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

Wendong Chen1
Yicheng Yang2
Yi Chen3
Fen Du3
Huan Zhan3

1Normin Health, Toronto, ON, Canada;
2Xian Janssen, Beijing, People’s Republic of China;
3Normin Health Changsha Representative Office, Changsha, People’s Republic of China

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 patients 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. MM is ranked as the second most common hematological malignancy...
effectiveness ("cost-effectiveness", "CEA", "cost-
MM"), treatment ("bortezomib" and "Velcade"), and cost-
myeloma", "myelomatosis", "Kahler’s disease", and
of Science. The literature search strategy was developed by
A literature search was conducted in the electronic biblio-
tical settings.
CEAs assessing BTZ or BTZ-containing regimens for MM
This study was designed as a systematic review of published
12%–15% of all cases).2 The 5-year survival rate of MM
has substantially improved since the launch of bortezomib
(BTZ),3 a breakthrough in the treatment of MM. Two open-
label, Phase II trials (SUMMIT4 and CREST5) 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 dexam-
ethasone (DEX) for any relapsed MM.6 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).7
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).8 Thus, BTZ has been approved and recommended in
treatment settings for MM.

Even though BTZ treatments have been proven to be effect-
tive 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 sys-
tems or third payers for health care. When compared to clinical
efficacies that are usually associated with strong internal valid-
ity,9 the cost-effectiveness could vary substantially because of
heterogeneity and bias associated with study design, data
sources, evidence synthesis methods, and country settings.10
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 bibli-
ographic databases, including MEDLINE, EMBASE, and Web
of Science. The literature search strategy was developed by
combining the keywords for disease ("myeloma", "multiple
myeloma", "myelomatisos", "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 inde-
dependently 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) contain-
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/refractory 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). 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, Mucha et al, and Van Beurden-Tan et al) assessing BTZ-containing regimens as induction treatment prior to SCT, 6 CEAs (Rickert et al, Garrison et al, Oster et al, Yoong et al, and Cavenagh et al) assessing VMP for previously untreated and SCT-ineligible MM, and 8 CEAs (Bagust et al, Mehta et al, Felix et al, Fragoulakis et al, Hornberger et al, Jiang et al, Liwing et al, and Moller et al) 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-containing regimens for multiple myeloma.
<table>
<thead>
<tr>
<th>Included study</th>
<th>Publication type</th>
<th>Country</th>
<th>Study design</th>
<th>Model design</th>
<th>Model cycle length</th>
<th>Time horizon</th>
<th>Cost perspective</th>
<th>Annual discount rate for health benefits (%)</th>
<th>Annual discount rate for costs (%)</th>
<th>Model health state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kouroukis et al</td>
<td>Abstract</td>
<td>Canada</td>
<td>Cost-utility</td>
<td>Markov</td>
<td>Not reported</td>
<td>50 years</td>
<td>Public health system</td>
<td>5</td>
<td>5</td>
<td>Progress free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First-line disease</td>
</tr>
<tr>
<td></td>
<td>Abstract</td>
<td>Poland</td>
<td>Cost-utility</td>
<td>Markov</td>
<td>Not reported</td>
<td>Lifetime</td>
<td>National Health Foundation</td>
<td>4</td>
<td>5</td>
<td>Second-line disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Third-line disease</td>
</tr>
<tr>
<td>Van Beurden-Tan et al</td>
<td>Abstract</td>
<td>Germany</td>
<td>Cost-effectiveness/ utility</td>
<td>Markov</td>
<td>I month</td>
<td>Lifetime</td>
<td>Third payer</td>
<td>3</td>
<td>3</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Full publication</td>
<td>USA</td>
<td>Cost-effectiveness/ utility</td>
<td>Markov</td>
<td>1 month</td>
<td>20 years</td>
<td>Third payer</td>
<td>3</td>
<td>3</td>
<td>Stable disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minor response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complete response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment free</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Progressive disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Progressive disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Second-line disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
</tbody>
</table>

**Table 1** Summary of study characteristics of the included cost-effectiveness analyses assessing bortezomib or bortezomib-contained regimens for multiple myeloma.
<table>
<thead>
<tr>
<th>Fragoulakis et al.</th>
<th>Full publication</th>
<th>Greece</th>
<th>Cost-effectiveness/utility</th>
<th>Discrete event simulation</th>
<th>Not reported</th>
<th>Lifetime</th>
<th>Public health system</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hornberger et al.</td>
<td>Full publication</td>
<td>Sweden</td>
<td>Cost-effectiveness/utility</td>
<td>Partitioned survival model</td>
<td>3 weeks</td>
<td>10 years</td>
<td>Public health system</td>
<td>3</td>
</tr>
<tr>
<td>Jiang et al.</td>
<td>Abstract</td>
<td>UK</td>
<td>Cost-effectiveness/utility</td>
<td>Partitioned survival model</td>
<td>Not reported</td>
<td>Lifetime</td>
<td>National health system</td>
<td>4</td>
</tr>
<tr>
<td>Liwing et al.</td>
<td>Abstract</td>
<td>Nordic four countries (Finland, Norway, Sweden, Denmark)</td>
<td>Cost-effectiveness/utility</td>
<td>Partitioned survival model</td>
<td>Not reported</td>
<td>Lifetime</td>
<td>Public health system</td>
<td>4</td>
</tr>
<tr>
<td>Moller et al.</td>
<td>Full publication</td>
<td>Norway</td>
<td>Cost-effectiveness/utility</td>
<td>Discrete event simulation</td>
<td>Not reported</td>
<td>2 years</td>
<td>Public health system</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-effectiveness/utility</td>
<td>Discrete event simulation</td>
<td>Not reported</td>
<td>Lifetime</td>
<td>Public health system</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Five included CEAs compared VMP versus MP for previously untreated MM patients in the USA, Sweden, UK, and Canada. Three of these CEAs used a partitioned survival model than decomposed survival by disease progression status. One CEA used a Markov model with disease progression states for simulation. One included CEA did not report the model design. The VISTA trial was the data source for the methods comparing VMP versus MP for survival outcomes in these CEAs. Five included CEAs compared VMP versus MP for previously untreated MM patients in the USA, Sweden, UK, and Canada. Three of these CEAs used a partitioned survival model than decomposed survival by disease progression status. One CEA used a Markov model with disease progression states for simulation. One included CEA did not report the model design. The VISTA trial was the data source for the methods comparing VMP versus MP for survival outcomes in these CEAs.
**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

<table>
<thead>
<tr>
<th>Treatment setting</th>
<th>Comparison</th>
<th>Included studies</th>
<th>Data source for treatment effects</th>
<th>Data sources for costs</th>
<th>Data source for utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction treatment prior to SCT</td>
<td>BTZ treatment versus non-BTZ treatment</td>
<td>Kouroukis et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>IFM2005-01 trial</td>
<td>Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events</td>
<td>Van Agthoven et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>VD versus CTD</td>
<td>Mucha et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>IFM2005-01 trial</td>
<td>Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events</td>
<td>Van Agthoven et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>VD versus VAD</td>
<td>Mucha et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>IFM2005-01 trial</td>
<td>Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events</td>
<td>Van Agthoven et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>VTD versus CTD</td>
<td>Mucha et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>PETHEMA trial</td>
<td>Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events</td>
<td>Van Agthoven et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>VTD versus TD</td>
<td>Mucha et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>PETHEMA trial</td>
<td>Medical costs for chemotherapy, maintenance therapy, SCT, palliative care, and adverse events</td>
<td>Van Agthoven et al&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>Previously untreated MM but ineligible for SCT</td>
<td>VMP versus MP</td>
<td>Rickert et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>VISTA trial</td>
<td>Medical costs for treatment, adverse events, disease relapse, and palliative care</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Garrison et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>VISTA trial</td>
<td>Medical costs for treatments, adverse events, and second-line treatment</td>
<td>VISTA trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oster et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Palumbo et al&lt;sup&gt;36&lt;/sup&gt;, San Miguel et al&lt;sup&gt;21&lt;/sup&gt;, Facon et al&lt;sup&gt;24&lt;/sup&gt;, Hulin et al&lt;sup&gt;23&lt;/sup&gt;, Palumbo et al&lt;sup&gt;35&lt;/sup&gt;, any</td>
<td>Medical costs for treatment and adverse events</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yoong et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>VISTA trial</td>
<td>Medical costs for treatment and adverse events, maintenance therapy, and second-line treatment</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>VMP versus MPT</td>
<td>Rickert et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>VISTA trial and Palumbo et al&lt;sup&gt;36&lt;/sup&gt;, San Miguel et al&lt;sup&gt;21&lt;/sup&gt;, Facon et al&lt;sup&gt;24&lt;/sup&gt;, Hulin et al&lt;sup&gt;23&lt;/sup&gt;, Palumbo et al&lt;sup&gt;35&lt;/sup&gt;, any</td>
<td>Medical costs for treatment and adverse events, maintenance therapy, and second-line treatment</td>
<td>Study mapping EORTC QLQ-C30 to EQ-5D&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Garrison et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>VISTA trial and IFM99-06 trial</td>
<td>Medical costs for treatment, adverse events, and second-line treatment</td>
<td>VISTA trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yoong et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>VISTA trial</td>
<td>Medical costs for treatment, adverse events, and second-line treatment</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>VMP versus MPR-R</td>
<td>Garrison et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>VISTA trial and MM-015 trial</td>
<td>Medical costs for treatment, adverse events, and second-line treatment</td>
<td>Study mapping EORTC QLQ-C30 to EQ-5D&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oster et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Palumbo et al&lt;sup&gt;36&lt;/sup&gt;, San Miguel et al&lt;sup&gt;21&lt;/sup&gt;, Facon et al&lt;sup&gt;24&lt;/sup&gt;, Hulin et al&lt;sup&gt;23&lt;/sup&gt;, Palumbo et al&lt;sup&gt;35&lt;/sup&gt;, MM-015, and VISTA trial</td>
<td>Medical costs for treatment, adverse events</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

(Continued)
not exactly the same. Three included CEAs 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 estimated the baseline hazard rate associated with MP for PFS and OS from five RCTs (VISTA trial, IFM 99/06, and MM-10 trial) and projected higher hazard ratio associated with VMP versus MP for PFS (0.48) and OS (0.695). However, the other two included CEAs reported conflicting data on cost-effectiveness of VMP by MPT. The other two included CEAs reported conflicting data on cost-effectiveness of VMP by MPT and dominance of VMP over MPT and dominance of VMP versus MPT. The 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 MP), the indirect comparisons generated conflicting results for OS associated with the two treatments. For example, a mixed treatment comparison meta-analysis in one CEA estimated longer OS associated with VMP (61 versus 50.2 months), whereas another CEA 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 reported that the base case ICERs per gained QALY for VMP versus MP were 2.0248 and 0.7323 GDPPC, respectively. The reported key factors affecting the cost-effectiveness of

VMP versus MPT
Four included CEAs compared VMP versus MPT for previously untreated and SCT-ineligible MM patients in Sweden, USA, UK, and Canada. 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 MP), the indirect comparisons generated conflicting results for OS associated with the two treatments. For example, a mixed treatment comparison meta-analysis in one CEA estimated longer OS associated with VMP (61 versus 50.2 months), whereas another CEA 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 reported that the base case ICERs per gained QALY for VMP versus MP were 2.0248 and 0.7323 GDPPC, respectively. The reported key factors affecting the cost-effectiveness of

Table 2 (Continued)

<table>
<thead>
<tr>
<th>Treatment setting</th>
<th>Comparison</th>
<th>Included studies</th>
<th>Data source for treatment effects</th>
<th>Data sources for costs</th>
<th>Data source for utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed/refractory MM</td>
<td>VMP versus RD</td>
<td>Cavenagh et al</td>
<td>FIRST trial and ViSTA trial</td>
<td>Medical costs for drugs, administration, medical care, second- and third-line antimyeloma regimens, and management of toxicity</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>BTZ versus BSC</td>
<td>Bagust et al</td>
<td>SUMMIT1 trial</td>
<td>Medical costs for treatment and adverse events</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Mehta et al</td>
<td>SUMMIT1 trial</td>
<td>Medical costs for treatment and adverse events</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BTZ versus THD</td>
<td>Mehta et al</td>
<td>SUMMIT1 trial</td>
<td>Medical costs for treatment and adverse events</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>BTZ versus DEX</td>
<td>Hornberger et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Medical costs for treatment and adverse events</td>
<td>Van Agthoven et al</td>
</tr>
<tr>
<td></td>
<td>Liwing et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Medical costs for treatment, adverse events, and palliative care</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Felix et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fragoulakis et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Medical costs for treatment, adverse events, and palliative care</td>
<td>Van Agthoven et al</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hornberger et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Medical costs for treatment, adverse events, and palliative care</td>
<td>Van Agthoven et al</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jiang et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liwing et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moller et al</td>
<td>APEX trial, MM-009 trial, and MM-10 trial</td>
<td>Medical costs for treatment, adverse events, and palliative care</td>
<td>Van Agthoven et al</td>
<td></td>
</tr>
</tbody>
</table>

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.
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)

<table>
<thead>
<tr>
<th>Treatment setting</th>
<th>Comparison</th>
<th>Included studies</th>
<th>Country</th>
<th>Adjusted ICER by 2014 GDPPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction treatment prior to SCT</td>
<td>BTZ-containing regimen versus non-BTZ treatment</td>
<td>Kouroukis et al12</td>
<td>Canada</td>
<td>2.2544/QALY</td>
</tr>
<tr>
<td>VD versus CTD</td>
<td>Mucha et al13</td>
<td>Poland</td>
<td>1.2584/QALY</td>
<td></td>
</tr>
<tr>
<td>VD versus VAD</td>
<td>Mucha et al13</td>
<td>Poland</td>
<td>1.0083/QALY</td>
<td></td>
</tr>
<tr>
<td>VTD versus CTD</td>
<td>Mucha et al13</td>
<td>Poland</td>
<td>0.5588/QALY</td>
<td></td>
</tr>
<tr>
<td>VTD versus TD</td>
<td>Van Beurden-Tan et al14</td>
<td>Germany</td>
<td>0.9864/QALY</td>
<td></td>
</tr>
<tr>
<td>Previously untreated MM but ineligible for SCT</td>
<td>VMP versus MP</td>
<td>Yoong et al19</td>
<td>Canada</td>
<td>1.1060/QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Garrison Jr et al16</td>
<td>USA</td>
<td>1.1622/QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rickert et al15</td>
<td>Sweden</td>
<td>2.3744/QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oster et al17</td>
<td>USA</td>
<td>2.0059/QALY</td>
</tr>
<tr>
<td></td>
<td>VMP versus MPT</td>
<td>Rickert et al15</td>
<td>Sweden</td>
<td>2.0248/QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Garrison Jr et al16</td>
<td>USA</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yoong et al19</td>
<td>Canada</td>
<td>0.7323/QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Picot et al18</td>
<td>UK</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>VMP versus MPR-R</td>
<td>Garrison Jr et al16</td>
<td>USA</td>
<td>Dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oster et al17</td>
<td>USA</td>
<td>1.3979/QALY</td>
</tr>
<tr>
<td></td>
<td>VMP versus CTD</td>
<td>Picot et al18</td>
<td>UK</td>
<td>1.1911/QALY</td>
</tr>
<tr>
<td></td>
<td>VMP versus RD</td>
<td>Cavenagh et al20</td>
<td>USA</td>
<td>1.5775/QALY</td>
</tr>
<tr>
<td>Relapsed/refractory MM</td>
<td>BTZ versus BSC</td>
<td>Bagust et al21</td>
<td>UK</td>
<td>0.9317–1.8210/LY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mehta et al22</td>
<td>USA</td>
<td>1.0933/LY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mehta et al22</td>
<td>USA</td>
<td>1.2004/LY</td>
</tr>
<tr>
<td></td>
<td>BTZ versus THD</td>
<td>Mehta et al22</td>
<td>Sweden</td>
<td>3.2062/QALY</td>
</tr>
<tr>
<td></td>
<td>Liwing et al27</td>
<td>Nordic countries</td>
<td>€54451–€81560/QALY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BTZ versus DEX</td>
<td>Hornberger et al25</td>
<td>Sweden</td>
<td>2.5332–3.0187/QALY</td>
</tr>
<tr>
<td></td>
<td>Felix et al23</td>
<td>Portugal</td>
<td>(LEN/DEX versus BTZ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fragoulakis et al24</td>
<td>Greece</td>
<td>2.0259/QALY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hornberger et al25</td>
<td>Sweden</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jiang et al25</td>
<td>UK</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liwing et al27</td>
<td>Nordic countries</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moller et al28</td>
<td>Norway</td>
<td>0.5205/QALY</td>
<td></td>
</tr>
</tbody>
</table>

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 CEA18 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.16,17 One included CEA16 used a Markov model with seven health states, and the other CEA17 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).37 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\textsuperscript{17} comparing VMP versus MPR-R estimated longer OS associated with MPR-R through an indirect comparison assuming the same post-progression 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.\textsuperscript{18} 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\textsuperscript{18} 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.\textsuperscript{21,22} These two CEAs took life year as health benefits measurement in CEA. The UK CEA used a 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.\textsuperscript{22} Both CEAs used the SUMMIT trial,\textsuperscript{39} 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.\textsuperscript{22} 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\textsuperscript{27} and four Nordic countries, including Finland, Norway, Sweden, and Denmark.\textsuperscript{27} 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,\textsuperscript{39} as the data source for the survival benefits associated with BTZ. The survival benefits of DEX were based on two trials (the MM-009\textsuperscript{40} and MM-010\textsuperscript{41} 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 ICER 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 per 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 and three in abstract) compared BTZ versus LEN/DEX for relapsed/refractory MM in Portugal, Greece, Sweden, UK, Nordic countries, and Norway. Of these included six CEAs, three CEAs used partitioned survival model, two CEAs used a discrete event simulation model, and one CEA used Markov model to simulate health benefits and costs. 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. However, two CEAs using DES model reported longer survival and higher costs associated with LEN/DEX. The base case ICER 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. 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, 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. 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. 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 was 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.

Acknowledgments
We want to thank the authors of the included CEAs who helped make our review comprehensive and meaningful for future clinical and reimbursement decision-making for patients with multiple myeloma. Dr Wendong Chen formulated the research idea and developed the study design for literature search, data extraction, and data analysis. Yi Chen 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.

References


Supplementary materials

Table S1 Summary of excluded references and their exclusion reasons

<table>
<thead>
<tr>
<th>Excluded references</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta et al1</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Fragoulakis et al2</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Wang et al3</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Wang et al4</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Wang et al5</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Wang et al6</td>
<td>Full manuscript has been published</td>
</tr>
<tr>
<td>Popat et al7</td>
<td>BTZ was not studied</td>
</tr>
<tr>
<td>Schey et al8</td>
<td>BTZ was not studied</td>
</tr>
<tr>
<td>Tuffaha et al9</td>
<td>BTZ was not studied</td>
</tr>
<tr>
<td>Gautney et al10</td>
<td>BTZ was not studied</td>
</tr>
<tr>
<td>Gautney et al11</td>
<td>Not CEA (cohort study for clinical outcomes)</td>
</tr>
<tr>
<td>Hornberger et al12</td>
<td>Not CEA (cost study)</td>
</tr>
<tr>
<td>Teitelbaum et al13</td>
<td>Not CEA (cost study)</td>
</tr>
<tr>
<td>Vitale et al14</td>
<td>Not CEA (cost study)</td>
</tr>
<tr>
<td>Gautney et al15</td>
<td>Insufficient information</td>
</tr>
<tr>
<td>Gibbons et al16</td>
<td>Insufficient information</td>
</tr>
<tr>
<td>Blommestein et al17</td>
<td>Insufficient information</td>
</tr>
<tr>
<td>Durie et al18</td>
<td>Outcome measures for health benefits were not LY and/or QALY</td>
</tr>
<tr>
<td>Gooding et al19</td>
<td>Outcome measures for health benefits were not LY and/or QALY</td>
</tr>
<tr>
<td>Schey and Higginson20</td>
<td>Review</td>
</tr>
<tr>
<td>Haycox and Tolley21</td>
<td>Review</td>
</tr>
<tr>
<td>Cecchi et al22</td>
<td>Letter</td>
</tr>
<tr>
<td>Lucioni et al23</td>
<td>Non-English</td>
</tr>
<tr>
<td>Vandekerckhove et al24</td>
<td>Not MM patients</td>
</tr>
<tr>
<td>Shustik et al25</td>
<td>Budget impact analysis</td>
</tr>
<tr>
<td>Blommestein et al26</td>
<td>Insufficient information</td>
</tr>
<tr>
<td>Gooding et al27</td>
<td>Control group was lacking for the calculation of ICER</td>
</tr>
</tbody>
</table>

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

References

ClinicoEconomics and Outcomes Research

Publish your work in this journal

ClinicoEconomics & Outcomes Research is an international, peer-reviewed open-access journal focusing on Health Technology Assessment, Pharmacoeconomics and Outcomes Research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal

Dovepress

Cost-effectiveness review of bortezomib for MM