sup>13</sup>	Poland	1.2584/QALY
	VD versus VAD	Mucha et al <sup>13</sup>	Poland	1.0083/QALY
	VTD versus CTD	Mucha et al <sup>13</sup>	Poland	0.5588/QALY
	VTD versus TD	Mucha et al <sup>13</sup>	Poland	0.9864/QALY
Previously untreated MM but ineligible for SCT	VMP versus MP	Van Beurden-Tan et al <sup>14</sup>	Germany	0.9299/QALY
		Yoong et al <sup>19</sup>	Canada	1.1060/QALY
	VMP versus MPT	Garrison Jr et al <sup>16</sup>	USA	1.1622/QALY
		Picot et al <sup>18</sup>	UK	1.2070/QALY
		Rickert et al <sup>15</sup>	Sweden	2.3744/QALY
		Oster et al <sup>17</sup>	USA	2.0059/QALY
		Rickert et al <sup>15</sup>	Sweden	2.0248/QALY
	VMP versus MPR-R	Garrison Jr et al <sup>16</sup>	USA	Dominant
		Yoong et al <sup>19</sup>	Canada	0.7323/QALY
		Picot et al <sup>18</sup>	UK	Dominated
	VMP versus CTD	Garrison Jr et al <sup>16</sup>	USA	Dominant
Oster et al <sup>17</sup>		USA	1.3979/QALY (MPR-R versus VMP)	
VMP versus RD	Picot et al <sup>18</sup>	UK	1.1911/QALY	
	Cavenagh et al <sup>20</sup>	USA	1.5775/QALY (RD versus VMP)	
Relapsed/refractory MM	BTZ versus BSC	Bagust et al <sup>21</sup>	UK	0.9317–1.8210/LY
		Mehta et al <sup>22</sup>	USA	1.0933/LY
		Mehta et al <sup>22</sup>	USA	1.2004/LY
	BTZ versus THD	Mehta et al <sup>22</sup>	USA	0.5178/QALY
		Hornberger et al <sup>25</sup>	Sweden	3.2062/QALY
	BTZ versus DEX	Liwing et al <sup>27</sup>	Nordic countries	€54451–€81560/QALY
		Felix et al <sup>23</sup>	Portugal	2.5532–3.0187/QALY (LEN/DEX versus BTZ)
	BTZ versus LEN/DEX	Fragoulakis et al <sup>24</sup>	Greece	2.0259/QALY (LEN/DEX versus BTZ)
		Hornberger et al <sup>25</sup>	Sweden	Dominant
		Jiang et al <sup>26</sup>	UK	Dominant
Liwing et al <sup>27</sup>		Nordic countries	Dominant	
Moller et al <sup>28</sup>		Norway	0.5205/QALY (LEN/DEX versus BTZ)	

**Abbreviations:** BSC, best supportive care; BTZ, bortezomib; CTD, cyclophosphamide/thalidomide/dexamethasone; DEX, dexamethasone; GDPPC, gross domestic product per capita; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MM, multiple myeloma; MP, melphalan/prednisone; MPR-R, melphalan/prednisone/lenalidomide with lenalidomide maintenance; MPT, melphalan/prednisone/thalidomide; RD, lenalidomide plus low-dose dexamethasone; SCT, stem cell transplantation; THD, thalidomide; TD, thalidomide/dexamethasone; VD, bortezomib/dexamethasone; VAD, vincristine/adriamycin/dexamethasone; VMP, bortezomib/melphalan/prednisone; VTD, bortezomib/thalidomide/dexamethasone.

VMP relative to MPT included drug costs of MPT and the survival differences between VMP and MPT. The PSA in the CEA<sup>18</sup> reporting the dominance of MPT over VMP projected that the probability of dominance of MPT over VMP was 95% at the cost-effectiveness thresholds of GBP 20,000 and 30,000 per QALY.

### VMP versus MPR-R

Two included CEAs compared VMP versus MPR-R for the previously untreated and SCT-ineligible MM patients in USA.<sup>16,17</sup> One included CEA<sup>16</sup> used a Markov model with

seven health states, and the other CEA<sup>17</sup> used a partitioned survival model decomposing survival by the onset of progressive disease to simulate lifetime health benefits and costs. The data sources for the survival outcomes associated with VMP and MPR-R were based on the VISTA trial (for VMP) and the MM-015 trial (for MPR-R).<sup>37</sup> The MM-015 trial showed significantly longer PFS but comparable OS for MPR-R versus MP. However, the VISTA trial showed longer PFS and OS associated with VMP when compared to MP. Thus, VMP was expected to generate more survival benefits than MPR-R and become dominant over MPR-R because of lower treatment



costs. However, the other included CEA<sup>17</sup> comparing VMP versus MPR-R estimated longer OS associated with MPR-R through an indirect comparison assuming the same postprogression survival associated with the two treatments to adjust “crossover” effects associated with patients receiving MP in the VISTA trial. The reported base case ICER per gained QALY for MPR-R versus VMP in this CEA was 1.3979 GDPPC, instead of the previously reported dominance of VMP when compared with MPR-R. The identified key model variables affecting the cost-effectiveness included the drug costs of MPR-R and the survival differences between MPR-R and VMP. No PSA was performed in these two CEAs.

### VMP versus CTD

One included CEA used a partitioned survival model comparing VMP versus CTD for health benefits and costs over a time frame of 30 years in patients with newly diagnosed MM who were ineligible for SCT in the UK.<sup>18</sup> The VISTA trial was used to estimate the hazard ratio for VMP versus MP for OS and PFS, and the MMIX trial was used to estimate the hazard ratios for CTD versus MP for OS and PFS outcomes. Indirect comparisons of PFS and OS were conducted to estimate the survival differences between VMP and CTD. The reported base case ICER per gained QALY for VMP versus CTD was 1.1911 GDPPC.

### VMP versus continuous RD

One included CEA compared continuous RD versus fixed duration VMP in previously untreated but SCT-ineligible patients. Due to the lack of clinical trials directly comparing continuous RD versus VMP for PFS and OS, this CEA assumed that VMP had the same treatment efficacy as MPT regarding PFS and OS. Thus, the superior treatment efficacy associated with continuous RD relative to MPT in the FIRST trial<sup>38</sup> was applied to the comparisons for continuous RD versus VMP. Thus, this CEA projected more health benefits and medical costs associated with continuous RD relative to VMP during the patient’s lifetime, and the estimated ICER was 1.5775 GDPPC per QALY.

### BTZ for relapsed/refractory MM

Eight included CEAs compared BTZ versus best supportive care (BSC), THD, DEX, and LEN/DEX for relapsed/refractory MM.

### BTZ versus BSC

Two included CEAs compared BTZ versus BSC for relapsed/refractory MM in UK and the USA.<sup>21,22</sup> These two CEAs took life year as health benefits measurement in CEA.

The UK CEA used partitioned survival model for simulation. The USA CEA constructed a decision analytic model to simulate life expectancy and lifetime medical costs associated with BTZ and BSC.<sup>22</sup> Both CEAs used the SUMMIT trial,<sup>39</sup> a multicenter, open-label, nonrandomized Phase II trial, assessing BTZ in 202 patients with relapsed/refractory MM, as the data source for treatment effects. Both CEAs projected longer life years and more medical costs associated with BTZ when compared to BSC. In the UK, the base case ICER per gained life year for BTZ versus BSC ranged from 0.9317 to 1.8210 GDPPC. In the United States, the base case ICER per gained life years for BTZ versus BSC ranged from 1.0933 to 1.2004 GDPPC.

### BTZ versus THD

One included CEA compared BTZ versus THD using a modified Delphi technique to survey OS and health resources utilization associated with the two treatments.<sup>22</sup> Based on this approach, BTZ was associated with longer OS and higher medical costs than THD in patients without the previous use of THD. The estimated base case ICER per gained life year for BTZ versus THD was 0.5178 GDPPC.

### BTZ versus DEX

Two included CEAs compared BTZ versus DEX for relapsed/refractory MM from the perspective of the public health systems in Sweden<sup>25</sup> and four Nordic countries, including Finland, Norway, Sweden, and Denmark.<sup>27</sup> Both studies used partitioned survival model with three health states (PFS, PPS, and death) to simulate health benefits and medical costs. Additionally, the two CEAs used the same trial, the APEX trial,<sup>39</sup> as the data source for the survival benefits associated with BTZ. The survival benefits of DEX were based on two trials (the MM-009<sup>40</sup> and MM-010<sup>41</sup> trials) comparing LEN/DEX versus DEX to avoid the bias associated with “crossover” effects in the APEX trial, in which patients in the DEX arm were switched to the BTZ arm after disease progression. The base case ICERs per gained LY and QALY for BTZ versus DEX were 1.8603 and 3.2062 GDPPC, respectively, in Sweden. The estimated base case ICER per gained LY ranged from €42,145 to €62,748, and the estimated base case ICER per gained QALY ranged from €54,451 to €81,560 in the four Nordic countries (we were unable to use GDPPC for adjustment because of the lack of ICER for each country). Of these four Nordic countries, Denmark was associated with the highest ICER per gained LY and QALY. The identified key model variables affecting the cost-effectiveness of BTZ in these two studies included utility and treatment costs of BTZ. The 95% credible interval of ICER per gained QALY

for BTZ versus DEX in Sweden ranged from 1.4453 to 2.7021 GDPPC.

### BTZ versus LEN/DEX

Six included CEAs (three in full publication<sup>24,25,28</sup> and three in abstract<sup>23,26,27</sup>) compared BTZ versus LEN/DEX for relapsed/refractory MM in Portugal,<sup>23</sup> Greece,<sup>24</sup> Sweden,<sup>25</sup> UK,<sup>26</sup> Nordic countries,<sup>27</sup> and Norway.<sup>28</sup> Of these included six CEAs, three CEAs used partitioned survival model,<sup>25–27</sup> two CEAs used a discrete event simulation model,<sup>24,28</sup> and one CEA used Markov model to simulate health benefits and costs.<sup>23</sup> The survival outcomes of BTZ were based on the APEX trial, which directly compared BTZ versus high-dose DEX for relapsed/refractory MM. The survival outcomes of LEN/DEX were based on the MM-009 and MM-010 trials, which used an identical study design for comparing LEN/DEX versus DEX. Indirect comparison methods were used to compare BTZ versus LEN/DEX for survival difference. Of these six CEAs, three CEAs using partitioned survival model reported the dominance of BTZ over LEN/DEX.<sup>25–27</sup> However, two CEAs using DES model reported longer survival and higher costs associated with LEN/DEX.<sup>24,28</sup> The base case ICERs per gained QALY for LEN/DEX versus BTZ in these two studies were 0.5205 GDPPC (CEA31) in Norway and 2.0259 GDPPC (CEA20) in Greece. The one CEA using Markov model also reported more health benefits and higher costs associated with LEN/DEX (base case ICER per gained QALY: 2.5532–3.0187 GDPPC). The identified main drivers for the cost-effectiveness of BTZ versus LEN/DEX included the costs of LEN/DEX and survival differences between BTZ and LEN/DEX. The proportion of cost-effectiveness for LEN/DEX versus BTZ was reported over 95% at the cost-effectiveness threshold of €60,000 per QALY in Greece.

## Discussion

This systematic review summarized 17 published CEAs assessing BTZ or BTZ-containing regimens in the treatment settings from previously untreated MM to relapsed/refractory MM. According to the cost-effectiveness threshold defined by the WHO (3 GDPPC per gained QALY), BTZ-containing regimens including VD and VTD appeared cost-effective when compared to non-BTZ treatments for previously untreated MM prior to SCT; VMP was cost-effective when compared to MP and CTD for previously untreated and SCT-ineligible MM patients; and BTZ was cost-effective when compared to BSC, THD, and DEX for relapsed/refractory MM. However, our review also found that indirect comparisons,

model assumptions, and model structure might introduce bias in the CEA comparing VMP versus MPT, MPR-R, and continuous RD for previously untreated but SCT-ineligible MM and the cost-effectiveness analysis comparing BTZ versus LEN/DEX for relapsed/refractory MM. The one-way sensitivity analyses conducted in the included CEAs had a common finding indicating that the survival difference was the driving factor for the cost-effectiveness of BTZ or BTZ-based regimens for MM. Thus, the cost-effectiveness of BTZ or BTZ-containing regimens was more reliable and consistent if the survival outcomes were based on the direct head-to-head comparisons of RCTs.

The included CEAs assessing VD and VTD for previously untreated MM prior to SCT treatment used the same data sources for treatment efficacy, health resources utilization, and quality of life.<sup>42,43</sup> Even though the reported cost-effectiveness was adjusted by country-specific GDPPC, the cost-effectiveness for the same comparison, such as VTD versus TD, was more attractive in Germany when compared to that for Poland. Thus, the country setting seems to have strong confounding effects on cost-effectiveness even after the adjustment of GDPPC. Our finding could be explained by the relatively small variance associated with treatment costs of patented drugs that are likely to be more affordable in countries with a higher income. Thus, caution is needed when interpreting the high-income countries-based cost-effectiveness for low-income countries. Additionally, interpreting the reported cost-effectiveness of VD and VTD as induction treatment in these three included CEAs should take into account the uncertainty associated with subsequent treatment patterns, which could significantly affect life expectancy, QALY, and health resources utilization after induction treatment.

In our review, apart from the observed impact of country setting on the cost-effectiveness of BTZ-containing regimens as induction treatment prior to SCT for previously untreated MM, indirect comparison of survival outcomes between treatment strategies due to the lack of direct head-to-head comparison trials was another significant bias affecting the cost-effectiveness of BTZ or BTZ-containing regimens. For example, the reported cost-effectiveness of VMP relative to MPT for previously untreated and SCT-ineligible MM patients was conflicting because of opposite survival outcomes estimated by the indirect comparison between VMP and MPT. Of the four included CEAs using indirect comparison methods to estimate the survival differences between VMP and MPT, three reported longer survival associated with VMP and one reported longer survival associated with MPT.

After careful review of the indirect comparison methods in these four CEAs, the method used to estimate survival from survival curves, potential confounding effects associated with patient baseline characteristics from different trials could not be adjusted. Because the survival difference between VMP and MPT was likely to be small and very sensitive to confounding effects, any slight confounding effect associated with patient baseline characteristics could completely change the dominance of survival and cause the change of cost-effectiveness dominance. Because the other three CEAs estimated longer survival and better cost-effectiveness associated with VMP using different indirect comparison methods, VMP might be more appropriate than MPT for previously untreated MM in patients who were ineligible for SCT from the cost-effectiveness perspective. However, future direct evidence comparing VMP versus MPT in this setting is still needed for confirmation. Additionally, the potential differences in treatment efficacy between VMP and MPT could have a profound impact on the included CEAs comparing continuous RD versus VMP as this study assumed the same treatment efficacy for VMP versus MPT, the control used to estimate relative treatment efficacy associated with continuous RD. Thus, the reported cost-effectiveness for continuous RD versus VMP could be overestimated. Finally, an indirect comparison method used for the CEA comparing VMP versus MPR-R was also controversial, as the survival advantage associated with VMP over MPR-R has not been fully established.

The included six CEAs assessing BTZ for relapsed/refractory MM suggested that CEA model design could introduce bias affecting cost-effectiveness. For example, the six CEAs used the same data sources for survival outcomes associated with BTZ and LEN/DEX but used different model designs for CEA. The CEAs using Markov model or partitioned survival model projected longer survival associated with BTZ. However, the two CEAs based on the same discrete event model projected longer survival associated with LEN/DEX. Because discrete event model was designed to predict survival outcomes using established relationship between patient baseline characteristics and treatment response,<sup>44</sup> the model assumed that the APEX trial comparing BTZ versus DEX had comparable patient baseline characteristics as the MM-009 and MM-010 trials comparing LEN/DEX versus DEX. This assumption could introduce bias if the relationship between patient baseline characteristics and treatment response derived from MM-009 and MM-010 trials was not validated in the APEX trial. This might explain why the discrete event model without the adjustment of patient

baseline characteristics projected longer OS associated with LEN/DEX (4.14 versus 3.14 years), while the other indirect comparison methods suggested lower mortality risk associated with BTZ when compared to LEN/DEX (0.59 versus 0.71). Thus, future studies directly comparing BTZ versus LEN/DEX are still needed to clarify the survival difference between the two treatments and confirm the cost-effectiveness of BTZ versus LEN/DEX for relapsed/refractory MM.

Because the included CEAs used highly similar methods to estimate health resources utilization, which usually took into account treatment cost, subsequent treatment, serious adverse events, and palliative care, the health resources utilization was unlikely to be the significant source of the discrepancies associated with cost-effectiveness in this review. However, the main source of quality of life in these included cost-effectiveness analyses is a cost-utility analysis assessing chemotherapy for MM.<sup>42</sup> Thus, these CEAs were unlikely to adjust for quality of life by treatment efficacy and treatment toxicity associated with assessed treatments. Thus, future studies assessing the quality of life in MM patients receiving varied treatments are needed to further improve the robustness of the included CEAs in this review. The data sources of treatment effects in these included CEAs were all based on RCTs, which usually had poorer generalizability because highly selected patients were included for analysis.<sup>45</sup> Thus, the generalizability of the summarized cost-effectiveness of BTZ or BTZ-containing regimens in our review could also be limited, and future cost-effectiveness based on real-world treatment effects, quality of life, and health resource utilization is needed to support more robust reimbursement decision making. Additionally, the RCTs seldom captured the impact of BTZ or BTZ-containing treatments on MM-related complication due to short follow-up time, and so the reported cost-effectiveness of BTZ or BTZ-containing regimens could be underestimated. Even though our literature search strategies were developed to identify any cost-effectiveness analysis comparing BTZ or BTZ-containing regimens versus any non-BTZ treatments, the published CEAs were unlikely to cover all possible treatments for MM. For example, we did not find any published CEAs comparing BTZ or BTZ-containing regimens versus cyclophosphamide or bendamustine-based regimens, the conventional regimens used to treat refractory/relapsed MM. Thus, future CEAs comparing BTZ or BTZ-containing regimens versus all existing non-BTZ regimens are needed for comprehensive assessment of BTZ or BTZ-containing regimens for MM. Another major limitation of our review is the lack of quality assessment of the data used in the included cost-effectiveness analysis. Even though almost all

included CEAs clearly indicated the data sources of treatment efficacy, the data sources for direct medical costs and quality of life were usually not well described. Thus, our review was unable to assess the quality of data for costs and utility and explore the potential bias associated with these data in the cost-effectiveness analysis. This systematic review also included CEAs published in abstracts that usually contain insufficient information for quality assessment. Thus, caution is needed when interpreting the cost-effectiveness of BTZ or BTZ-containing regimens from abstracts. Finally, the administration practices for BTZ treatment has been evolving, and the current practices might differ from the practices applied in the included cost-effectiveness analysis. For example, BTZ administration is now changing from being an intravenous to a subcutaneous injection, which could reduce neuropathic toxicity and improve treatment convenience. The treatment schedule for less intensively treated patients could change from a twice weekly schedule to a weekly schedule. Thus, the published cost-effectiveness of BTZ should be interpreted after taking into account the potential impact of health benefits and costs associated with current practices for BTZ treatment.

In summary, the systematic review of published CEAs suggested that BTZ and BTZ-containing regimens appeared cost-effective treatment strategies for MM in most circumstances according to the cost-effectiveness threshold defined by WHO. However, this systematic review also observed conflicting cost-effectiveness for the comparisons of VMP versus MPT for previously untreated and SCT-ineligible MM patients and BTZ versus LEN/DEX for relapsed/refractory MM due to the bias associated with indirect comparison and model structure. Thus, the conflicting cost-effectiveness of VMP relative to MPT and BTZ relative to LEN/DEX needs further head-to-head comparison studies for clarification. Finally, this systematic review found that the impact of a country setting on the cost-effectiveness could be substantial. Because most of the included CEAs were based in high-income countries, caution is needed when interpreting the published cost-effectiveness of BTZ or BTZ-containing regimens for middle or low-income countries.

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and Fen Du conducted the literature search and assessed the studies for inclusion eligibility. Yi Chen, Fen Du, and Huan Zhan conducted the data extraction and data analysis. Dr Yicheng Yang participated in the discussion on study design and critically reviewed the manuscript. Dr Wendong Chen developed the manuscript. All authors read the manuscript and have approved the submission of this developed manuscript. The abstract of this paper was presented at the ISPOR 18th Annual European Congress as a poster presentation in Milan, Italy. The poster's abstract was published in "Poster Abstracts" in *Value in Health*, 2015;18(7):A456.

## Disclosure

Dr Wendong Chen is the founder of Normin Health, a Canadian organization receiving industry funds for health economics and outcomes research. Dr Yicheng Yang is the employee of Xian Janssen. Yi Chen, Fen Du, and Huan Zhan are the employees of the representative office of Normin Health in Changsha, People's Republic of China. The authors report no other conflicts of interest in this work.

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## Supplementary materials

**Table S1** Summary of excluded references and their exclusion reasons

Excluded references	Exclusion reason
Mehta et al <sup>1</sup>	Full manuscript has been published
Fragoulakis et al <sup>2</sup>	Full manuscript has been published
Wang et al <sup>3</sup>	Full manuscript has been published
Wang et al <sup>4</sup>	Full manuscript has been published
Wang et al <sup>5</sup>	Full manuscript has been published
Wang et al <sup>6</sup>	Full manuscript has been published
Popat et al <sup>7</sup>	BTZ was not studied
Schey et al <sup>8</sup>	BTZ was not studied
Tuffaha et al <sup>9</sup>	BTZ was not studied
Gaultney et al <sup>10</sup>	BTZ was not studied
Gaultney et al <sup>11</sup>	Not CEA (cohort study for clinical outcomes)
Hornberger et al <sup>12</sup>	Not CEA (cost study)
Teitelbaum et al <sup>13</sup>	Not CEA (cost study)
Vitale et al <sup>14</sup>	Not CEA (cost study)
Gaultney et al <sup>15</sup>	Insufficient information
Gibbons et al <sup>16</sup>	Insufficient information
Blommestein et al <sup>17</sup>	Insufficient information
Durie et al <sup>18</sup>	Outcome measures for health benefits were not LY and/or QALY
Gooding et al <sup>19</sup>	Outcome measures for health benefits were not LY and/or QALY
Schey and Higginson <sup>20</sup>	Review
Haycox and Tolley <sup>21</sup>	Review
Cecchi et al <sup>22</sup>	Letter
Lucioni et al <sup>23</sup>	Non-English
Vandekerckhove et al <sup>24</sup>	Not MM patients
Shustik et al <sup>25</sup>	Budget impact analysis
Blommestein et al <sup>26</sup>	Insufficient information
Gooding et al <sup>27</sup>	Control group was lacking for the calculation of ICER

**Abbreviations:** BTZ, bortezomib; CEA, cost-effectiveness analyses; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MM, multiple myeloma.

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