PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bortezomib (Velcade) for Multiple Myeloma

March 25, 2013

DISCLAIMER

Not a Substitute for Professional Advice
This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability
pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of bortezomib (Velcade) as monotherapy or combination therapy prior to autologous stem cell transplantation (ASCT) (induction), immediately post-ASCT (consolidation or maintenance) or both pre-ASCT (induction) and post-ASCT (consolidation or maintenance) on patient outcomes compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT. The recommended dose of bortezomib is 1.3 mg/m^2 intravenously or subcutaneously on days 1, 4, 8, and 11 of 3-week cycles along with dexamethasone. Alternatively, dosing schedules could be 1.5 mg/m2 weekly when used with cyclophosphamide and dexamethasone. Although it does not have Health Canada regulatory approval for this indication, bortezomib was submitted to pCODR by Cancer Care Ontario, Hematology DSG tumor group for the review in patients with multiple myeloma who are candidates for autologous stem cell transplantation (ASCT). Bortezomib-based combination therapy can include the addition of dexamethasone, alkylator or anthracycline chemotherapy, or immunomodulator-based therapy to the bortezomib backbone.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Seven randomized controlled trials were identified investigating the use of bortezomib either pre- or post-ASCT, in patients with multiple myeloma who were candidates for ASCT. Of these, three trials investigated the use of bortezomib in induction therapy followed by ASCT [1-3], one trial investigated the use of bortezomib following ASCT only[4] and three trials investigated the use of bortezomib in both induction therapy and in post-ASCT therapy [5-8].

Three studies, GIMEMA[5], HOVON-65/GMMG-HD4[6] and IFM 2005-01[1] were the bases of the systematic review presented. Four of the seven included studies provided only a limited amount of useful information related to the questions of interest in the review and so are not focused on in detail in this review.

1. GIMEMA[5] was a multi-centre, open-label randomized controlled trial that compared the efficacy and safety of thalidomide/dexamethasone (TD) in the induction phase and the consolidation phase (n=238) to bortezomib/thalidomide/dexamethasone (BTD) in the induction phase and the consolidation phase (n=236). The primary outcome was post-induction complete or near-complete response rate and the study met the necessary sample size requirement. Neither patients nor investigators were blinded to treatment assignment. Outcomes were assessed by investigators and centrally re-assessed by the study team.
2. HOVON-65/GMMG-HD4[6] was an investigator-sponsored, open-label, randomized phase III trial that compared the efficacy and safety of bortezomib, doxorubicin, and dexamethasone (BAD) followed by ASCT followed by bortezomib maintenance (n=413) to vincristine, doxorubicin, dexamethasone (VAD) followed by ASCT followed by thalidomide maintenance (n=414). The primary outcome was PFS and the study met the required sample size. Neither patients nor investigators were blinded to treatment assignment and no mention was made regarding the blinding of outcome assessors.

3. IFM 2005-01[1] was an open-label randomized phase III trial that compared the efficacy and safety of one of four induction treatment arms: BD vs. BD plus dexamethasone, cyclophosphamide, etoposide, cisplatinum (DCEP) vs. vincristine, doxorubicin, dexamethasone (VAD) vs. VAD plus DCEP. The authors reported results for the BD arm combined with the BD+DCEP arm (n=240 for both arms combined) compared to the VAD arm combined with the VAD+DCEP arm (n=242 for both arms combined). None of the patients or investigators were blinded to treatment; however, the outcome assessors were. The primary outcome of the study was the rate of complete and near-complete response following induction therapy.

Efficacy

In the GIMEMA study, statistically significant differences were observed in the rates of post-induction overall response, very good partial response or better, and complete or near-complete response in favour of the BTD induction arm compared to the TD induction arm. Statistically significant difference in PFS in favour of the BTD→double ASCT→BTD consolidation arm compared to the TD→double ASCT→TD consolidation arm (PFS estimates of 68% vs. 56% at three years, respectively; HR=0.63, 95% confidence interval [CI] 0.45-0.88, p=0.0061)[9]. No statistically significant difference was reported in overall survival between the two study arms.

In the HOVON-65/GMMG-HD4 study, statistically significant differences were observed in the post-induction rates of overall response, very good partial response or better, and complete or near-complete response in favour of the BAD induction arm compared to the VAD induction arm. In addition, a statistically significant difference in PFS was reported in favour of the BAD→ASCT→bortezomib maintenance arm (median 35 months) compared to the VAD→ASCT→thalidomide maintenance arm (median 28 months; HR=0.75, 95% CI 0.62-0.90, p=0.002)[6]. No statistically significant difference in overall survival was reported between the two study arms.

In the IFM 2005-01 study, statistically significant differences were observed in the rates of overall response, very good partial response or better, and incomplete or near-complete response; all favouring the BD/BD+DCEP arms compared to the VAD/VAD+DCEP arms. After a median follow-up of 31.2 months, median PFS was not statistically different for the BD/BD+DCEP arms compared to the VAD/VAD+DCEP arms; however, the trial was not powered to detect a difference in PFS.[1]

Harms

The IFM 2005-01 study reported significant differences in the rates of Grade 3/4 neutropenia (VAD 10% vs. BD 5%, p<0.05) and anemia (VAD 8.8% vs. BD 4.2%, p<0.05) and treatment-related deaths (VAD 29% vs. BD 0, p=0.02)[1]. The HOVON-65/GMMG-HD4 study reported statistically significant differences in the rates of grade 3/4 thrombocytopenia (BAD 10% vs. VAD 5%, p<0.01) and any Grade 3/4 adverse event (BAD 63% vs. VAD 54%, p<0.01)[6]. The GIMEMA study also reported a statistically significant difference in any Grade 3/4 adverse events (BTD 56% vs. TD 33%, p<0.0001)[5].

The HOVON-65/GMMG-HD4 study reported a statistically significant difference in the proportion of patients who experienced toxicity leading to discontinuation of maintenance therapy, with 30.4% of those who received maintenance thalidomide experiencing such an event compared to 11.4% of those who received maintenance bortezomib (p<0.001)[6].

1.2.2 Additional Evidence

pCODR received input on bortezomib from the following patient advocacy group, Myeloma Canada. Provincial Advisory group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada.[10] Myeloma increases in incidence with age, with a median age at presentation of 70 years [11], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1400 deaths from the disease expected in Canada in 2012.[10]

Multiple myeloma is relatively common and autologous stem cell transplant is frequently performed as part of front line myeloma therapy. This treatment is not curative and improving patient survival, remission duration and quality of life are important goals. While improvement in response rate is seen as a positive sign of the activity of a drug, it is not considered as sufficient evidence to adopt a change in practice without evidence of benefit in the other aforementioned domains.

Two fully published, randomized controlled trials, GIMEMA[5] and HOVON-65/GMMG-HD4[6], have demonstrated a statistically and clinically significant improvement in PFS with the addition of bortezomib, and a third trial, IFM 2005-01[1], has shown a trend towards improved PFS of similar magnitude relative to the other trials. The Harousseau trial has to be interpreted with some caution since most of the patients were enrolled in a subsequent trial of lenalidomide maintenance therapy post transplant, which could have impacted the PFS outcomes, and the primary endpoint was response rate rather than PFS or OS. In the Cavo trial the primary endpoint was also response rate, whereas with Sonneveld et al. the primary endpoint was PFS. In all three trials, the point estimate of the increase in PFS with the addition of bortezomib was clinically meaningful.

The preferred bortezomib containing regimen, while currently unknown, is the subject of ongoing study and will continue to evolve, however, the three trials evaluated suggest that adding bortezomib to front line therapy improves PFS in transplanted myeloma patients. In addition, none of these three trials were designed in a way that would distinguish the effects of induction bortezomib from additional bortezomib given later in the course of therapy. As such, it is difficult to determine the optimal timing of bortezomib in front line therapy for transplant-eligible patients.

While the addition of bortezomib has been associated with increased toxicity, the degree of toxicity appears to be manageable as few patients had to discontinue protocol therapy due to toxicity. Peripheral neuropathy is the most significant and potentially irreversible toxicity of bortezomib and this toxicity is increased in the bortezomib arms of the three trials of interest. There is no quality of life data available from these trials.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to the use of bortezomib as part of front line therapy that includes high dose melphalan and autologous hematopoietic stem cell transplantation for patients with multiple myeloma. This conclusion is based on two high quality randomized controlled trials, GIMEMA[5] and HOVON-65/GMMG-HD4[6], showing improvement in PFS with treatment regimen that include bortezomib compared to treatment regimen that do not include bortezomib, with increased but manageable toxicity, and a third trial of similar design that showed comparable but not statistically significant trends in PFS.

The Clinical Guidance Panel also considered that from a clinical perspective uncertainty remains regarding the optimal schedule and route of administration of bortezomib, the preferred bortezomib-containing regimen to use, and the incremental value of the addition of bortezomib as consolidation or maintenance post transplant. All three trials included three to four cycles of twice-weekly intravenous bortezomib at 1.3 mg/m^2 on days 1,4,8 and 11 every three to four weeks induction therapy prior to transplant, and the two positive trials provided some post-transplant bortezomib as consolidation or maintenance.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding bortezomib (Velcade) for multiple myeloma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding bortezomib (Velcade) conducted by the Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on bortezomib (Velcade) and a summary of submitted Provincial Advisory Group Input on bortezomib (Velcade) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada.[10] Myeloma increases in incidence with age, with a median age at presentation of 70 years.[11]

Patients with symptomatic myeloma are treated primarily with anti-myeloma drug therapy. For many years the mainstay of myeloma treatment was a combination of oral melphalan (chemotherapy) and prednisone (corticosteroid therapy). Other, older drug combinations did not improve survival in comparison to melphalan and prednisone, and median survival was approximately 2.5 years regardless of the therapy chosen.[12]

High dose intravenous melphalan supported by autologous hematopoietic stem cell transplantation has improved survival for myeloma patients who are eligible for this treatment. Eligibility criteria generally include good performance status and sufficient organ function and is generally reserved for patients aged less than about 70 years but the decision to use this treatment is ultimately left to the discretion of the treating physician, in discussion with the patient. For eligible patients high dose melphalan and autologous stem cell transplant is generally prescribed as part of the initial treatment, rather than deferring this therapy until relapse, in order to maximize the duration of the first remission. Delaying the transplant until relapse can produce similar long term survival rates but has been associated with inferior symptom control. Sufficient stem cells are usually collected in order to allow more than one autologous transplant; this approach can facilitate the administration of two consecutive cycles of high dose melphalan with stem cell transplant support, an approach known as tandem transplantation, or can be used to allow high dose melphalan to be administered again at the time of relapse in patients who benefited from a prior autologous transplant. The advantage of tandem transplantation relative to a single transplant up front is not clearly established.

High dose melphalan is generally preceded by a three to four month course of induction therapy with conventional doses of anti-myeloma drugs. The goals are to

improve the functional status of the patient prior to high dose therapy and to clear sufficient amounts of myeloma cells from the bone marrow to facilitate hematopoietic stem cell collection. Care must be taken to choose induction therapy which will not impair the ability to collect hematopoietic stem cells for autologous transplantation.

Newer anti-myeloma drugs have further improved the survival of myeloma patients, including bortezomib, thalidomide and lenalidomide. These drugs are generally used in combination with corticosteroids and/or chemotherapy agents, and are of proven benefit in both newly diagnosed patients not eligible for transplant and those with relapsed disease.[13]

2.1.2 Objectives and Scope of pCODR Review

1. To evaluate the effect of bortezomib, as monotherapy or combination therapy prior to autologous stem cell transplantation (ASCT) (i.e., induction), compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.
2. To evaluate the effect of bortezomib, as monotherapy or combination therapy, immediately post-ASCT (i.e., consolidation or maintenance) compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.
3. To evaluate the effect of bortezomib, as monotherapy or combination therapy both pre-ASCT (induction) and post-ASCT (consolidation or maintenance), compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.

Candidates for ASCT include patients whom the treating clinician (e.g., oncologist, haematologist) deems fit for ASCT based upon factors including, but not limited to, age, performance status, and co-morbidities.

Post-ASCT treatment (i.e., consolidation or maintenance) is generally started within 3-6 months of ASCT.

Outcomes of interest included, but were not limited to, overall survival, progression-free survival (PFS), response to induction therapy, and adverse events. Quality of life (QOL) was considered by patients to be the most important outcome. For additional details on outcomes of interest, please see Section 6.2.1.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

An evidence-based clinical practice guideline[14], developed by the Hematology Disease Site Group (DSG) of Cancer Care Ontario's (CCO) Program in Evidence-based Care (PEBC), was included in this Clinical Guidance Report (CGR). A systematic review of bortezomib in multiple myeloma formed the basis of the guideline. That systematic review was used to to inform this CGR.

The literature search in the PEBC guideline was current to August 2012. That systematic review identified a total of seven randomized trials investigating the use of bortezomib either pre- or post-ASCT, in patients with multiple myeloma who were candidates for ASCT. The pCODR Methods Team updated the literature search from August 2012 and identified four additional publications, all of which were publications of trials previously identified in the PEBC guideline. Therefore a total of seven randomized trials were included in this CGR.[1-8,15]

Table 1 provides a brief overview of the treatment arms of each study, as well as select quality characteristics for each trial. For additional details on the included patient populations and in-depth information on the treatments administered in each trial, please refer to Section 6 (Systematic Review) of this CGR.

Three trials investigated the use of bortezomib in induction therapy followed by ASCT.[1-3] Different regimens and comparators were used in all three studies. Of note, the study reported by Ludwig et al[2] was not designed to be comparative, therefore the authors did not report nor conduct statistical comparisons between the two treatment arms. This study is not discussed further as it provides limited evidence on the use of bortezomib in induction therapy compared to currently used treatments. For further information on this trial, please refer to Section 6. In addition, the IFM 2007-02 study[3] compared the use of bortezomib/dexamethasone (BD) to reduced-dose boretzomib/thalidomide plus dexamethasone (btD) in 199 patients. As both treatment arms included bortezomib, this trial's usefulness in determining whether bortezomib should be used in induction therapy compared to currently used therapies is extremely limited.

The IFM 2005-01 study[1] randomized patients to one of four induction treatment arms: BD vs. BD plus dexamethasone, cyclophosphamide, etoposide, cisplatinum (DCEP) vs. vincristine, doxorubicin, dexamethasone (VAD) vs. VAD plus DCEP. The authors reported results for the BD arm combined with the BD+DCEP arm (n=240 for both arms combined) compared to the VAD arm combined with the VAD+DCEP arm (n=242 for both arms combined). None of the patients or investigators were blinded to treatment; however, the outcome assessors were. The primary outcome of the study was the rate of complete and near-complete response following induction therapy. Efficacy results can be found in Table 2. The authors reported statistically significant differences in the rates of overall response, very good partial response or better, and in complete or near-complete response all favouring the BD/BD+DCEP arms compared to the VAD/VAD+DCEP arms (Table 2). After a median follow-up of 31.2 months, the authors reported median PFS was not statistically different for the BD/BD+DCEP arms compared to the VAD/VAD+DCEP arms; however, it should be noted that the trial was not powered to detect a difference in PFS.

One trial investigated the use of bortezomib following ASCT only. Mellqvist et al[4] reported in abstract form, a trial that enrolled patients who had received ASCT in the past five weeks and who had no prior exposure to bortezomib. A total of 372 patients were randomized to receive consolidation therapy with bortezomib monotherapy or to no consolidation therapy. The primary outcome was event-free survival; however, no further information regarding the study has been published, making an assessment of its quality impossible. To date, no final analysis has been published. The efficacy results of this trial can be found in Table 2; however, this study is not discussed further given the limited information that is available regarding its quality.

Three trials investigated the use of bortezomib in both induction therapy and in post-ASCT therapy. Two of those trials, the GIMEMA study[5] and HOVON-65/GMMG-HD4 study[6] randomized patients to the one of two treatment algorithms of induction (either with or without bortezomib) followed by ASCT followed by post-ASCT therapy, where every patient in a specific arm received the same post-ASCT treatment (Table 1). Of note, neither trial used the same regimens.

The GIMEMA study[5] randomized a total of 474 patients to either a treatment regimen consisting of thalidomide/dexamethasone (TD) in the induction phase and the consolidation phase (n=238) or to a treatment regimens of botezomib/thalidomide/dexamethasone (BTD) in the induction phase and the consolidation phase (n=236). The primary outcome was post-induction complete or near-complete response rate and the study met the necessary sample size requirement (Table 1). Neither patients nor investigators were blinded to treatment assignment. Outcomes were assessed by investigators and centrally re-assessed by the study team. It is not known if the centralized re-assessment was blinded. Statistically significant differences in the rates of post-induction overall response, very good partial response or better, and complete or near-complete response were reported in favour of the BTD induction arm compared to the TD induction arm (Table 2). The authors also reported a statistically significant difference in PFS for the BTD→ASCT→BTD consolidation→maintenance arm compared to the TD→ASCT→TD consolidation→maintenance arm, with 3-year estimates of PFS of 68% vs. 56%, respectively (HR 0.63 95% CI 0.45-0.88, p=0.0061).[9] No statistically significant difference was reported in overall survival between the two study arms (Table 2).

The HOVON-65/GMMG-HD4 study randomized a total of 827 patients to receive bortezomib, doxorubicin, and dexamethasone (BAD) followed by ASCT followed by bortezomib maintenance (n=413) or to receive vincristine, doxorubicin, dexamethasone (VAD) followed by ASCT followed by thalidomide maintenance (n=414).[6] The primary outcome was PFS and the study met the required sample size (Table 1). Neither patients nor investigators were blinded to treatment assignment and no mention was made regarding the blinding of outcome assessors. Statistically significant differences in the post-induction rates of overall response, very good partial response or better, and complete or near-complete response were reported in favour of the BAD induction arm compared to the VAD induction arm (Table 2). In addition, a statistically significant difference in PFS was reported in favour of the BAD→ASCT→bortezomb maintenance arm (median 35 months) compared to the VAD→ASCT→thalidomide maintenace arm (median 28 months; HR=0.75, 95% CI 0.62-0.90, p=0.002).[6] No statistically significant difference in overall survival when adjusted for International Staging System (ISS) was reported between the two study arms (Table 2). A multivariate Cox regression of OS adjusted for ISS demonstrated a statistically significant difference for the BAD arm compared to the VAD arm (HR 0.77; 95% confidence interval [CI] 0.60 to 1.00; p=0.049).

The PETHEMA study included two randomizations.[7] The first randomized 386 patients to receive induction therapy with thalidomide and dexamethasone (TD; n=127) or bortezomib, thalidomide, and dexamethasone (BTD; n=130) or combination chemotherapy with bortezomib (Combination chemotherapy/B; n=129; Table 1). The second randomized 266 patients to receive maintenance therapy with bortezomib and thalidomide (BT; n=89), or thalidomide alone (n=87), or alfa-2b-interferon (interferon; n=90). The primary outcome of the induction randomization was the post-induction rate of complete response. A total of 130

patients were required per arm. Althought the study was four patients short of the required sample size, the affect on the study results would be minimal. No information was available on the blinding of patients or investigators. Outcomes were assessed by the investigators and centrally re-assessed; however, no mention of blinding of the centralized re-assessment was made. Statistically significant differences in the rates of post-induction complete response were reported in favour of the BTD arm (35%) compared to the TD arm (14%; p=0.0001) and compared to the combination chemotherapy/B arm (21%; p=0.01). No statistical comparisons were reported for the rates of overall response or very good partial response or better (Table 2). In addition, a statistically significant difference in PFS was reported in favour of the BTD arm (median 56.2 months; p=0.01)) compared to the TD arm (median 28.2 months) or the combination chemotherapy/B arm (median 35.3 months). For the second randomization to choice of maintenance therapy, the primary outcome was PFS (from start of maintenance therapy). The second randomization has only been reported in abstract form and there is little information available to determine the overall study quality (Table 1).[8] A statistically significant difference in PFS was reported in favour of the BT arm (median 44 months; p=0.00093) compared to the thalidomide alone arm (median 40 months) or the interferon arm (median 28.5 months). Of note, it is unclear if the significant difference was for a comparison of the BT arm to both the thalidomide arm and the interferon arm combined, or if two comparisons were made, one between the BT arm and the thalidomide arm and another between the BT arm and the interferon arm, with with same p-value obtained for each.

Of the reported Grade 3/4 adverse events, the rate of peripheral neuropathy was reported as significantly higher in the bortezomib-containing induction arm in four of the five trials that compared induction with bortezomib to induction without bortezomib (See Section 6, Table 6). The IFM 2005-01 study reported significant differences in the rates of Grade 3/4 neutropenia (VAD 10% vs. BD 5%, p<0.05) and anemia (VAD 8.8% vs. BD 4.2%, p<0.05) and treatment-related deaths (VAD 29% vs. BD 0, p=0.02).[1] The HOVON-65/GMMG-HD4 study reported statistically significant differences in the rates of grade 3/4 thrombocytopenia (BAD 10% vs. VAD 5%, p<0.01) and any Grade 3/4 adverse event (BAD 63% vs. VAD 54%, p<0.01).[6] The GIMEMA study also reported a statistically significant difference in any Grade 3/4 adverse events (BTD 56% vs. TD 33%, p<0.0001).[5]

The HOVON-65/GMMG-HD4 study reported a statistically significant difference in the proportion of patients who experienced toxicity leading to discontinuation of maintenance therapy, with 30.4% of those who received maintenance thalidomide experiencing such an event compared to 11.4% of those who received maintenance bortezomib (p<0.001).[6]

Table 1. Select quality characteristics of included RCTs of bortezomib in newly diagnosed multiple myeloma.

Author, year	Treatment	Primary outcome	Required sample size (80% power, α=0.05)	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical Approval
Trials Investigating Only Induction with Bortezomib											
IFM 2005/01 Harousseau, 2010[1]	BD vs. BD+DCEP vs. VAD vs. VAD+DCEP	Post-induction CR/ nCR	110 pts per arm to detect a 10% difference post induction	BD: 121 BD+DCEP: 119 VAD: 121 VAD+DCEP: 121	Central	Yes	No[A]	Yes	Yes	No	Yes
Ludwig, 2013[2]	BTD vs. BTDC	Post-induction CR/nCR	Not designed to compare treatment arms[B]	BTD: 49 BTDC: 49	NR	NR	No[A]	No[C]	Yes	No	Yes
IFM-2007-02 Moreau, 2011[3]	BD vs btD	Post induction CR	200 needed to provide 80% power, α 5% (two-sided test) to detect a 18% difference in CR assuming a 7% difference with BD.	BD: 99 btD: 100	Central	Yes	No[D]	Yes	Yes	No	Yes
Trials Investigating Only Post-transplant Treatment with Bortezomib (Consolidation or Maintenance)											
Mellqvist, 2009[4] [abs]	B consol vs. No consol	EFS	400 pts: no calculation provided	372	NR	NR	No	Yes	No	NR	NR
Trials Investigating Both Induction and Post-Transplant Therapy with Bortezomib											
GIMEMA Cavo, 2010[5]	BTD→ASCT→BTD consol→D maint vs. TD→ASCT→TD consol→D maint	Post-induction CR/nCR	225 pts per arm to provide 80% power to detect a significant increase in CR + nCR from 15% with TD to 27% with BTD	BTD arm: 236[E] TD arm: 238[E]	Central	Yes	No[F]	Yes	Yes	No	Yes
HOVON-65/GMMG-HD4 Sonneveld, 2012[6]	BAD→ASCT→B maint vs. VAD→ASCT→T maint	PFS	800 pts or 356 events were needed to detect a HR = 0.74 with a power of 80%, and α = 0.049.	BAD arm: 413 VAD arm: 414	Central	Yes	No[G]	Yes	Yes	No	Yes
PETHEMA/ GEM Rosinol 2012[7,8]	Induction: TD vs BTD vs VBMCP/VBAD/B All pts received ASCT	Post-induction and post-ASCT CR	130 pts per arm to provide 80% power, with α=0.05, were needed to detect a 15% difference among groups in post-induction and	TD: 127 BTD: 130 VBMCP/VBAD/B : 129	Central	NR	NR[F]	Yes	Yes	No	Yes

Author, year	Treatment	Primary outcome	Required sample size (80% power, α=0.05)	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical Approval
			post-ASCT CR rates.								
	Maintenance: BT vs T vs alfa-2b-interferon	PFS	NR	TB: 89 T: 87 Interferon: 90	NR	NR	NR[D]	Yes	Yes	NR	Yes

Notes: abs = abstract; ASCT = autologous stem cell transplantation; B = bortezomib; BAD = bortezomib, doxorubicin, dexamethasone; BD = bortezomib, dexamethasone; BT = bortezomib, thalidomide; btD = reduced dose bortezomib and thalidomide plus dexamethasone; BTD = bortezomib, thalidomide, dexamethasone; BTDC = bortezomib, thalidomide, dexamethasone, cyclophosphamide; consol = consolidation; CR = complete response; D = dexamethasone; DCEP = dexamethasone, cyclophosphamide, etoposide, cisplatinum; EFS = event-free survival; ITT = intention-to-treat; maint = maintenance; N= number of patients; nCR = near complete response; NR = not reported; PFS = progression-free survival; pts = patients; T = thalidomide; TD = thalidomide, dexamethasone; VAD = vincristine + doxorubicin + dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone.

[A]Blinded assessors of outcomes.

[B]Sample size was determined for each group, using a one-sided test at α=0.10, with 80% power, a null hypothesis for CR/nCR rate of 20%, and an alternative hypothesis for CR/nCR rate of 35%. A total of 46 patients were required per group. The study was not powered or designed to be comparative.

[C]Response endpoints were assessed in the response-evaluable population (patients with measurable disease at baseline who received at least one dose of any study drug and had at least one post-baseline response assessment); Time-to-event endpoints were assessed in the intention-to-treat population (all randomly assigned patients).

[D]Outcomes assessed centrally; however, no mention of blinding of outcome assessments.

[E]480 patients were randomly assigned: 241 to BTD and 239 to TD. 5 patients in the BTD arm and 1 patient in the TD arm withdrew consent prior to starting treatment and were not included in the intent-to-treat population.

[F]Outcomes assessed by investigators and centrally reassessed by study team; however, no mention of blinding of outcome assessments.

[G]No mention of blinding of outcome assessments.

Table 2. Results of studies of bortezomib in patients with newly diagnosed multiple myeloma.

Author, year (ref)	Interventions Controls	Response to induction			% of pts who received ASCT	% of pts who received post-ASCT therapy	PFS, median (mos)	OS, median (mos)	Follow-up, median (mos)
		OR (%)	VGPR+ (%)	CR/nCR (%)					
Trials with bortezomib in induction only									
IFM 2005/01 Harousseau, 2010[1]	IG_1: BD + no consolidation IG_2: BD + DCEP consolidation → ASCT N=240	78.5	37.7	14.8*	88.3	63.8[A]	36.0 mos	NE[B]	31.2
	CG_1: VAD + no consolidation CG_2: VAD + DCEP consolidation → ASCT N=242	62.8 p<0.001	15.1 p<0.001	6.4* p=0.004	84.4	63.2[A]	29.7 mos p=0.057	NE[B]	
IFM 2007-02 Moreau, 2011[3]	BD N=99	81	36	22*	89.9	NR	30	NR	32
	btD n=100	88 p = 0.19	49 p=0.05	31* p=0.15	91.0	NR	26 p=0.22	NR p=NS,NR	
Ludwig, 2013[2]	BTD N=49	100	69	51*	98	NR	25.1	NE	33.3
	BTDC N=49	94	67	43*	82	NR	23.5	NE	33.1
Trials with bortezomib in post-ASCT therapy only (consolidation and/or maintenance)									
Mellqvist, 2009[4] [abs] Mellqvist, 2011[15] [abs]	B consolidation N=NR	N/A	N/A	At randomization: 20	-	-	27 mos (95% CI 24-29 mos)	2-year 90%	NR
	No consolidation N=NR	N/A	N/A	21	-	-	20 mos (95% CI 17-23 mos); p=0.02	90%	
Trials with bortezomib in induction therapy and in post-ASCT therapy									

Author, year (ref)	Interventions Controls	Response to induction			% of pts who received ASCT	% of pts who received post-ASCT therapy	PFS, median (mos)	OS, median (mos)	Follow-up, median (mos)
		OR (%)	VGPR+ (%)	CR/nCR (%)					
GIMEMA Cavo, 2010[5] Cavo, 2012[9]	BTD → double ASCT → BTD consolidation N=236	93.2	61.9	44*	92.4%	69.9%	Estimated at 3 years: 68%	NS[C]	36
	TD → double ASCT → TD consolidation N=238	78.6 p<0.0001	27.7 p<0.0001	11* p<0.0001	84.5%	69.3%	56% P=0.0057 HR = 0.63 (95% CI 0.45-0.88, p=0.0061)	NS	
HOVON-65/GMMG-HD4 Sonneveld, 2012[6]	BAD + Hi-M+ASCT → Maintenance B N=413	78	42	11	85.2	55.4	35*	Estimated 5-year 61%	41
	VAD+Hi-M+ASCT → Maintenance T N=414	54 p<0.001	14 p<0.001	5 p<0.001	83.8	65.2	28* HR 0.75 (95% CI 0.62-0.90) p=0.002	55% HR 0.81 (95% CI 0.63-1.05; p=0.11) OS analysis adjusted for ISS	
PETHEMA/GEM Rosinol, 2012[7]	***Induction arms:*** BTD n=130	85	60	CR: 35*	79.2	NR	56.2 p=0.01[D]	Estimated at 4-years: 74%	35.2
	TD n=127	62	29	14* BTD vs. TD: p=0.0001	62.2	NR	28.2	65%	
	VBMCP/VBAD/B N=129	75	36	21* BTD vs. VBMCP/VBAD/B: p=0.01	78.3	NR	35.3	70%	
Rosinol 2012[8,16] [abs]	***Maintenance Arms:*** BT maintenance N=89	-	-	-	-	-	Estimated[E]: 44 p=0.00093[F]	NS	34.9[G]
	T maintenance N=87	-	-	-	-	-	40	NS	
	IFN maintenance N=90	-	-	-	-	-	28.5	NS	

Notes: *Results for primary outcome—if not indicated, primary outcome was not reported; "→" = followed by; abs = abstract; ASCT = autologous stem cell transplantation; B = bortezomib; BAD = bortezomib, doxorubicin, dexamethasone; BD = bortezomib, dexamethasone; BT = bortezomib, thalidomide; BTD = bortezomib, thalidomide, dexamethasone; btD = reduced-dose bortezomib and thalidomide, plus dexamethasone; BTDC = bortezomib, thalidomide, dexamethasone, cyclophosphamide; CI = confidence interval; CR = complete response; DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; HR = hazard ratio; Hi-M = high-dose melphalan; IFN = interferon; ISS = International Staging System; mos = months; N = number of patients; N/A = not applicable; nCR = near complete response; NE = not reached, not estimable; NR = not reported; NS = not statistically significant; OR = overall response; OS = overall survival; PFS = progression-free survival; pts=patients; ref = references; T = thalidomide; TD = thalidomide, dexamethasone; VAD = vincristine,

doxorubicin and dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VGPR+ = very good partial response or better.

[A]Patients who received further treatment. Patients who achieved at least partial response post-ASCT were enrolled in a different study where they received 2 months of lenalidomide consolidation followed by randomization to lenalidomide maintenance or placebo. 127 (83.0%) of VAD arm patients and 140 (91.5%) of BD arm patients were enrolled in that trial.

[B]Median OS has not been reached in either group. OS rates were BD: 81.4%; VAD: 81.4%.

[C]The estimated 3 years OS was 86% vs. 84% (p=0.30).

[D]The authors did not report to which arm the BTD arm was significantly different with respect to PFS.

[E]Median PFS was estimated from the Kaplan-Meier survival curve reported in Rosinol et al, 2012.[8]

[F]The authors reported that the PFS in the BT arm was significantly longer compared with T and IFN (p=0.01); however, it was unclear whether the analysis was for the BT-arm compared to the T-arm and IFN-arm combined, or if the analysis compared the BT-arm to the other arms in separate analyses and obtained the same p-value for both comparisons.

[G]Follow-up from initiation of maintenance therapy; data obtained from Rosinol et al, 2012.[8]

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Myeloma Canada, provided input on bortezomib for the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation (ASCT) and their input is summarized below.

Myeloma Canada conducted an anonymous online survey to gather information from patients and caregivers about the impact of myeloma on their lives and the effect of treatments, particularly bortezomib, on their myeloma. The survey link was sent by email to 1810 myeloma patients and caregivers across Canada registered on the Myeloma Canada database. Leaders of local Canadian support groups were encouraged to forward the survey to their members. The survey was available online from Thursday, October 18, 2012 to Sunday, October 28, 2012. Myeloma Canada reports a total of 476 respondents completed the survey; of this total, 322 were individuals living with myeloma, 130 were caregivers and 26 did not specify if they were a patient or a caregiver.

A total of 218 respondents indicated that either they or the person they provide care for, used bortezomib for their myeloma. Respondents were from across Canada with each province represented. There were no respondents from the territories and three (3) respondents were from outside of Canada, one (1) each from the UK, US and Australia. The survey had a combination of multiple choice, rating and open ended questions. A copy of the survey was provided to pCODR. Certain open responses that reflected the sentiment of a majority of the respondents are included verbatim to provide a deeper understanding of the patient and caregiver perspective. Cited responses are not corrected for spelling or grammar.

From a patient perspective, drug therapies for multiple myeloma with less toxic side effect profiles that offer an improvement in efficacy and convenience over currently available therapies are important aspects when consideration is given to treatment. Patients are seeking a therapy that will help to improve their quality of life and enable them to partake in normal daily activities. Patients with multiple myeloma also seek choice and flexibility in selecting therapy to manage their disease.

Please see below for a summary of specific input received from the patient advocacy group

PAG Input

Input on the bortezomib (Velcade) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG noted that some jurisdictions already fund bortezomib as an induction regimen. However, bortezomib as maintenance therapy would be a new treatment regimen for all jurisdictions and may increase chemotherapy clinic time and use of clinic resources. PAG noted that there would be a small patient population receiving maintenance bortezomib and thus would likely have a smaller budgetary impact. PAG noted that the alternative route of administration of bortezomib (subcutaneous) and the availability of the combination drugs as oral doses to increase access of treatment to patients.

Barriers to implementation included the treatment schedule of the CyBorD regimen which may be burdensome to patients and concerns for drug wastage in jurisdictions that do not allow extended drug stability protocols.

Other

Quality of life was the outcome that was considered most important to patients. No high-quality evidence regarding quality of life with the use of bortezomib was identified.

2.2 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada.[10] Myeloma increases in incidence with age, with a median age at presentation of 70 years [11], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1400 deaths from the disease expected in Canada in 2012.[10] The five and ten year survival rates for all patients are approximately 35% and 17%, respectively; for those younger than 60 years of age the ten year survival rate is 30%.[17]

Multiple myeloma is relatively common and autologous stem cell transplant is frequently performed as part of front line myeloma therapy. This treatment is not curative and improving patient survival, remission duration and quality of life are important goals. While improvement in response rate is seen as a positive sign of the activity of a drug, it is not considered as sufficient evidence to adopt a change in practice without evidence of benefit in the other aforementioned domains.

Effectiveness

Two fully published, randomized controlled trials, GIMEMA[5] and HOVON-65/GMMG-HD4[6], have demonstrated a statistically and clinically significant improvement in PFS with the addition of bortezomib, and a third trial, IFM 2005-01[1], has shown a trend towards improved PFS of similar magnitude relative to the other trials. The IFM 2005-01 trial reported by Harousseau et al has

to be interpreted with some caution since most of the patients were enrolled in a subsequent trial of lenalidomide maintenance therapy post transplant, which could have impacted the PFS outcomes, and the primary endpoint was response rate rather than PFS or OS. In the GIMEMA trial reported by Cavo et al, the primary endpoint was also response rate, whereas with Sonneveld et al. the primary endpoint was PFS. In all three trials, the point estimate of the increase in PFS with the addition of bortezomib was clinically meaningful.

The fact that three somewhat different bortezomib-containing regimens were included in the three trials suggests the generalizability of the idea that adding bortezomib to front line therapy improves PFS in transplanted myeloma patients. However, the best bortezomib containing regimen is the subject of ongoing study and will continue to evolve. In addition, none of these three trials were designed in a way that would distinguish the effects of induction bortezomib from additional bortezomib given later in the course of therapy. The existing literature on this topic does not clearly answer the question of the value of additional bortezomib post-transplant as part of front line therapy. As a result, it difficult to determine the optimal timing of bortezomib in front line therapy for transplant-eligible patients.

Prolongation of progression-free survival is a meaningful endpoint in myeloma trials, as patients continually relapse and a substantial PFS improvement should be regarded as the basis for a change in standard of care.[18] It is also increasingly difficult to demonstrate an overall survival advantage in multiple myeloma due in large part to the number of treatment options that can be applied subsequent to the initial therapy. To our knowledge, there is no clear cut overall survival advantage demonstrated to date in any randomized controlled trial associated with the addition of bortezomib therapy to front line treatment in patients receiving high dose chemotherapy and autologous hematopoietic stem cell transplantation.

Safety

While the addition of bortezomib has been associated with increased toxicity, the degree of toxicity appears to be manageable as few patients had to discontinue protocol therapy due to toxicity. Peripheral neuropathy is the most significant and potentially irreversible toxicity of bortezomib and this toxicity is increased in the bortezomib arms of the three trials of interest. There is no quality of life data available from these trials.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to the use of bortezomib as part of front line therapy that includes high dose melphalan and autologous hematopoietic stem cell transplantation for patients with multiple myeloma. This conclusion is based on two high quality randomized controlled trials, GIMEMA (Cavo et al)[5] and HOVON-65/GMMG-HD4 (Sonneveld et al)[6], showing improvement in PFS with treatment regimen that include bortezomib compared to treatment regimen that do not include bortezomib, with increased but manageable toxicity, and a third trial of similar design that showed comparable but not statistically significant trends in PFS.

The Clinical Guidance Panel also considered that from a clinical perspective uncertainty remains regarding the optimal schedule and route of administration of bortezomib, the preferred bortezomib-containing regimen to use, and the incremental value of the addition of bortezomib as consolidation or maintenance post transplant. All three trials included three to four cycles of twice-weekly intravenous bortezomib at 1.3 mg/m^2 on days 1,4,8 and 11 every three to four weeks induction therapy prior to transplant, and the two positive trials provided some post-transplant bortezomib as consolidation or maintenance.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada.[10] Characteristic disease features include the presence of excess, malignant bone marrow plasma cells; bone disease including osteolytic lesions, osteoporosis and pathological fractures; anemia and other cytopenias; and hypercalcemia. The malignant plasma cells usually secrete monoclonal immunoglobulin into the blood and urine that can be used as a measure of disease burden, including detection of disease progression (rising monoclonal protein levels) or response to therapy (falling levels). Monoclonal immunoglobulin light chains can deposit in the kidneys, leading to renal insufficiency.[11]

Myeloma increases in incidence with age, with a median age at presentation of 70 years[11], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1400 deaths from the disease expected in Canada in 2012.[10] The five and ten year survival rates for all patients are approximately 35% and 17%, respectively; for those younger than 60 years of age the ten year survival rate is 30%.[17]

3.2 Accepted Clinical Practice

A subset of patients with multiple myeloma are diagnosed in an asymptomatic phase, with no clinical manifestations of organ damage and no symptoms attributable to the disease. These patients are generally not treated immediately but rather are observed closely for the development of symptoms or signs of disease before embarking on treatment.

Patients with symptomatic myeloma are treated primarily with anti-myeloma drug therapy. For many years the mainstay of myeloma treatment was a combination of oral melphalan (chemotherapy) and prednisone (corticosteroid therapy). Other, older drug combinations did not improve survival in comparison to melphalan and prednisone, and median survival was approximately 2.5 years regardless of the therapy chosen.[12]

High dose intravenous melphalan supported by autologous hematopoietic stem cell transplantation has improved survival for myeloma patients who are eligible for this treatment. Eligibility criteria generally include good performance status and sufficient organ function and is generally reserved for patients aged less than about 70 years but the decision to use this treatment is ultimately left to the discretion of the treating physician, in discussion with the patient. For eligible patients high dose melphalan and autologous stem cell transplant is generally prescribed as part of the initial treatment, rather than deferring this therapy until relapse, in order to maximize the duration of the first remission. Delaying the transplant until relapse can produce similar long term survival rates but has been associated with inferior symptom control. Sufficient stem cells are usually collected in order to allow more than one autologous transplant; this approach can facilitate the administration of two consecutive cycles of high dose melphalan with stem cell transplant support, an approach known as tandem transplantation, or can be used to allow high dose melphalan to be administered again at the time of relapse in patients who benefited from a prior autologous transplant. The advantage of tandem transplantation relative to a single transplant up front is not clearly established.

High dose melphalan is generally preceded by a three to four month course of induction therapy with conventional doses of anti-myeloma drugs. The goals are to improve the

functional status of the patient prior to high dose therapy and to clear sufficient amounts of myeloma cells from the bone marrow to facilitate hematopoietic stem cell collection. Care must be taken to choose induction therapy which will not impair the ability to collect hematopoietic stem cells for autologous transplantation.

Newer anti-myeloma drugs have further improved the survival of myeloma patients, including bortezomib, thalidomide and lenalidomide. These drugs are generally used in combination with corticosteroids and/or chemotherapy agents, and are of proven benefit in both newly diagnosed patients not eligible for transplant and those with relapsed disease.[13]

For patients in whom high dose melphalan and autologous stem cell transplantation is the planned treatment, strategies to further increase therapeutic efficacy have been explored including the incorporation of novel agents into treatment before (induction), during (conditioning), or after (consolidation, maintenance) high dose melphalan therapy. Thalidomide and lenalidomide have been shown to prolong remission when administered as maintenance therapy post transplant, with some studies showing an overall survival advantage with either of these drugs.[19] At present the access to thalidomide and lenalidomide as post-transplant maintenance therapy is limited in Canada. Neither thalidomide nor lenalidomide has been clearly shown to prolong remission when incorporated into induction therapy pre-transplant, although response rates are increased as compared to the use of older induction regimens like VAD (vincristine, adriamycin, dexamethasone). So far, there is no evidence that incorporation of agents other than high dose melphalan into the conditioning regimen improves outcome, although this subject continues to be investigated.

The use of bortezomib as part of intial therapy for myeloma patients undergoing high dose melphalan and autologous stem cell transplantation is the subject of this review and will be discussed in depth later.

Allogeneic stem cell transplantation is used infrequently to treat myeloma because of high treatment related morbidity and mortality, but can achieve long term disease control in some patients.[20]

When patients relapse following initial treatment, therapy is generally given again incorporating either previously effective agents and/or those that have not yet been administered. Novel agents are expanding the therapeutic armamentarium. Multiple myeloma eventually relapses repeatedly following courses of effective therapy, and eventually patients succumb to progressive disease and its complications. Resistance to treatment and the cumulative adverse effects of both disease and treatment have adverse effects on patient quality of life. Important supportive measures can have a positive impact on both quality of life and survival, including medical pain management, the use of palliative radiotherapy for symptomatic bone lesions, prevention and treatment of infections and venous thrombosis, hematopoietic support with blood products and growth factors, bisphosphonates for hypercalcemia and bone disease, and dialysis for renal failure.[11]

3.3 Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with newly diagnosed, symptomatic multiple myeloma who are candidates for high dose chemotherapy and autologous hematopoietic stem cell transplantation, which is estimated to be less than half of all newly diagnosed myeloma patients.

3.4 Other Patient Populations in Whom the Drug May Be Used

Bortezomib is already widely available in Canada as part of initial therapy for multiple myeloma patients who are ineligible for high dose chemotherapy and stem cell transplant, and is also widely available for patients with relapsed myeloma.

The use of bortezomib as part of initial therapy could potentially be considered in induction, conditioning, or as post transplant consolidation or maintenance for myeloma patients undergoing high dose chemotherapy and autologous stem cell transplantation. The drug could reasonably also be used in this same fashion for those few patients who are selected for allogeneic transplantation.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada, provided input on bortezomib for the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation (ASCT) and their input is summarized below.

Myeloma Canada conducted an anonymous online survey to gather information from patients and caregivers about the impact of myeloma on their lives and the effect of treatments, particularly bortezomib, on their myeloma. The survey link was sent by email to 1810 myeloma patients and caregivers across Canada registered on the Myeloma Canada database. Leaders of local Canadian support groups were encouraged to forward the survey to their members. The survey was available online from Thursday, October 18, 2012 to Sunday, October 28, 2012. Myeloma Canada reports a total of 476 respondents completed the survey; of this total, 322 were individuals living with myeloma, 130 were caregivers and 26 did not specify if they were a patient or a caregiver.

A total of 218 respondents indicated that either they or the person they provide care for, used bortezomib for their myeloma. Respondents were from across Canada with each province represented. There were no respondents from the territories and three (3) respondents were from outside of Canada, one (1) each from the UK, US and Australia. The survey had a combination of multiple choice, rating and open ended questions. A copy of the survey was provided to pCODR. Certain open responses that reflected the sentiment of a majority of the respondents are included verbatim to provide a deeper understanding of the patient and caregiver perspective. Cited responses are not corrected for spelling or grammar.

From a patient perspective, drug therapies for multiple myeloma with less toxic side effect profiles that offer an improvement in efficacy and convenience over currently available therapies are important aspects when consideration is given to treatment. Patients are seeking a therapy that will help to improve their quality of life and enable them to partake in normal daily activities. Patients with multiple myeloma also seek choice and flexibility in selecting therapy to manage their disease.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Multiple Myeloma

Multiple myeloma is a cancer of the plasma cells (white blood cells that reside in the bone marrow) and can lead to anemia, infections, bone lesions, vertebral compressions, osteoporosis, severe pain and renal dysfunction. Patients with multiple myeloma can experience many symptoms early in the disease, including fatigue, recurrent infections (such as cold sores) and bone pain.

From a patient perspective, quality of life while living with multiple myeloma is an important consideration. In the Myeloma Canada survey, 370 respondents of the total 476 patients and caregivers provided an answer to the question *which aspects of myeloma are more important to control than others? Please describe.* Pain (61%) and fatigue (56%)are the top two aspects of myeloma that were considered important to control by the majority of the respondents to this question, followed by infections (38%), kidney problems (30%) and mobility (30%), all of which affect a patient's quality of life.

"Fatigue, Pain, Reduced Mobility, Shortness of Breath are the things that bother me the most. Reduced activity levels (I spent the first two years confined to bed due to a Pinched Sciatic Nerve before the disease was diagnosed and addressed. I was pretty much wheelchair – bound from December of 2007. The disease was diagnosed in March, 2009. I began receiving treatment immediately and progress has been positive but slow. I have what I describe as "short vertical time" in that I can be active for short periods, but excruciating lower back pain manifests very quickly and I have to find a place to sit immediately. I attribute at least some of my weight gain to this reduced / limited activity level and the extra weight contributes to the problem(s)."

One of the questions on the survey asked respondents *how do symptoms and problems associated with myeloma impact or limit your day-to-day life and quality of life? Please describe.* Of those who answered this question, 92% of patients and caregivers are negatively impacted by their myeloma in their day-to-day life and quality of life, and only 8% reported no major change. The respondents indicated that the biggest impact has been on their ability to work or volunteer (30%). In many cases, individuals retired early or went on extended leave due to the increased fatigue and pain of living with the disease. Limited ability to participate in day-to-day activities, social activities and to exercise led to challenges, such as depression and weakened muscles were expressed by many respondents.

"Symptoms and problems at this time impact my day-to-day life and quality of life to a great extent. In the past 10 months I have gone from not walking to now being able to walk without assistance. Participating in outside the house activities is limited. I have limited energy – do not yet drive, walk the dog or play golf (previous to onset played 2-3 times a week). I have also found that I needed to build up stamina to cook and many times I over exert myself with any day to day housekeeping activities. I still need to rest for a minimum of 1-2 hours each afternoon and go to bed between 8-9 each evening. The limitations of this disease are frustrating and can bring about fits of depression at not being able to."

4.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

In patients who are eligible for stem cell transplant, standard induction protocols often require surgery to insert catheters to allow for drug administration. This surgery increases the risk of infection. Given that myeloma is essentially a cancer of the immune system, any increased risk of infection, especially one acquired in a hospital setting, coupled with the administration of immunosuppressive chemotherapy can increase the likelihood of serious adverse events. Patients seek the availability of less toxic, more targeted bortezomib-based induction protocols.

"My personal experience provides a real-life case study of the serious iatrogenic, potentially life-threatening outcomes of this now outdated protocol. At the completion of my first VAD cycle, I returned to the hospital to have the pump removed until the next round of chemotherapy. I was experiencing malaise and nausea, which I attributed to the chemotherapy. The nurse remarked that this was unusual and immediately removed the bandages over the catheter (which has been inserted in the upper right shoulder area) to reveal a festering infection. The surgeon was summoned to the nursing station and the catheter was immediately removed. Vancomycin (a potent antibiotic) was administered and I was sent home. The following morning, the severe pain in my right shoulder rendered me immobile and an ambulance was called to bring me to the hospital. Thus began a month-long treatment using an intravenous antibiotic to clear the infection.

Moreover, given that my catheter had been removed, I was no longer able to continue the VAD treatment and continued my induction with high-dose dexamethasone monotherapy, which in my case resulted in a less-than-optimal outcome post-ASCT."

The survey asked respondents *have you or your doctor experienced any hardships in accessing treatment for your myeloma? Please describe.* Twenty-three percent (63 respondents) of individuals living with myeloma and their caregivers indicated that they did experience some hardship in accessing treatment for their myeloma. The hardships included:

- the need to pay out-of-pocket for treatments
- the need to travel great distances to receive treatment
- the need to meet significant criteria to qualify for treatment, including extra trips to the hospital
- discontinuance of the treatment when the funding ran out
- lack of access by the hospital or drug plan to necessary treatment.

"I would of had a hard ship if I was not able to access through the clinical trial Velcade, I have watched my girls grow up and I was able to live, and remain in remission after 6 years with advanced MM with bone leisons plus plus. If I need treatment I would need it sooner than later, to avoid, hospitalizations and advancing disease leading to death. Choice and different treatments need to be available in timely fashion, sick people should not need to fight for medication and therefore adding to their stress both mentally and physically All provinces should have equal access to Cancer Multiple Myeloma Drugs When you have a drug in your province not available, it takes up too much energy to lobby for this drug."

4.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of multiple myeloma on caregivers and families is significant. Caregivers of multiple myeloma patients were asked *how do treatments impact your caregiver's daily routine or lifestyle?* Eighty (80) caregivers answered this question, the biggest impact expressed by caregivers on their daily routine or lifestyle was the limitation to their daily and social activities (54%). Many caregivers expressed the need to put their life on hold in order to provide care for their loved one, such as managing his or her appointments, treatments, meals and other personal care matters. As a result, caregivers are often limited in the amount of time they can spend with their children, other family members and friends.

The second largest impact expressed by caregivers (35%) was the emotional toll of caring for someone with multiple myeloma. This included depression, frustration, worry, anxiety and compassion for the patient. Another significant impact (26%) was a change in lifestyle, which usually involved a reduction or inability of the caregiver to work, volunteer, attend school, while he or she attended appointments and took care of their loved one's day-to-day needs. In some cases, the inability of the caregiver and patient to work led to financial hardship for the family.

"As a caregiver, I am unable to work as I have to tend to the needs of the patient. Since the patient is susceptible to infections which could be a set back, the caregiver needs to tend to the patient 24/7. Proper nourishment is also crucial to help build up the patient's weight. Treatments are given every week and this renders the patient down for a good 3 days after each treatment. Side effects like vomiting/diarrhea/acidity restricts the patient's overall health. By the time the patient gets back to feeling a wee bit better the next treatment is

due – so it is tending for the patient constantly. Tending to the patient's needs gives me very little time to prepare wholesome meals. Family steps in here with providing meals for us. Basically my life grinds to a halt too but it is fulfilling to see the patient's progress with the treatments."

Patients (242) reported that their disease adds more responsibility on the caregiver in terms of household chores, family responsibilities. It also meant more time at doctors' appointments and hospitals. In some cases patients reported that they had to make major changes to lifestyle that included relocating closer to a hospital, putting plans on hold, such as a job or school, moving closer to the family member or a loved one to be able to provide care.

Eighty-eight percent of caregivers (88% of 78) indicated there are challenges in dealing with the side effects of treatment for their loved one. A large proportion reported that emotional strength is required to deal with mood swings, erratic behaviour following certain treatments at a time when the caregiver feels weak, and physically and emotionally tired. Sixty-three percent of the individuals living with myeloma (228) responded that there are challenges for the caregiver as a result of the side effects related to treatment. The two most reported challenges are the irritability of the patient caused by some of the treatments (16%), and the additional personal care required (16%), often including personal hygiene.

The side effects lead to extra stress for the caregiver (14% of 228) usually in the form of extra work, driving to appointments, more chores around the home, taking over sole family responsibility. Additional stress also included financial stress to pay for medical treatments as well as the fear and constant worry of not knowing what to do if something goes wrong. It also related to loss of sleep by the caregiver due to nausea and pain felt throughout the night by the patient.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Bortezomib

Survey respondents were asked *if* [they would] *consider taking a treatment proven to be effective for* [their] *myeloma, what severity of side effects are you willing to tolerate*? (*For example: nausea, fatigue, vomiting, diarrhea, constipation, neuropathy). Rate on a scale of 1-10, 1 being "no side effects", and 10 being "significant side effects'."* A total of 329 respondents answered this question. The majority of respondents expressed that they would be willing to tolerate some level of side effects if the treatment was proven to be effective. The average rating was 6, which means that more respondents are willing to tolerate side effects than those who would not tolerate any side effects. As many as 89 (27%), of the respondents gave a rating of 8 or higher and 64 (19%) gave this a rating of 3 or lower.

Another survey question asked respondents *if [they] were to consider taking a new treatment for [their] myeloma, how important is it for you and your physician to have choice in deciding which drug to take*? *Rate on a scale of 1-10, 1 being "not important as long as there is a drug", and 10 being "very important to choose which drug would be better suited for me".* The large majority of respondents (78% of 333) indicated that if they were to consider taking a new treatment for their myeloma, it would be "very important to choose which drug would be better suited for me". Ninety-one percent (91%) rated this 8 or higher and 8 (2.4%) respondents rated this as 1.

Respondents were also asked *have you, or the person you provide care for, used bortezomib for your myeloma?* A total of 218 (46%) respondents, both patients and caregivers, have experience with bortezomib.

Those who took bortezomib were asked *how does bortezomib compare in terms of side effects to each of the other treatments you have taken?* Thirty percent (30%) of the respondents could not compare the side effects of bortezomib to other treatments because they either did not experience other treatments, were taking bortezomib in combination with other treatments, or they did not know. More respondents found that bortezomib had fewer side effects (24%) than those who said it had the same level of side effects (9%) or had more side effects (7%).

"The valcade [sic] and dex treatment really kncked the crap out of the myeloma. It reduced it to almost zero before the stem cell transplant. The bortezomib was tollerated very well but the high dose dex had the expexted [sic]side effects. (irratiblity and road rage etc)."

Those who had personal experience with bortezomib were asked to provide comments on the positive and negative effects of bortezomib. The majority of respondents (61%) expressed that bortezomib had a positive effect on their myeloma. Positive effects included: lowered protein levels to proceed to stem cell transplantation, improved kidney function, return to normal function, (appetite, energy level), and improved quality of life. As many as 10% of respondents indicated that they had achieved a partial or complete remission with the help of bortezomib combined with other treatments.

Conversely, 8% of respondents indicated that the treatment was not effective and 4% stopped the treatment because it was either ineffective or the side effects were intolerable. Side effects such as neuropathy, shingles, nerve damage, constipation, rash, infections, insomnia and fatigue were mentioned by 16% of respondents and the inconvenience, as a result of travel to a hospital to receive treatment, was mentioned by 2% of the respondents.

"My myeloma was affected in a positive way during my velcade treatments. It improved my position so I was able to have an Autologous Stem Cell Transplant. Since my transplant, my results show a near complete remission."

"It was very positive, I am alive and in remission and currently not on any medication for 6 years quality of life is great, I work, play and I enjoy every day with my family and friends. I was very lucky to have so many years ago access to this drug or possibly I would be dead like many of my MM friends who did not have Velcade."

"I(t) worked great on the disease but gave me some nausea and mostly neuopathy in my feet."

Survey participants were also asked *about [their] personal experience with bortezomib: On a scale of 1 – 10, with 1 being "not effective" and 10 being "extremely effective",* please rate how effective bortezomib is in controlling your myeloma. Forty-three percent (43% of 182) of the respondents found bortezomib to be "extremely effective" in controlling their myeloma, while 4% found that it was not effective. As many as 37 (75%) respondents gave a rating of 8 or higher, with 10 being "extremely effective". A total of 13 (7%) respondents gave a rating of 3 or lower with 1 being "not effective" and 4% gave a rating of 1.

A large number of respondents (35%, 63 of 182 respondents) experienced fatigue and neuropathy (23%) with the use of bortezomib. Twenty respondents indicated that

neuropathy is not an acceptable side effect. As many as 14% of respondents, indicated that they did not experience side effects with bortezomib.

In an open-ended question, 16 respondents indicated that bortezomib was positive for them. Positive comments referred to the effectiveness of the treatment and that it slowed down progression, controlled the cancer, attributed to remission and provided tolerable side effects.

"I love the fact that you don't lose your hair!"

"I am convinced the velcade saved my husband's life. He was stabilizing on the thalidomide and dexasone, but there was no improvement and no long term prospect of any quality of life."

"I feel it contributed to my remission."

"I would not be filing this survey out today if it had not been for Velcade. At the time of diagnose the doctors were not sure that I would survive."

In this open-ended question, 2 respondents provided a negative comment.

"This is dangerous stuff."

"My experience with bortezomib was not pleasant. I would not wish to repeat this, provided there is an acceptable alternative."

In an open-ended question, 2 respondents indicated that the drug didn't work for them and 1 respondent indicated that the treatment was effective but that it had a serious side effect.

"Although velcade might be an effective treatment for Multiple Myeloma, attention needs to be paid to the serious side effect of peripheral neuropathy."

4.3 Additional Information

No information was provided in this section by Myeloma Canada.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for bortezomib (Velcade) for multiple myeloma pre and post ASCT. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the bortezomib (Velcade) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG noted that some jurisdictions already fund bortezomib as an induction regimen. However, bortezomib as maintenance therapy would be a new treatment regimen for all jurisdictions and may increase chemotherapy clinic time and use of clinic resources. PAG noted that there would be a small patient population receiving maintenance bortezomib and thus would likely have a smaller budgetary impact. PAG noted that the alternative route of administration of bortezomib (subcutaneous) and the availability of the combination drugs as oral doses to increase access of treatment to patients.

Barriers to implementation included the treatment schedule of the CyBorD regimen which may be burdensome to patients and concerns for drug wastage in jurisdictions that do not allow extended drug stability protocols.

5.1 Factors Related to Comparators

PAG noted that some jurisdictions have been funding bortezomib as a single agent or in combination with dexamethasone +/- cyclophosphamide (CyBorD) as an induction regimen prior to autologous stem cell transplantation (ASCT). Funding for induction use of bortezomib has been in place for several years in some jurisdictions and within the context of their transplant program. PAG noted that bortezomib as a maintenance therapy post-ASCT would be a new treatment program requiring additional chemotherapy clinic and chair time.

5.2 Factors Related to Patient Population

PAG noted that in those jurisdictions treated with CyBorD prior to ASCT as an induction regimen; it has been their experience that patients respond more positively and quickly to ASCT, which not only benefits patients but allows for reduced use of health services. PAG noted this to be an enabler to funding as it facilitates efficiencies in the treatment regimen.

As an additional enabler to implementation, PAG noted that bortezomib maintenance therapy would be used in a small patient population as the number of patients eligible for undergoing ASCT is small.

5.3 Factors Related to Accessibility

Bortezomib as part of the CyBorD regimen is available as an iv or subcutaneous treatment which allow for improved accessibility. The drugs used in combination with bortezomib, dexamethasone or cyclophosphamide + dexamethasone, are orally administered, also making accessibility to treatment easier for patients. PAG did note that bortezomib

administration may require patients to visit chemotherapy clinics once or twice a week as maintenance therapy is normally scheduled biweekly for two years, a treatment schedule that may be burdensome for patients.

5.4 Factors Related to Dosing

None

5.5 Factors Related to Implementation Costs

PAG clarified that in some jurisdictions bortezomib has been included into the standard of care (CyBorD) for induction therapy as a significant number of patients were not achieving adequate response with the previous treatment containing high dose dexamethasone. This was done despite the increase in chemotherapy clinic time that would be required with bortezomib treatment compared to oral administration of dexamethasone. As such, PAG noted that funding implementation of bortezomib maintenance therapy post-ASCT would further increase the chemotherapy clinic time required to provide this treatment.

PAG noted that in jurisdictions where extended stability of bortezomib is not permitted, drug wastage may become an issue and present as a barrier to implementation. Extended stability protocols allow for sharing of vials between patients to help maximize the number of doses that can be obtained from each vial. PAG identified that as bortezomib is widely used, the addition of a new indication that has a low frequency of use will result in little incremental wastage of the drug.

5.6 Other Factors

None

6 SYSTEMATIC REVIEW

6.1 Objectives

1. To evaluate the effect of bortezomib, as monotherapy or combination therapy prior to autologous stem cell transplantation (ASCT) (i.e., induction), compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.
2. To evaluate the effect of bortezomib, as monotherapy or combination therapy, immediately post-ASCT (i.e., consolidation or maintenance) compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.
3. To evaluate the effect of bortezomib, as monotherapy or combination therapy both pre-ASCT (induction) and post-ASCT (consolidation or maintenance), compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.

See Table 1 in Section 6.2.1 for outcomes of interest and appropriate comparators.

Candidates for ASCT include patients whom the treating clinician (e.g., oncologist, haematologist) deems fit for ASCT based upon factors including, but not limited to, age, performance status, and co-morbidities.

Post-ASCT treatment is generally started within 3-6 months of ASCT.

Note: No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Bortezomib pre-ASCT (induction)				
Published or unpublished RCT	Newly diagnosed MM who are candidates for ASCT	Induction with bortezomib, (monotherapy or in combination) any dose or schedule, followed by ASCT	Induction with: • Dex-alone; • VAD; • Thal/dex; • Len/dex; or, • Other combinations including Dex, Thal, or Len All of the above are to be followed by ASCT	OS PFS Response to induction Proportion of patients who receive ASCT **QOL** Adverse events Second malignancy†
Bortezomib post-ASCT (consolidation or maintenance)				
Published or unpublished RCT	Newly diagnosed MM, who have received induction followed by ASCT	Bortezomib (monotherapy or in combination) any dose or schedule, immediately following ASCT	Any agent or combination, placebo, or no therapy; immediately following ASCT	OS PFS **QOL** Adverse events Second malignancy†

ASCT=autologous stem cell transplantation; Dex=dexamethasone; Len=lenalidomide; MM=multiple myeloma; OS=overall survival; PFS=progression-free survival; QOL=quality of life; Thal=thalidomide; VAD=vincristine, doxorubicin, dexamethasone.

* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).*
† *Second malignancy was identified as a harm outcome that was of particular interest.*

6.2.2 Literature Search Methods

The submission for bortezomib in newly diagnosed MM[21] from the CCO PEBC Hematology Disease Site Group included an evidence-based series consisting of a clinical practice guideline with a systematic review of bortezomib in MM[14]. The pCODR Methods Team applied the "Checklist for Including a Guideline in a pCODR Clinical Guidance Report." All of the items were checked 'yes' for the PEBC guideline; therefore, the evidence-based series' systematic review component was used by the pCODR Methods Team to answer the questions of this CGR.

In addition to searches of MEDLINE, EMBASE, and the Cochrane Library databases, the PEBC systematic review also included searches of the conference proceedings for the American Society of Clinical Oncology (ASCO) for 2005-2012 and for the American Society of Hematology (ASH) for 2005-2011. The literature search of the PEBC systematic review was complete to August 2012. The eligibility criteria of the PEBC systematic review were broader than that of the pCODR CGR. Using the results of the

PEBC literature search as a starting point, the pCODR Methods Team applied the selection criteria in Table 1 to the studies identified in the PEBC systematic review.

A literature search was performed by the pCODR Methods Team to update the PEBC search, using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (August 2012-) with in-process records & daily updates via Ovid; EMBASE (August 2012-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 1) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were bortezomib (Velcade) and multiple myeloma.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of February 6, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were conducted only conference years held after the last year that was searched in the PEBC systematic review. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

The PEBC systematic review[14] included a total of 13 RCTs of patients with newly diagnosed MM. Of those 13 RCTs, seven RCTs investigated the use of bortezomib either in induction or in post-ASCT therapy in patients with newly diagnosed MM who were candidates for ASCT. A total of 21 publications were included in the systematic review that described those seven RCTs. All seven of the RCTs and the associated 21 publications met the eligibility criteria for and were included in this pCODR CGR.[1,3-6,9,15,16,22-34]

The pCODR update search identified six potentially relevant reports, of which, four studies met the eligibility criteria and were included in the pCODR systematic review[2,7,8,35] and two studies were excluded (Figure 1). Studies were excluded because they were a case report[36] or the trial did not include the population of interest[37]. Two of the identified studies were full publications of studies previously identified in the PEBC systematic review. Table 4 lists the seven identified studies, the primary publications, and additional publications. One US FDA review was identified that reviewed the use of bortezomib.[38] No additional data were available in that review regarding the trials included in this pCODR CGR; therefore it is not discussed further.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies

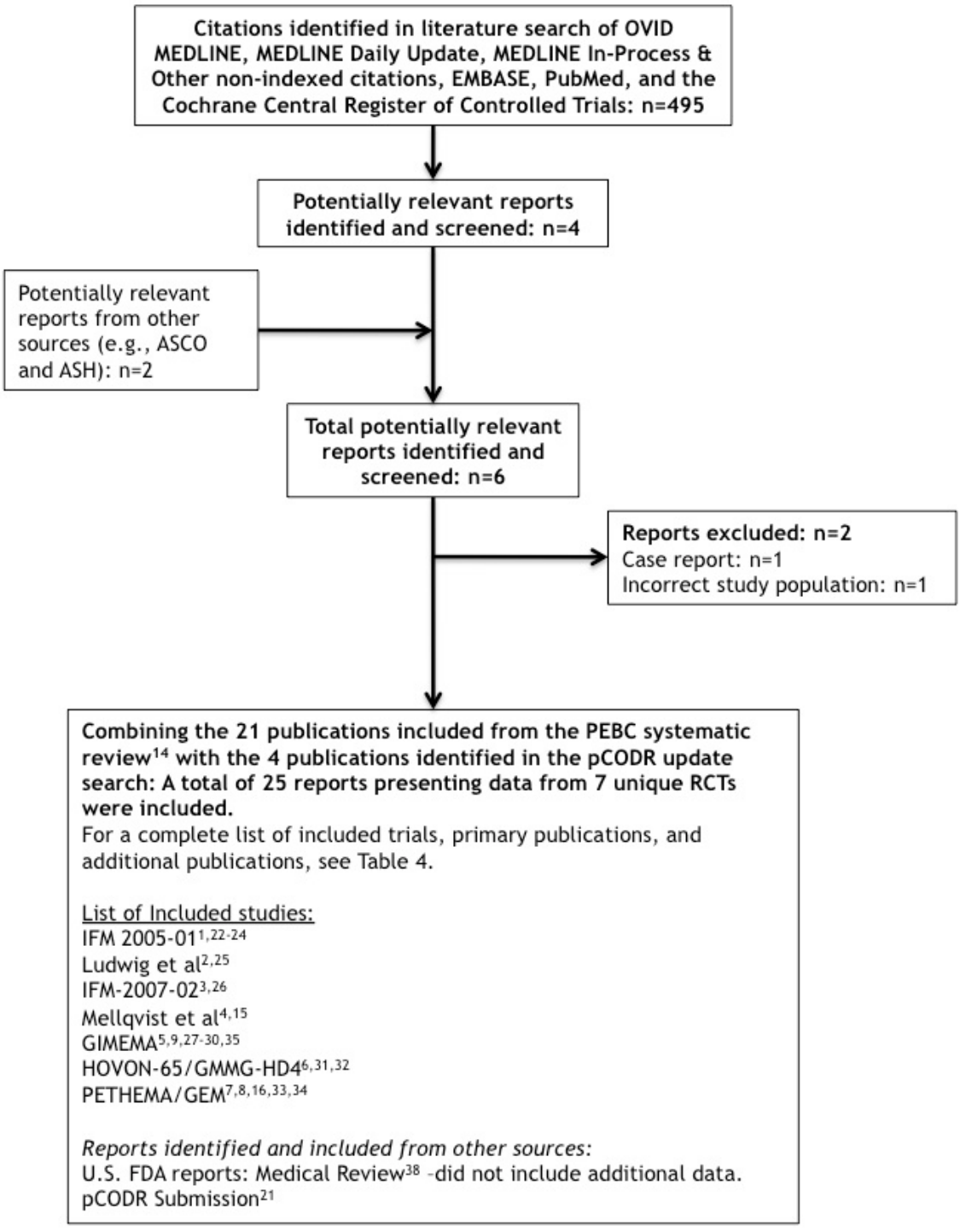

Table 4. Primary and additional publications of identified randomized trials of bortezomib in multiple myeloma and their objectives.

Study	Primary publication	Additional publications
Trials Investigating Only Induction with Bortezomib		
IFM 2005/01	Harousseau, 2010[1]: Compare BD vs. VAD as induction before ASCT.	Avet-l'Oiseau, 2010[22] [abs]: effectiveness in overcoming the poor prognosis linked to translocation t(4;14) (p16;q32) in elderly pts. Moreau, 2010[23]: evaluate stem cell collection in the dexamethasone arm. Moreau, 2011[24]: Achievent of VGPR at induction as a prognostic factor for longer PFS.
Ludwig	Ludwig, 2013[2]: Evaluate efficacy and toxicity of BTD and BTD + C in previously untreated pts.	Ludwig, 2009[25] [abs]: abstract publication of study results
IFM-2007-02	Moreau, 2011[3] Compare B+D vs. reduced-dose B+T+D before ASCT in newly diagnosed MM pts.	Moreau, 2010[26] [abs]: prior abs publication of main study
Trials Investigating Only Post-transplant Treatment with Bortezomib (Consolidation or Maintenance)		
Mellqvist (abstract only)	Mellqvist, 2009[4] [abs] Explore the effect of a 21-week consolidation period of single agent B given during months 3-8 after ASCT.	Mellqvist, 2011[15] [abs]: Updated results. ClinicalTrials.gov record[39]
Trials Investigating Both Induction and Post-Transplant Therapy with Bortezomib		
GIMEMA	Cavo, 2010[5]: Evaluate the effectiveness of BTD→double ASCT→BD vs. TD→double ASCT→TD in newly diagnosed MM.	Cavo, 2009[27] [abs]. Preliminary publication Brioli, 2011[28] [abs]: Impact of novel agents on peripheral stem cell collection. Cavo 2011[29] [abs]: Per protocol analysis of 321 pts who received the entire treatment program. Cavo, 2012[9] Compare efficacy and safety of BTD vs. TD as consolidation therapy after ASCT in newly diagnosed MM pts. Tacchetti, 2011[30] [abs]. Analysis of B- and T-induced peripheral neuropathy in pts with MM. Cavo, 2012[35] [abs]. Longer follow-up of GIMEMA study.
HOVON-65/GMMG-HD4	Sonneveld, 2012[6] Compare VAD→high dose M+ASCT→T maintenance vs. B+A+D + high dose M+ASCT→B maintenance in newly diagnosed MM.	Sonneveld, 2008[31] [abs]: Abstract of interim analysis. Neben 2012[32]: Prognostic value of 12 chromosomal abnormalities
PETHEMA/GEM	Induction: Rosinol 2012[7] Maintenance: Rosinol, 2012[8] [abs].	Rosinol, 2009[33] [abs]: interim analysis (induction) Rosinol, 2011[34] [abs] – Preliminary abstract (induction) Rosinol 2012[16] [abs]- Preliminary abstract (maintenance) ClinicalTrials.gov record[40]

Study	Primary publication	Additional publications
	Induction→ASCT→maintenance in newly diagnosed MM: Induction: Randomization to TD vs. BTD vs. VBMCP/VBAD/B. All patients received high-dose M + ASCT. Maintenance: 3 months post-transplant, patients were randomized to receive TB, T, or interferon.	

Notes: A=doxorubicine; abs=abstract; ASCT = autologous stem cell transplant; B = bortezomib; C = cyclophosphamide; D = dexamethasone; M = melphalan; MM = multiple myeloma; P = prednisone; PFS = Progression free survival; pts=patients; T = thalidomide; VAD = vincristine + doxorubicin + dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VGPR= very good partial response; yrs = years.

6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

For a detailed description of the objectives, design, population, intervention, control, and outcome for each included study, please see Table 5. For details regarding select quality characteristics for each study, please see Table 1.

Table 5. Bortezomib in newly diagnosed multiple myeloma: characteristics of included studies (from PEBC Evidence-based Series).

Study primary publication, Study name, Funding source	Study Objective, Design, Follow-up	Population	Intervention	Control	Outcomes
Harousseau, 2010[1] IFM2005-01 Start Date: August 9, 2005 End Date: January 18, 2008 Data cut-off: June 5, 2009 Sites: 89 in France, Belgium, Switzerland. **Funding:** Millennium Pharmaceuticals, Celgene, Janssen-Cilag, Proteolix, Genzyme, Amgen, Novartis.	Objectives: To compare the efficacy and safety of BD and VAD as induction before ASCT in previously untreated pts. **Design:** Open label Phase III RCT. **Follow-up:** mdn 31.2 months	Newly diagnosed MM pts ≤ 65 years old. **Study Arms:** A1: VAD; n=121 A2: VAD + D, cyclophosphamide, etoposide and cisplatin (DCEP); n=121 B1: BD; n=121 B2: BD + DCEP; n=119. All arms were followed by ASCT. **Age:** VAD (A1+A2): mdn 57.1 years BD (B1+B2): mdn 57.2 years	BD: 4 3-wk cycles of B 1.3 mg/m^2 iv d1, 4, 8, and 11 + D 40 mg/d (d1-4, all cycles, and d9-12, cycles 1 and 2). DCEP: 2 4-wk cycles of D 40 mg/d (ds 1-4) + cyclophosphamide 400 mg/m^2, etoposide 40 mg/m^2, and cisplatin 15 mg/m^2 ds 1-4.	VAD: 4-wk cycles of vincristine 0.4 mg/d and doxorubicin 9 mg/m^2/d on ds 1-4, + D 40 mg on ds 1-4 (all cycles) and ds 9-12 and ds 17-20 (cycles 1 and 2).	Primary: Post-induction CR/nCR rate Secondary: Postinduction overall response rate; CR rate with and without DCEP; CR and at least VGPR rates post first transplantation; Proportion of pts requiring a second transplant; Safety and toxicity of induction.
Ludwig, 2013[2] Start Date: October 2007 End Date: September 2008 Data cut-off: January 31, 2011 Sites: 22 in 8 countries (Europe) **Funding**: Jansen Research & Development, Millennium Pharmaceuticals.	**Objective**: Evaluate efficacy and toxicity of BTD and BTDC. **Design**: Randomized phase II trial, non comparative **Follow-up**: mdn 33.3 months	Pts with MM of 18-70 years of age. **Study Arms:** CG: BTD n = 49 IG: BTDC n = 48 Both arms followed by ASCT **Age:** CG: mdn 57 years IG: mdn 58 years	**Dose and Schedule:** BTDC: same as BTD + C 400 mg/m^2 on ds 1 and 8 as induction before ASCT.	**Dose and Schedule:** BTD: Four 21-d cycles of B 1.3 mg/m^2 on ds 1, 4, 8 and 11, T100 mg/d, D 40 mg/d on ds 1-4 and ds 9-12; as induction before ASCT.	Primary: Post-induction CR/nCR rate Secondary: Post-ASCT CR/nCR Pre- & Post-ASCT OR rate TTP PFS OS HRQOL Safety

Study primary publication, Study name, Funding source	Study Objective, Design, Follow-up	Population	Intervention	Control	Outcomes
Moreau, 2011[3] **IFM 2007-02** Start Date: March 2008 End Date: January 2009 Data cut-off: December 31, 2010 Sites: 50 in France **Funding:** Millennium pharmaceuticals.	**Objective**: to compare reduced-dose btD to BD as induction treatment prior to ASCT **Design**: Open-label phase 3 RCT **Follow-up**: mdn 32 months	Pts newly diagnosed with MM <66 years old. **Study Arms:** BD; n=99 btD; n=100 Both arms followed by ASCT **Age:** BD: mdn 57 years btD: mdn 58 years	**Dose and schedule:** Four 21-d cycles of induction including: btD: (B 1 mg/m^2 on ds 1,4,8, 11 and T 100 mg/d on ds 1-21) plus D same dose as BD.	**Dose and schedule:** Four 21-d cycles of induction including: BD: (B 1.3 mg/m^2/d on ds 1,4,8,11; D 40 mg/d on ds 1-4 and ds 9-12 for the first 2 cycles, and on ds 1-4 for the last 2 cycles)	Primary: Post-induction CR rate. Secondary: CR + VGPR rate OR rate Safety and toxicity of induction
Mellqvist, 2009[4] [abs] Mellqvist, 2011[15] [abs] Start Date: November 2005 End Date: April 2009 Data cut-off: ongoing study Sites: number NR (multicenter) in Sweden, Norway, Iceland, Finland, Denmark **Funding**: Janssen Cilag, Johnson & Johnson GenMab, Schering Plough, Bristol Myers Squibb, Celgene,	**Objective**: Explore the effect of a 21-week consolidation period of single agent B given during months 3-8 after ASCT. **Design**: Open-label phase III RCT Unknown if abstract is for final analysis. **Follow-up**: NR	Patients with symptomatic MM that have received ASCT in last five weeks. No prior exposure to B. **Study Arms:** IG: consolidation with B; n=149 CG: no drug; n=150 Total of 372 pts. Preliminary data on 299 pts in 2009 abstract. 2011 abstract does not report whether analysis was final or interim.	**Dose and Schedule:** Consolidation with B 1.3 mg/m^2 twice weekly (ds 1,4,8 and 11) in a 3-wk schedule for the first 2 cycles. In the following 4 cycles, B was given once weekly (ds 1, 8, 15) in a 4-wk schedule	No consolidation therapy.	Primary: Event-free survival; Secondary: OS from ASCT OS from start of Response rate, toxicity, OS, QOL and cost utility.
Cavo, 2010[5]	**Objective**: to evaluate the effectiveness of BTD induction and consolidation as compared with TD induction and	Young, newly diagnosed pts with MM undergoing double ASCT.	**BTD:** Induction: B 1.3 mg/m^2 on ds	**TD:** Induction: T 100 mg/d for the first	Primary: CR/nCR post-induction Secondary:

Study primary publication, Study name, Funding source	Study Objective, Design, Follow-up	Population	Intervention	Control	Outcomes
GIMEMA Start Date: May 2006 End Date: April 2008 Data cut-off: June 30, 2010 Sites: 73 in Italy **Funding:** Seragnoli institute of Hematology, University of Bologna, Italy, Janssen-Cilag (provided the drug), University of Bologna.	consolidation as front line therapy for MM. **Design**: Open-label phase III RCT. **Follow-up**: mdn 36 months.	**Study Arms:** CG: TD→double ASCT with TD→TD; n = 238 IG: BTD→double ASCT with TD→BTD; n = 236 **Age:** 18-65 years; IG: mdn 58 yrs. CG: mdn 57 yrs **Gender:** IG: 58% male CG: 57% male	1,4,8,11; T 100 mg/d for the first 14 ds and 200 mg/d thereafter; D:40 mg on ds 1,2,4,5,8,9,11,12. Three 21 d cycles. <u>ASCT with TD :</u> ASCT→T 100 mg/d + D 40 mg/d d1-4 every 28 ds→ASCT <u>Consolidation</u>: B: 1.3 mg/m^2 on ds 1,8,15 and 22 T 100 mg/d D: 40 mg on ds 1,2, 8, 9,15,16, 22, 23. Two 35 d cycles <u>Maintenance :</u> D 40 mg d1-4, every 28 ds.	14 ds and 200 mg/d thereafter; D D: 40 mg on ds 1-4 and 9-12. Three 21 d cycles. <u>ASCT with TD :</u> ASCT→T 100 mg/d + D 40 mg/d d1-4 every 28 ds→ASCT <u>Consolidation</u>: T 100 mg/d D:40 mg on ds 1-4 and ds 20-23. Two 35 d cycles. <u>Maintenance :</u> D 40 mg d1-4, every 28 ds.	CR/nCR post-double ASCT and consolidation PFS OS Safety
Sonneveld, 2012[6] **HOVON-65/GMMG-HD4** Start Date: May 2005 End Date: May 2008 Data cut-off: April 21, 2011 Sites: number NR. Multicenter study conducted by the Dutch-Belgian Hemato-Oncology	**Objective:** To evaluate B treatment effectiveness during induction and maintenance. **Design:** Open-label phase III	Newly diagnosed patients with Durie-Salmon Stage II to III MM. Age 18-65 years. **Study Arms:** IG: BAD→ASCT→maintenance B; n=414 CG: VAD→ASCT→maintenance	BAD→ASCT→maint B <u>Induction:</u> BAD: B 1.3 mg/m^2 d1,4,8,11 + doxorubicin 9 mg/m^2 d1-4 + D 40 mg/d d1-4,9-12,17-20; every 28 ds; number of cycles NR.	VAD→ASCT→maint T <u>Induction:</u> VAD: vincristine 0.4 mg/d d1-4 + doxorubicin 9 mg/m^2 d1-4 + D 40 mg/d d1-4,9-12, 17-20; every 28 days; number	<u>Primary:</u> PFS <u>Secondary:</u> Response PFS (without censoring patients with alloSCT) OS Safety

Study primary publication, Study name, Funding source	Study Objective, Design, Follow-up	Population	Intervention	Control	Outcomes
Cooperative Group (HOVON) and the German Multicenter Myeloma Group (GMMG) **Funding:** Dutch Cancer Foundation. German Federal Ministry of Education and Research (with unrestricted grant from Janssen-Cilag-Ortho Biotech). German Multicenter Myeloma Group (with grants from Novartis, Amgen, Chugai, and Roche).	RCT **Follow-up: mdn** 41 months	T; n=413 N = 827 **Age:** IG (B-arm): mdn 57 years CG (VAD/T-arm): mdn 57 years	ASCT: HOVON standard: single ASCT GMMG standard: double ASCT Maintenance: B 1.3 mg/m^2 once every 2 weeks for 2 years starting 4 weeks after high-dose melphalan.	of cycles NR. ASCT: HOVON standard: single ASCT GMMG standard: double ASCT Maintenance: T 50 mg/d for 2 years, starting 4 weeks after high-dose melphalan.	
Rosinol, 2012[7] [Induction study] **Rosinol, 2012[8] [Maintenance study)** **PETHEMA/ GEM** Start Date: April 6, 2006 End Date: August 5, 2009 Data cut-off: August 13, 2011 Sites: 66 sites in Spain **Funding**: Janssen Cilag, Pharmion (Celgene).	**Objective**: Compare the effectiveness of TD vs. BTD vs. VBMCP/VBAD/B (first randomization) and to compare the effectiveness of maintenance interferon vs. T vs. T+B (second randomization). **Design**: Open-label phase III RCT. **Follow-up**: Induction: mdn 35.2 months Maintenance: mdn 34.9 months from initiation of maintenance therapy	Patients newly diagnosed with MM, age ≤65 years. **Induction Study Arms:** **CG:** TD; n = 127 **IG$_1$:** BTD n = 130 **IG$_2$:** VBMCP/VBAD/B: n=129 ***Age:*** CG: mdn 56 years; IG$_1$: mdn 56 years; IG$_2$: mdn 57 years. **All patients to undergo ASCT→second randomization to maintenance 3 months after ASCT.** **Maintenance Study Arms:** CG$_1$: Interferon alfa-2b, n=90 CG$_2$: T, n=87 IG: T + B, n=89	**Induction Study:** IG$_1$ (BTD): same as TD plus B 1.3 mg/m^2 on ds 1,4,8,11 of each cycle every 4 weeks for 6 cycles. IG$_2$ (Combination therapy + B): 4 cycles of VBMCP/VBAD on an alternating basis plus two cycles of B 1.3 mg/m^2 d1,4,8,11 every 3 weeks **Maintenance Study:** IG (T+B): T 100 mg/d + B 1.3 mg/m^2 on d1,4,8,11 (B only on first cycle), every 3	**Induction Study:** CG (TD): T 200 mg/d (escalating doses in the first cycle) plus D 40 mg on ds 1-4 and ds 9-12 every 4 weeks for 6 cycles. **Maintenance Study:** CG$_1$ (Interferon): Interferon alfa-2b 3 MU subcutaneously 3 times per week. CG$_2$(T): T 100 mg/d	**Induction Study** Primary: CR rate post-induction and post-ASCT. Secondary: PFS OS Safety **Maintenance Study** Primary: PFS Secondary: Increase of response rate OS

Study primary publication, Study name, Funding source	Study Objective, Design, Follow-up	Population	Intervention	Control	Outcomes
			months for 3 years or until disease progression or toxicity.	Both CGs: for 3 years or until disease progression or toxicity.	Safety

Notes: abs = abstract; alloSCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplant; B = Bortezomib; BAD = bortezomib, doxorubicin, dexamethasone; BD = bortezomib, dexamethasone; BTD = bortezomib, thalidomide, dexamethasone; btD = reduced-dose bortezomib and thalidomide plus dexamethasone; BTDC = bortezomib, thalidomide, dexamethasone, cyclophosphamide; C = cyclophosphamide; CG = control Group; CR = complete response defined as asence of monoclonal immunoglobulin (M protein) in serum and urine; D = dexamethasone; d = day(s); DCEP = dexamethasone, cyclophosphamide, etoposide, cisplatin; HRQOL = health related quality of life; IG = intervention group; iv = intravenous; M = melphalan; mdn = median; MM = multiple myeloma; n = sample size; nCR = near complete response defined as absence of M protein on electrophoresis, but immunofixation positive; NR = not reported; OR = overall response; OS = overall survival; P = prednisone; PFS = progression-free survival; pts= patients; RCT = randomized controlled trial; T = thalidomide; TTP = time to disease progression; VAD = vincristine, doxorubicin, dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VGPR = very good partial response; wk(s) = week(s) yr(s) = years(s).

a) Trials

A total of seven trials met the inclusion criteria for this CGR. Six trials were randomized controlled trials (RCTs)[1,3-8] and one was a randomized trial that was not designed or powered to compare the treatment arms[2]. All of the trials, with the exception of Ludwig et al[2], were designed as superiority trials.

Trials investigating bortezomib added only to induction therapy

The IFM 2005-01 study[1], the Ludwig et al study[2], and the IFM 2007-02 study[3] all investigated adding bortezomib only to induction therapy, followed by ASCT. All three trials compared different induction regimens in patients with newly diagnosed MM who were candidates for ASCT.

The IFM 2005-01 study[1] centrally randomized patients to one of four arms: bortezomib + dexamethasone (BD); or, BD + consolidation with dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) (BD + DCEP); or, vincristine, doxorubicin, dexamethasone (VAD); or, VAD + consolidation with DCEP (VAD + DCEP). All arms were followed by ASCT. The analyses for efficacy and safety compared the BD and BD + DCEP groups combined to the VAD and VAD + DCEP groups combined. The primary outcome was the combined post-induction complete response (CR) and near-complete response (nCR) rate. The study met the reported sample size requirement for the primary outcome (Table 4). The study was open-label; however, the outcome assessors were blinded to treatment allocation. The reported analysis was final, used the intent-to-treat population, and the study was not terminated early. Response was assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Response comparisons were made using the X^2-test. Time-to-event outcomes were compared by the log-rank test and the Kaplan-Meier method was used to estimate survival curves. Adverse event rates were compared between treatment arms using the Cochran-Mantel-Haenszel X^2-test adjusted for stratification factors. Progression-free survival (PFS) was defined as the time from treatment start to progression, relapse, or death.

The Ludwig et al study[2] randomized patients to induction treatment with bortezomib, thalidomide, and dexamethasone (BTD) or to BTD combined with cyclophosphamide (BTDC). All arms were followed by ASCT. The primary outcome was post-induction CR/nCR rate; however, the study was not designed or powered to compare the treatment arms. The sample size for each arm was determined using a method designed for single-arm trials. Response was assessed centrally using the International Myeloma Working Group (IMWG) criteria with the addition of nCR (defined as absence of M-protein on electrophoresis, but immunofixation-positive); however, it was not reported if the outcome assessors were blinded to treatment assignment. It is important to note that the authors did not conduct any comparative analyses of the treatment arms for efficacy, safety, or health-related quality-of-life, as such analyses would have been inappropriate given the design of the trial.[2]

The IFM 2007-02 study[3] centrally randomized patients to induction with BD or reduced-dose bortezomib and thalidomide plus dexamethasone (btD). All arms were followed by ASCT. The primary outcome was post-induction CR rate. The required sample size was 200 patients, with 199 patients randomized across the

two arms. Response was assessed by the investigators and centrally re-assessed by the study team using IMWG criteria; however, it was not reported if the outcome assessors were blinded to treatment assignment. Response was compared between the study arms using the X^2-test. PFS was estimated using the Kaplan-Meier method and compared using the log-rank test. PFS was defined only as starting from randomization. The final analysis was on the intent-to-treat population.

Trials investigating bortezomib post-ASCT only (maintenance/consolidation only)

Mellqvist et al[4,15] reported in abstract form only, an RCT that investigated the use of bortezomib as consolidation following ASCT in patients with newly diagnosed MM that had received ASCT in the last five weeks and who had no prior exposure to bortezomib. Patients were randomized to receive bortezomib consolidation or to no consolidation. As the study is reported in abstract form only, there is limited information available on many aspects of the study design. The ClinicalTrials.gov record indicates that the projected enrolment is 400 patients; however, it is not known if this is the required sample size.[39] Between November 2005 and April 2009, 372 patients were randomized to the two study arms. The abstract does not state if the reported analysis was the final analysis or an interim analysis. No further information regarding the study design was reported.

Trials investigating bortezomib in induction and post-ASCT therapy

Three trials, GIMEMA[5], HOVON-65/GMMG-HD4[6], and PETHEMA/GEM[7,8] investigated the use of bortezomib in both the induction phase and as consolidation or maintenance following ASCT. All three trials had different study designs.

The GIMEMA study[5] centrally randomized patients with newly diagnosed MM to therapy with either: induction with thalidomide and dexamethasone (TD) followed by double ASCT with TD followed by TD consolidation followed by dexamethasone maintenance; or, induction with bortezomib and TD (BTD) followed by double ASCT with TD followed by BTD consolidation followed by dexamethasone maintenance. The primary outcome was the post-induction CR/nCR rate. The study met the reported sample size requirement for the primary outcome (Table 4). The reported analysis was the final analysis using the intent-to-treat population. The trial was not terminated early. Response was assessed using the EBMT criteria with the addition of nCR (defined as absence of M-protein on electrophoresis, but immunofixation-positive). Response was compared using the X^2-test. PFS was defined as the time from start of treatment to progression, relapse, or death. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared by the log-rank test.

The HOVON-65/GMMG-HD4 study[6] randomized patients with newly diagnosed MM (Durie-Salmon Stage II to III) to either: bortezomib, doxorubicin, dexamethasone (BAD) followed by ASCT followed by maintenance bortezomib; or, VAD followed by ASCT followed by maintenance thalidomide. The primary outcome was PFS and with 827 patients randomized, the study met the required sample size of 800 patients. The reported analysis was the final analysis using the intent-to-treat population. The trial was not terminated early. PFS was defined as the time from randomization to progression, relapse, or death. Response was assessed using the EBMT criteria with the addition of nCR (defined as by the IMWG criteria). PFS was analyzed by multivariate Cox regression analysis with adjustment for International

Staging System stage. Adverse event rates were analyzed using the X^2-test or Fisher's exact test using whichever was most appropriate. Overall survival was defined as the time from randomization to death from any cause.

The PETHEMA/GEM study[7,8] conducted a trial with randomization to induction therapy followed by ASCT followed by a second randomization to maintenance therapy three months after ASCT. The first randomization was to induction therapy with either: thalidomide and dexamethasone (TD); or, bortezomib and TD (BTD); or, chemotherapy and bortezomib (Chemo/B; see Table 3).[7] The primary outcome was post-induction and post-ASCT CR. The sample size requirement was 130 patients per arm, based on the primary outcome, with 127, 130, and 129 patients randomized to the TD, BTD, and Chemo/B arms, respectively (Table 4). The method of randomization and allocation concealment was not reported. The reported analysis was the final analysis for the induction randomization portion of the trial. Response was assessed using the EBMT criteria and was compared using the X^2-test. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Overall survival was defined as the time from randomization to death or last visit. The second randomization was to maintenance therapy with either: bortezomib and thalidomide (BT); or, thalidomide; or, interferon alfa-2b. The primary outcome was PFS; however, no sample size calculation or requirement was reported. It is therefore, unknown if the maintenance randomization was adequately powered for the primary outcome. A total of 266 patients were randomized across the three maintenance study arms (Table 3). The final intent-to-treat analysis of the maintenance randomization portion of the study were reported in abstract form only by Rosinol et al, 2012.[8]

b) Populations

Trials investigating bortezomib added only to induction therapy

The IFM 2005-01 study[1] randomized a total of 482 patients. The Ludwig et al study[2] randomized a total of 97 patients. The IFM 2007-02 study[3] randomized a total of 199 patients. Baseline patient characteristics were well-balanced across study arms in all three trials with the exception of the IFM 2007-02 study[3] in which a higher proportion of patients with t(4;14) and/or Del 17p in the btD arm (26%) than in the BD arm (15%). The median age of the patients was similar in all three trials and in every arm of each trial, and ranged from 57 years to 58 years (Table 5).

Trials investigating bortezomib post-ASCT only (maintenance/consolidation only)

The Mellqvist et al study[4,15] randomized a total of 299 patients. The median age was not reported. Baseline patient characteristics between the study arms were not reported.

Trials investigating bortezomib in induction and post-ASCT therapy

The GIMEMA study[5] randomized a total of 480 patients. Six patients withdrew consent prior to receiving any study drug (five patients in the BTD arm and one patient in the TD arm). The HOVON-65/GMMG-HD4 study[6] was the largest trial and randomized a total of 827 patients. The PETHEMA/GEM study[7] randomized a total of 386 to induction therapy. Of those patients, 266 were randomized a second time to maintenance therapy following ASCT.[8] The study arms in all three trials

were well balanced for a number of patient characteristics. The median age of the patients was similar in all three trials and in every arm of each trial, and ranged from 56 years to 58 years (Table 5).

c) Interventions

The trials investigating the use bortezomib in newly diagnosed MM who were candidates for ASCT all used varying regimens both in the intervention arms and the comparator arms. Details regarding the study interventions and comparators can be found in Table 5.

Trials investigating bortezomib added only to induction therapy

The IFM 2005-01 study[1] compared BD or BD+DCEP consolidation followed by ASCT to VAD or VAD+DCEP consolidation followed by ASCT. The Ludwig et al study[2] compared BDT vs. BDTC, followed by ASCT. The IFM 2007-02 study[3] compared BD to reduced-dose BTD. All three trials used the same dose or bortezomib, 1.3 mg/m^2 on days 1,4,8, and 11 of a 21-day cycle for 4 cycles. Table 5 provides additional information on the regimens and schedules given in each trial.

Trials investigating bortezomib post-ASCT only (maintenance/consolidation only)

The Mellqvist et al study[4] compared bortezomib consolidation following ASCT to no consolidation following ASCT. Bortezomib was administered at 1.3 mg/m^2 twice weekly (days 1,4,8, and 11) in a 3-week cycle for the first 2 cycles. In the following 4 cycles, bortezomib was administered once weekly (days 1,8,15) in a 4-week cycle.

Trials investigating bortezomib in induction and post-ASCT therapy

The GIMEMA study[5] compared TD→double ASCT with TD→TD consolidation to treatment with BTD→double ASCT with TD→BTD consolidation. The dose and schedule of thalidomide was the same in both arms. The schedule of administration of dexamethasone was slightly different in the two arms; however, the total dose remained the same (Table 5). Details regarding dose and schedule of bortezomib can be found in Table 5.

The HOVON-65/GMMG-HD4 study[6] compared BAD→ASCT→maintenance B to treatment with VAD→ASCT→maintenance T. The dose and schedule of doxorubicin and dexamethasone was the same in both treatment arms (Table 5). Of note, in study centres run by the Dutch Cancer Foundation (HOVON), patients in both arms received single ASCT, which is the standard in that country. In study centres affiliated with the German Multicenter Myeloma Group (GMMG), patients in both arms received double ASCT, which is the standard in that country.[6] Bortezomib was administered at 1.3 mg/m^2 on days 1,4,8, and 11 of a 28-day cycle. The number of cycles was not reported.

The PETHEMA/GEM study[7,34] made two comparisons. The first was a randomization to induction with: TD vs. BTD vs. combination chemotherapy plus bortezomib (4 cycles of vincristine-carmustine-melphalan-cyclophosphamide-prednisone alternating with vincristine-carmustine-doxorubicin-high-dose dexamethasone followed by 2 cycles of bortezomib). The TD dose and schedule was the same in

the TD arm and the BTD arm. Bortezomib was administered at a dose of 1.3 mg/m^2 on days 1,4,8, and 11 of a 4-week cycle for 6 cycles in the BTD arm and for 2 cycles in the combination chemotherapy plus bortezomib arm. The second randomization compared maintenance with BT vs. thalidomide vs. interferon. The dose and schedule of thalidomide was the same in the thalidomide arm and the BT arm (Table 5). Bortezomib was administered at 1.3 mg/m^2 on days 1,4,8, and 11 of the first cycle, every 3 months. Interferon was administered at 3 MU three times per week. Maintenance therapy continued for 3 years or until disease progression or toxicity.

d) Patient Disposition

Five of the seven studies reported that they included all randomized patients in the final intent-to-treat analysis.[1,3,5-7] Of note, the GIMEMA study[5] enrolled and randomized 480 patients. Six patients (five in the BTD arm and one in the TD arm) withdrew consent and did not receive any study drug. Those patients were excluded from the analysis, thus the intent-to-treat population cited by the authors is for 474 randomized patients (TD arm, n=238; BTD arm, n=236).[5] The trial reported by Mellqvist et al[4] has not had a final analysis reported to date.

e) Limitations/Sources of Bias

A summary of select quality characteristics can be found in Table 1. Of note, a common concern across five of the trials was the lack of information on blinding of outcome assessors: IFM2007-02[3], Mellqvist et al[4], GIMEMA[5], HOVON-65/GMMG-HD4[6], PETHEMA/GEM[7]. While there are valid reasons to conduct an open-label trial, it is still possible to blind outcome assessors to study arm assignment. This is especially important in studies where outcomes are susceptible to bias such as determining response.

Five of the trials, IFM 2005-01[1], Ludwig et al[2], IFM 2007-02[3], GIMEMA[5], PETHEMA/GEM[7], used CR and/or nCR as th primary outcome and were not designed to have adequate power to detect significant differences in PFS or overall survival. In addition, response has not been demonstrated to be a surrogate outcome for overall survival or PFS, therefore the usefulness of response in assessing the clinical effectiveness of a regimen may be limited. However, if the goal of induction treatment is to get patients to ASCT, and attainment of CR/nCR predicts who will get a transplant, then this is a reasonable primary outcome for trials investigating the use of bortezomib as induction therapy preceeding ASCT.

IFM 2005-01[1]:

- No blinding of patients or investigators. Outcome assessors were blinded therefore low impact on results.
- Post-ASCT, 153 patients in each arm received further treatment. Of those, 127 patients who received VAD and 140 who received BD were enrolled onto another IFM study (IFM 2005-02). Patients received lenalidomide consolidation within six months of ASCT followed by randomization to lenalidomide maintenance or placebo. Since not all patients in the IFM 2005-01 study went on to the IFM 2005-02 study, interpreting the post-ASCT results of the IFM 2005-01 study beyond the trial population is difficult.

Ludwig et al[2]:

- Trial was not designed or powered to compare the study arms and no comparisons were conducted for the study arms. Although the authors did not compare the treatment arms, this was appropriate given the design of the study; therefore, the usefulness of the results in the clinical context is limited as the study was not designed to evaluate effectiveness of the treatment arms.
- No blinding of patients or investigators. Outcome assessors were blinded therefore low impact on results.

IFM 2007-02[3]:

- The number of patients randomized was one short of the required sample size. The affect of this on the statistical assessment of primary outcome, CR is unclear. The reported result was not statistically significant; however, as the trial technically didn't meet the required the sample size, it may not have been powered to detect a difference, even if one did exist. The likely impact of this on the analysis is limited—it is likely that if one patient were added to the study, the difference in CR/nCR rate would have remained not statistically significant.
- Outcomes were assessed centrally; however, there is no mention of whether the assessors were blinded to treatment assignment. There is a potential for the study results to have been biased either for or against any treatment arm.

Mellqvist et al[4]:

- In the absence of further information regarding the study design and quality, it is not possible to determine the quality of this trial.

GIMEMA[5]:

- Outcomes were assessed by the investigators and re-assessed centrally by the study team; however, there is no mention of whether the assessors were blinded to treatment assignment. There is a potential for the study results to have been biased either for or against any treatment arm.

HOVON-65/GMMG-HD4[6]:

- No mention of how response outcomes were assessed. There is the potential for the study results to have been biased either for or against any treatment arm.

PETHEMA/GEM[7,8,34]:

- Outcomes were assessed centrally; however, there is no mention of whether the assessors were blinded to treatment assignment. There is a potential for the study results to have been biased either for or against any treatment arm.
- The number of patients randomized was four short of the required sample size for the induction randomization (three patients in the TD arm and one in the combination chemotherapy + bortezomib arm). The affect of this on the statistical assessment of primary outcome, CR is limited. The reported result was statistically significant, which means that the trial was adequately powered to detect a difference in CR rate between the

treatment arms. In addition, given that the five patients made up only 1.3% of the planned sample size, the effect of their absence on the primary outcome was likely limited.

- There are limitations with respect to the assessment of the maintenance arms. Although the reported primary outcome was PFS, no sample size requirement was reported. As the power of the study is unknown, any differences detected between the arms may be due to random chance and not be a difference that is generalizable to clinical practice. Much of the information regarding the maintenance randomization has been published in abstract form only, with only limited information reported in the full publication of the induction portion of the study,(Rosinol, 2012 Blood) making an assessment of the quality of the maintenance randomization portion difficult.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy outcomes for the included trials can be found in Table 2. The Ludwig et al randomized phase II study[2] was non-comparative by design. The data for that trial can be found in Table 2; however, as no statistical comparisons were made between the treatment groups, the efficacy results of that study are not discussed further.

Overall Survival

Six of the seven trials included in this CGR reported no statistically significant differences in overall survival (Table 2). However, none of the trials were powered to detect a difference in that outcome, and longer follow-up would have been required in order to detect such a difference. The remaining trial, the HOVON-65/GMMG-HD4 study, reported that OS, when adjusted for International Staging System (ISS) was not statistically significant (Table 2). However, the authors also conducted an analysis of OS using a multivariate Cox regression with adjustment for International Staging System, and reported a statistically significant difference in the BAD arm compared to the VAD arm (HR 0.77, 95% CI 0.60 to 1.00, p=0.049).[6] The multivariate Cox regression OS analysis was reported as the primary analysis in the full publication.[6]

Progression-Free Survival

Neither the IFM 2005-01 study[1] or the IFM 2007-02 study[3] reported a statistically significant difference in PFS; however, neither study was powered to detect differences in that outcome. The IFM 2005-01 study[1] reported a median PFS of 36.0 months compared to 29.7 months (p=0.057) for the BD + BD-DCEP consolidation arm vs. VAD + VAD-DCEP consolidation arm, respectively. Median follow-up was 31.2 months. The IFM 2007-02 study[3] reported a median PFS of 30 months compared to 26 months (p=0.22) for the BD induction arm compared to the reduced-dose btD arm, respectively. Median follow-up was 32 months.

Mellqvist et al[4] reported a statistically significant difference in median PFS of 27 months (95% CI 24-29 months) compared to 20 months (95% CI 17-23 months; p=0.02) for the bortezomib consolidation arm compared to the no consolidation arm, respectively. Although 372 patients were randomized, the number assigned to each study arm is unknown. Additionally, the median follow-up time was not reported.

The GIMEMA study[5] reported a statistically significant difference in PFS for the BTD→ASCT→BTD consolidation→maintenance arm (n=236) compared to the TD→ASCT→TD consolidation→maintenance arm (n=238), with 3-year estimates of PFS of 68% vs. 56%, respectively (HR 0.63 95% CI 0.45-0.88, p=0.0061). The median follow-up was 36 months. In an abstract reported at ASH in 2012, Cavo et al[35] reported median PFS of 56 months in the BTD arm compared to 42 months in the TD arm with HR=0.64, p<0.001. Median follow-up was 52 months.

The HOVON-65/GMMG-HD4 study[6] also reported a statistically significant difference in PFS for the BAD→ASCT→maintenance bortezomib arm (n=413) compared to the VAD→ASCT→maintenance thalidomide arm (n=414), with median PFS of 35 months vs. 28 months, respectively (HR 0.75, 95% CI 0.62-0.90, p=0.002). The median follow-up was 41 months.

The PETHEMA/GEM study had fully published results for the induction randomization[7], but not for the maintenance randomization[8,16]. For the induction randomization, a statistically significant difference in PFS was reported for the BTD induction arm (n=130) compared to the TD arm (n=127) and the combination chemotherapy/bortezomib arm (n=129), with median PFS of 56.2 months vs. 28.2 months, and 35.3 months, respectively.[7] A p-value of 0.01 was reported for this analysis; however, it is unclear if the analysis

compared the BTD arm to the two other arms combined, or if the BTD arm was compared to each of the other two arms in separate analyses. Median follow-up was 35.2 months. For the maintenance randomization, a statistically significant difference in PFS was reported for the BT maintenance arm (n=89) compared to the thalidomide maintenance arm (n=87) and the interferon maintenance arm (n=90), with median PFS estimated from the reported Kaplan-Meier survival curve of 44 months, 40 months, and 28.5 months, respectively.[8] As with the analysis of the induction randomization, and due to the fact that the results of this portion of the trial have only been reported in abstract form, it is unclear if the reported p-value of 0.00093 refers to an analysis of the BT maintenance arm compared to the other two arms combined or if the BT maintenance arm was compared to each of the other two arms in separate analyses. Median follow-up was 34.9 months, beginning on the date of randomization to maintenance therapy.

Response

Response to induction was identified as an outcome of interest for this CGR for trials investigating the use of bortezomib as part of induction therapy followed by ASCT. Five trials reported comparative data on response after induction and had a study design that included bortezomib as part of induction in at least one study arm: IFM 2005-01[1], IFM 2007-02[3], GIMEMA[5], HOVON-65/GMMG-HD4[6], and PETHEMA/GEM[7]. Post-induction CR was the primary outcome in IFM 2007-02[3] and PETHEMA/GEM[7]. Post-induction CR/nCR was the primary outcome in IFM 2005-01[1] and GIMEMA[5].

IFM 2005-01[1] reported a statistically significant difference in the rate of CR/nCR for the BD + BD-DCEP combined arm compared to the VAD + VAD-DCEP combined arm (14.8% of 240 patients vs. 6.4% of 242 patients, respectively; p=0.004). Statistically significant differences in favour of the bortezomib arm were also observed in overall response (partial response or better; 78.5% vs. 62.8%, p<0.001) and very good partial response or better (VGPR+; 37.7% vs. 15.1%, p<0.001).

IFM 2007-02[3] reported no significant differences between the BTD arm and the reduced-dose btD arm rate of CR/nCR (22% of 99 paitents vs. 31% of 100 patients, p=0.15), or overall response (81% vs. 88%, p=0.19). The authors did report a statistically significant difference in the rate of VGPR+ in favour of the reduced-dose btD arm compared to the BTD arm (49% vs. 36%, respectively; p=0.05).

GIMEMA[5] reported statistically significant differences in the post-induction rates of CR/nCR, VGPR+, and overall response in favour of the BTD→ASCT→BTD consolidation→maintenance dexamethasone arm compared to the TD→ASCT→TD consolidation→maintenance dexamethasone arm. The rate of CR/nCR was 44% of 236 patients in the BTD arm compared to 11% of 238 patients in the TD arm, p<0.0001. The rate of VGPR+ was 61.9% vs. 27.7% in favour of the BTD arm, p<0.0001. The rate of overall response was 93.2% vs. 78.6% in favour of the BTD arm, p<0.0001.

HOVON-65/GMMG-HD4[6] reported statistically significant differences in the post-induction rates of CR/nCR, VGPR+, and overall response in favour of the BAD

induction arm compared to the VAD induction arm. The rate of CR/nCR was 11% of 413 patients in the BAD arm compared to 5% of 414 paitents in the VAD arm, p<0.0001. The rate of VGPR+ was 42% vs. 14% in favour of the BAD arm, p<0.001, and the rate of overall response was 78% vs. 54% in favour of the BAD arm, p<0.001.

The PETHEMA/GEM study[7] reported statistically significant differences in the rate of CR for patients in the BTD arm (35% of 130 patients) compared to the TD arm (14% of 127 patients; p=0.0001) and compared to the combination chemotherapy with bortezomib arm (21% of 129 paitents; p=0.01). Higher rates of VGPR+ and overall response were reported in the BTD arm than in the TD or combination chemotherapy with bortezomib arms (Table 2); however, no statistical comparisons were reported on those two response outcomes.

Proportion of Patients Who Received ASCT

IFM 2005-01[1] reported that similar proportions of patients in both arms received an ASCT after induction therapy: 88.3% of 240 patients in the bortezomib arm and 84.4% of 242 patients in the VAD arm. Of note, 63.8% of patients in the bortezomib arm and 63.2% of patients in the VAD arm received further treatment after ASCT.

IFM 2007-02[3] reported that similar proportions of patients in both arms received an ASCT after induction therapy: 89.9% of 99 patients who received BD induction and 91.0% of 100 patients who received reduced-dose btD induction. The authors did not report information on post-ASCT treatment.

The GIMEMA study[5] reported that 92.4% of 236 patients in the BTD induction arm and 84.5% of 238 patients in the TD induction arm started ASCT following induction. A total of 69.9% of patients in the BTD arm received BTD consolidation and 69.3% of patients in the TD arm received TD consolidation.

The HOVON-65/GMMG-HD4 study[6] reported that 85.2% of 413 patients in the BAD induction arm and 83.8% of 414 patients in the VAD induction arm received ASCT following induction. A total of 55.4% of patients in the BAD induction arm received maintenance therapy with bortezomib following ASCT, and 65.2% of patients in the VAD induction arm received maintenance therapy with thalidomide following ASCT.

The PETHEMA/GEM study[7] reported that 79.2% of 130 patients in the BTD induction arm, 62.2% of 127 patients in the TD induction arm and 78.3% of 129 patients in the combination chemotherapy with bortezomib induction arm received ASCT following induction therapy. The authors did not report the proportion of patients in each induction arm who received therapy following ASCT other than to state that a total of 266 patients were randomized after ASCT to receive maintenance with BT, thalidomide, or interferon.

Quality of Life

None of the comparative RCTs included data on quality of life. However, the Ludwig et al study[2] included an assessment of health-related quality of life (HRQOL). The assessment was not designed to compare the BDT induction arm to the BDTC induction arm, instead it was designed to compare the baseline HRQOL to the HRQOL assessments on the first day of cycle 2,3, and 4, following induction treatment, at stem cell collection and transplantation, and at the

first follow-up visit post-transplantation. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the EuroQoL EQ-5D health status questionnaire were used to evaluate patients HRQOL. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) questionnaire was used to assess patient perceptions of treatment toxicities, including peripheral neuropathy. At baseline, the mean EORTC QLQ-C30 scores were similar between the BDT (53.6; n=46) and BDTC (56.2; n=46) arms. In the VDT arm, Global Health scores indicated that patients' perceptions of overall health steadily increased and exceeded the threshold for clinical significance at the first post-transplantation follow-up visit (mean score 71.0). The Global Health score worsened in the VDTC arm by the first post-transplantation follow-up visit (mean score 60.9). Ludwig et al[2] reported that similar patterns were observed in the individual domain scores of the EORTC QLQ-C30. The authors also reported that the same pattern of change was observed with the EuroQoL EQ-5d questionnaire. Ludwig et al[2] also reported the no notable difference was observed across arms in patient-reported neurotoxicity scores. It is important to note that the trial reported by Ludwig et al[2] was not designed to compare the treatment arms; therefore it is inappropriate to compare the HRQOL data between the two treatment arms.

Harms Outcomes

Induction Therapy With Bortezomib

Six trials investigated induction therapy with bortezomib and had data available on the rates of adverse events during induction therapy (Table 6). Four trials comparing an induction regimen with bortezomib to a regimen without bortezomib reported a significant difference in the rate of Grade 3/4 peripheral neuropathy (Table 6). IFM 2005-01[1] reported statistically significantly higher rates of both Grade 2 and Grade 3/4 peripheral neuropathy in the BD + BD-DCEP consolidation arms (15.5% and 7.1%, respectively, of 239 patients) compared to the VAD + VAD-DCEP consolidation arms (8.0% and 2.1% of 239 patients; $p<0.05$ and $p<0.05$). The GIMEMA study[5] reported a statistically significant higher rate of Grade 3/4 peripheral neuropathy in the BTD induction arm (10% of 236 patients) compared to the TD induction arm (2% of 238 patients; $p=0.0004$). The HOVON-65/GMMG-HD4 study[6] reported a statistically significant higher rate of Grade 3/4 peripheral neuropathy in the BAD induction arm (24% of 410 patients) than in the VAD induction arm (10% of 411 patients; $p<0.001$). Finally, the PETHEMA/GEM study[7] reported a statistically significantly higher rate of Grade 3/4 peripheral neuropathy in the BTD arm (14% of 130 patients) compared to the TD arm (5% of 127 patients; $p=0.01$). No statistically significant difference was found in the rate of Grade 3/4 peripheral neuropathy for the BTD arm compared to the combination chemotherapy with bortezomib arm (Table 6). The IFM 2007-02 study[3] reported a statistically significant difference in Grades 1-4 peripheral neuropathy for the BD arm (70% of 99 patients) compared to the reduced-dose btD arm (53% of 100 patients; $p=0.01$).

The GIMEMA study[5] and the HOVON-65/GMMG-HD4 study[6] both reported statistically significant differences in the rate of any Grade 3/4 adverse events

for the bortezomib induction arm compared to the non-bortezomib induction arm: GIMEMA, 56% vs. 33% (BTD vs. TD, p<0.0001) and HOVON-65/GMMG-HD4, 63% vs. 54% (BAD vs. VAD, p<0.01). The IFM 2005-01 study reported no statistically significant difference between the VAD induction arm and the BD induction arm for the rates of Grade 3/4 adverse events (46.0% vs. 46.9%, p=not reported).[1]

The IFM 2005-01 study[1] also reported statistically significant differences in the rates of the following adverse events (VAD n=239 vs. BD n=239): Grade 3/4 neutropenia (10% vs. 5%; p<0.05), Grade 3/4 anemia (8.8% vs. 4.2%; p<0.05), and Grade 3/4 infections (12.1% vs. 8.8%; p<0.05). However, statistically significant differences in the rates of the following adverse events were higher in the BD induction compared to the VAD induction arm: treatment-related deaths (2.9% vs. 0; p=0.02) and Grade 1-4 infections (48.1% vs. 38.1%; p<0.05).

The HOVON-65/GMMG-HD4 study[6] also reported statistically significant difference in the rates of Grade 3/4 thrombocytopenia for the BAD induction arm (10% of 410 patients) compared to the VAD induction arm (5% of 411 patients; p<0.01) as well for Grade 3/4 gastrointestinal symptoms (11% vs. 7%, respectively; p<0.05).

Table 6. Randomized trials of bortezomib in patients with newly diagnosed multiple myeloma: adverse events experienced during induction phase.

Author, year (ref)	Intervention	N	Neut* (%)	Thromb* (%)	Anemia* (%)	PN* (%)	Infections* (%)	Toxicity leading to discontinuation during or after induction (%)	Treatment-related deaths (%)	Any G3/4 AE (%)
IFM 2005/01 Harousseau, 2010[1] [abs]	VAD or VAD + DCEP	239	10	1.3	8.8	2.1	12.1[A]	13.4	2.9	46.0
	BD or BD + DCEP	239	5 p<0.05	2.9 NS	4.2 p<0.05	7.1 p<0.05	8.8[A] NS	18.4 NS	0 p=0.02	46.9 NS
IFM 2007-02 Moreau, 2011[3]	BD	99	NR	0	3	11	14	5.1	NR	37
	btD	100	NR	3	3	3 p=0.03	10	0	NR	43
Ludwig, 2013[2]	BTD	49	14	6	8	10	NR	6	0	47
	BTDC	49	18	6	18	8	NR	6	2.0	57
GIMEMA Cavo, 2010[5]	BTD→ double ASCT	236	NR	NR	NR	10	3	4	<1	56
	TD → double ASCT	238	NR	NR	NR	2 p=0.0004	5 p=0.35	3 p=0.45	0 p=0.31	33 p<0.0001
HOVON-65/GMMG-HD4 Sonneveld, 2012[6]	Ind: BAD → Hi-M+ASCT	410	3	10	8	24	26	6.1	2	63
	Ind: VAD → Hi-M+ASCT	411	1	5 p<0.01	7	10 p<0.001	21	3.4	2	54 p<0.01
PETHEMA/ GEM Rosinol 2012[7]	BTD	130	10	8	NR	14	21	7	2	NR
	TD	127	14	5	NR	5 p=0.01[B]	16	3	2	NR
	VBMCP/VBAD/B	129	22	6	NR	9 p=NS[B]	15	3	3	NR

Notes: * Grade 3 or 4 adverse events; → = followed by; abs = abstract; AE = adverse events; ASCT = autologous stem cell transplantation; B = bortezomib; BAD = bortezomib, doxorubicin, dexamethasone; BD = bortezomib, dexamethasone; BT = bortezomib, thalidomide; BTD = bortezomib, thalidomide, dexamethasone; btD = reduced-dose bortezomib and thalidomide, plus dexamethasone; BTDC = bortezomib, thalidomide, dexamethasone, cyclophosphamide; DCEP = dexamethasone, cyclophosphamide, etoposide, cisplatinum; G3 = grade 3; G4 = grade 4; Hi-M = High-dose melphalan; N = number of patients; neut = neutropenia; NR = not reported; NS = not statistically significant; PN = peripheral neuropathy; ref = reference; T = thalidomide; TD = thalidomide, dexamethasone; thromb = thrombocytopenia; VAD = vincristine, doxorubicin, dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone.

[A]A significant difference was reported for between-groups Grade 1-4 herpes zoster with p<0.05.
[B]Comparisons reported between BTD arm vs. TD arm and BTD arm vs. VBMCP/VBAD/B arm.

Post-ASCT therapy (consolidation or maintenance) With Bortezomib

Three trials investigated the addition of bortezomib in post-ASCT therapy either as consolidation or maintenance: GIMEMA[9], HOVON-65/GMMG-HD4[6], and PETHEMA/GEM[7,8]. Data on adverse events for post-ASCT therapy in these trials can be found in Table 7. None of the trials reported statistically significant differences in Grade 3/4 adverse events (Table 7). Specifically, the GIMEMA study[9] reported that no significant differences were observed for the following adverse events for the BTD consolidation arm compared to the TD consolidation arm: Grade 3/4 peripheral neuropathy (0.6% of 160 patients vs. 0% of 161 patients, respectively; p=0.315), Grade 3/4 infections (1.2% vs. 3.1%; p=0.255), and for any Grade 3/4 adverse event (10.6% vs. 9.3%; p=0.696). A total of 2.5% of patients in the BTD consolidation arm and 0.6% of patients in the TD consolidation arm experienced toxicity that led to discontinuation during or after consolidation therapy (Table 7).

The HOVON-65/GMMG-HD4 study[6] did not report any statistical comparisons on the rates of adverse events. The rates of Grade 3/4 peripheral neuropathy were 5% of 229 patients who received maintenance bortezomib and 8% of 270 patients who received maintenance thalidomide. The rates of Grade 3/4 infections were 24% of patients who received maintenance bortezomb and 18% of patients who received maintenance thalidomide. A total of 11.4% of 229 patients who received maintenance bortezomib experienced toxicity that led to discontinuation from the study compared to 30.4% of 270 patients who received maintenance thalidomide: this difference was statistically significant, p<0.001.

The PETHEMA/GEM study[8] reported that no patients experienced a Grade 4 peripheral neuropathy in any of the maintenance arms (BT, thalidomide, or interferon). Also, no statistically significant differences were demonstrated in the proportion of patients who experienced an adverse event that led to study discontinuation for the maintenance BT arm (15.6% of 89 patients) compared to maintenance thalidomide (30.3% of 87 patients; p=0.08) or compared to maintenance interferon (18.3% of 90 patients; p=0.17).

Table 7. Randomized trials of bortezomib in patients with newly diagnosed multiple myeloma: adverse events experienced during post-ASCT therapy (maintenance or consolidation).

Author, year (ref)	Intervention	N	Neut* (%)	Thromb* (%)	Anemia* (%)	PN* (%)	Infections* (%)	Toxicity leading to discontinuation during or after post-ASCT therapy (%)	Treatment-related deaths (%)	Any G3/4 AE (%)
GIMEMA Cavo, 2012[9]	BTD consolidation	160	NR	NR	NR	0.6	1.2	2.5	NR	10.6
	TD consolidation	161	NR	NR	NR	0 p=0.315	3.1 p=0.255	0.6	NR	9.3 p=0.696
HOVON-65/GMMG-HD4 Sonneveld, 2012[6]	Maintenance B	229	0	4	1	5	24	11.4	0	48
	Maintenance T	270	1	2	1	8	18	30.4 p<0.001	0	46
PETHEMA/GEM Rosinol 2012[7,8]	Maintenance BT	89	NR	NR	NR	G4: 0	NR	15.6	NR	NR
	Maintenance T	87	NR	NR	NR	G4: 0	NR	30.3 p=0.08	NR	NR
	Maintenance IFN	90	NR	NR	NR	G4: 0	NR	18.3 p=0.17	NR	NR

Notes: * Grade 3 or 4 adverse events; abs = abstract; AE = adverse events; ASCT = autologous stem cell transplantation; B = bortezomib; BT = bortezomib, thalidomide; BTD = bortezomib, thalidomide, dexamethasone; G3 = grade 3; G4 = grade 4; Hi-M = High-dose melphalan; IFN = interferon; N = number of patients; neut = neutropenia; NR = not reported; PN = peripheral neuropathy; ref = reference; T = thalidomide; TD = thalidomide, dexamethasone; thromb = thrombocytopenia; VAD = vincristine, doxorubicin, dexamethasone; VBAD = vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone; VBMCP = vincristine, BCNU, melphalan, cyclophosphamide, prednisone.
[A]A significant difference was reported for between-groups Grade 1-4 herpes zoster with p<0.05.
[B]Comparisons reported between BTD arm vs. TD arm and BTD arm vs. VBMCP/VBAD/B arm.

6.4 Ongoing Trials

Table 8. Study NCT01208766[41]: A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01208766 Open-label, prospective randomized phase III trial, parallel assignment. Start date: January 2011 Expected completion date: October 2015 Estimated enrolment: 1500 Study Sponsor: Stichting Hemato-Oncologie voor Volwassenen Nederland	Patients with symptomatic multiple myeloma, previously untreated, ISS stages 1-3, age 18-65 years inclusive	**Two randomizations:** **First randomization (R1) to one of two arms:** R1 Arm 1 (VMP): 4 cycles of VMP 4 to 6 weeks after stem cell collection: Bortezomib: 1.3 mg/m^2 i.v. rapid infusion days 1,4,8,11,22,25,29,32 Melphalan: 9 mg/m^2 p.o. days 1-4 Prednisone: 60 mg/m^2 p.o. days 1-4 ***Or*** R1 Arm 2 (HDM ASCT): 1 or 2 cycles of HDM (High dose Melphalan) 4 to 6 weeks after stem cell collection: Melphalan: 100 mg/m^2 i.v. rapid infusion -3, -2* (*Patients with renal insufficiency 100 mg/m2 only at day -3) **Secondary randomization (R2) to one of two arms:** R2 Arm1 (no consolidation): No consolidation, patients will continue to Lenalidomide maintenance. ***Or*** R2 Arm 2 (VRD consolidation: 2 cycles of VRD: Bortezomib: 1.3 mg/m2 i.v. rapid infusion days	<u>Primary outcomes:</u> Progression-free survival (from registration) R1: Progression-free survival from randomization 1 R2: Progression-free survival from randomization 2 <u>Secondary outcomes:</u> Overall survival (from registration, R1, R2) Toxicity Response (PR, VGPR, CR, stringent CR)

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
		1,4,8,11 Lenalidomide: 25 mg p.o. days 1-21 Dexamethasone: 20 mg p.o. days 1,2,4,5,8,9,11,12	

Available from: = http://clinicaltrials.gov/ct2/show/NCT01208766?term=NCT01208766&rank=1

Table 9. Study NCT00416208[42]: Consolidation Therapy With Bortezomib in Patients With Multiple Myeloma Aged 61 to 75

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00416208 Open-label, randomized phase III trial, parallel assignment Start date: October 2006 Expected completion date: May 2013 Estimated enrolment: 154 Study Sponsor: Janssen-Cilag G.m.b.H	Patients with multiple mylenoma aged 61 to 75 who have had pretreatment with single or tandem high dose melphalan therapy and autologous stem cell transplantation as first line therapy. At least stable disease after stem cell transplantation. Adequate hematological, hepatic and renal lab parameters. Karnofsky status of 70 or more.	**Two arms:** Bortezomib: 1.6 mg/m2 i.v. d1 d8 d15 d22 for 4 cycles each of 35 days ***Or*** No intervention	Primary outcomes: Event-free survival time Secondary outcomes: Best response Response rate Duration of response Toxicities Quality of life

Available from: http://clinicaltrials.gov/ct2/show/NCT00416208?term=NCT00416208&rank=1

Table 10. Study NCT01286077[43]: A Phase 2, Multicentre, Randomised, Open-Label, Parallel Group Study to Evaluate the Effect of VELCADE on Myeloma Related Bone Disease

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01286077 Open-label, randomized phase II trial, parallel assignment Start date: September 2009 Expected completion date: April 2014 Estimated enrolment: 106	Adult Multiple Myeloma patients in partial response or better after high dose chemotherapy and autologous stem cell transplantation.	**Two arms:** Bortezomib: 1.6 mg/m² bolus injection on Days 1, 8, 15 and 22 every 5 weeks for 4 cycles ***Or*** No intervention	Primary outcomes: Bone mineral density Secondary outcomes: Progression-free survival Biochemical bone markers Skeletal events Number of subjects with skeletal-related events New bone lesions

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study Sponsor: Janssen-Cilag International NV			Change from baseline bone mineral density overtime Change in Karnofsky performance status Change in Karnofsky performance status compared to screening Overall survival

Available from: http://clinicaltrials.gov/ct2/show/NCT01286077?term=NCT01286077&rank=1

Table 11. Study NCT01191060[44]: Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone (RBD) to High-Dose Treatment With ASCT in the Initial Management of Myeloma in Patients up to 65 Years of Age

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01191060 Open-label, randomized phase III trial, parallel assignment Start date: October 2010 Expected completion date: September 2020 Estimated enrolment: 700 Study Sponsor: University Hospital, Toulouse	Patients diagnosed with multiple myeloma based on International Myeloma Foundation 2003 Diagnostic Criteria. Patients must have symptomatic myeloma with myeloma-related organ damage. Patients must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. Age between 18 and 65 years at the time of signing the informed consent document. ECOG performance status <2 (Karnofsky ≥ 60%) Negative HIV blood test	**Two arms:** RBD Treatment with ASCT 2 cycles: Lenalidomide: 25 mg/day on days 1-14 of each cycle Bortezomib: 1.3 mg/m2 on days 1, 4, 8, and 11 for 1 cycle of each cycle ASCT 2 cycles RBD: Maintenance phase (12 months): Lenalidomide: 10 mg/day continuously for 28 days during 3 months and if the participant tolerates 10 mg/day without complication, a dose increase to 15 mg/day will be allowed ***Or*** 2 cycles RBD: Lenalidomide: 25 mg/day on days 1-14 of	<u>Primary outcomes:</u> Progression-free survival <u>Secondary outcomes:</u> Response rates Time to progression Toxicity Genetic prognostic groups definition Best treatment examination

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
		each cycle Bortezomib: 1.3 mg/m2 on days 1, 4, 8, and 11 for 1 cycle of each cycle PBSC collection, then 5 cycles of RBD Maintenance phase (12 months): Lenalidomide: 10 mg/day continuously for 28 days during 3 months and if the participant tolerates 10 mg/day without complication, a dose increase to 15 mg/day will be allowed	

Available from: http://clinicaltrials.gov/ct2/show/NCT01191060?term=NCT01191060&rank=1

Table 12. Study NCT01109004[45]: A Trial of Single Autologous Transplant With or Without Consolidation Therapy Versus Tandem Autologous Transplant With Lenalidomide Maintenance for Patients With Multiple Myeloma (BMT CTN 0702)

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01109004 Open-label, randomized phase III trial, parallel assignment Start date: May 2010 Expected completion date: May 2020 Estimated enrolment: 750 Study Sponsor: National Heart, Lung, and Blood Institute (NHLBI)	Patients meeting the criteria for symptomatic multiple myeloma who are 70 years of age, or younger, at time of enrollment. Patients who have received at least two cycles of any regimen as initial systemic therapy and are within 2 - 12 months of the first dose of initial therapy. Patients with an adequate autologous graft defined as a cryopreserved PBSC graft containing greater than or equal to 4 x 10^6 CD34+ cells/kg patient weight. The graft may not be CD34+	**Three arms:** Initial autologous transplant followed by a second autologous transplant and lenalidomide maintenance for 3 years(10 mg daily for 3 months and increase to 15mg daily) ***Or*** Initial autologous transplant followed by lenalidomide, bortezomib and dexamethasone (RVD) consolidation (lenalidomide 15 mg/day on Days 1-14, dexamethasone 40mg on Days 1, 8 and 15, and bortezomib 1.3mg/m2 on Days 1, 4, 8 and 11 of every 21	Primary outcomes: Progression-free survival Secondary outcomes: Myeloma-stable survival Overall survival Progression Toxicities Infections Treatment related mortality Non-compliance with medication Quality of life

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	selected or otherwise manipulated to remove tumor or other cells. The graft can be collected at the transplanting institution or by a referring center. The autograft must be stored so that there are two products each containing at least 2 x 10^6 CD34+ cells/kg patient weight.	day cycle, patients will receive four cycles) and lenalidomide maintenance for 3 years(10 mg daily for 3 months and increase to 15mg daily) ***Or*** Initial autologous transplant followed by lenalidomide maintenance for 3 years(10 mg daily for 3 months and increase to 15mg daily)	

Available from: http://clinicaltrials.gov/ct2/show/NCT01109004?term=NCT01109004&rank=1

Table 13. Study NCT01208662[46]: A Randomized, Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib, and Dexamethasone (RVD) to High-Dose Treatment With Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients Up to 65 Years of Age

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01208662 Open-label, randomized phase III trial, parallel assignment Start date: September 2010 Expected completion date: September 2016 Estimated enrolment: 300 Study Sponsor: Dana-Farber Cancer Institute	Patients with diagnosis of Multiple Myeloma, according to the International Myeloma Foundation 2003 Diagnostic Criteria with no prior therapy. Documented symptomatic myeloma, with organ damage related to myeloma with laboratory assessments performed within 21 days of registration Myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. ECOG performance	**Two arms:** Lenalidomide: Oral, 25 mg/day, days 1-14 for 8 total cycles for Arm A. Oral, 25 mg/day, days 1-14 for 5 total cycles for Arm B. Oral, 10-15 mg/day, daily for 12 months in maintenance for Arm A and Arm B. Bortezomib: IV, days 1, 4, 8 and 11 for 8 total cycles for Arm A. IV, days 1, 4, 8 and 11 for 5 total cycles for Arm B. Dexamethasone: Oral, days 1, 2, 4, 5, 8, 9, 11 and 12 for 8 total cycles for Arm A. Oral, days 1, 2, 4, 5, 8, 9, 11 and 12 for 5 total cycles for	<u>Primary outcomes:</u> Progression-free survival <u>Secondary outcomes:</u> Response rate Time to progression Overall survival Toxicity Genetic prognostic groups Best treatment Quality of life Medical resource utilization

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	status </= 2 Negative HIV blood test	Arm B. Dose of 20 mg/day for first 3 cycles. Dose of 10 mg/day for remaining cycles. ***Or*** Lenalidomide: Oral, 25 mg/day, days 1-14 for 8 total cycles for Arm A. Oral, 25 mg/day, days 1-14 for 5 total cycles for Arm B. Oral, 10-15 mg/day, daily for 12 months in maintenance for Arm A and Arm B. Bortezomib: IV, days 1, 4, 8 and 11 for 8 total cycles for Arm A. IV, days 1, 4, 8 and 11 for 5 total cycles for Arm B. Dexamethasone: Oral, days 1, 2, 4, 5, 8, 9, 11 and 12 for 8 total cycles for Arm A. Oral, days 1, 2, 4, 5, 8, 9, 11 and 12 for 5 total cycles for Arm B. Dose of 20 mg/day for first 3 cycles. Dose of 10 mg/day for remaining cycles. Autologous Stem Cell Transplant	

Available from: http://clinicaltrials.gov/ct2/show/NCT01208662?term=NCT01208662&rank=1

Table 14. Study NCT01706666[47]: A Phase II Randomized Study of Three Subcutaneous Bortezomib-based Consolidation Treatments for Patients Completing Induction Therapy and Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01706666 Open-label, randomized phase II trial, parallel	Patients with treated myeloma: Prior induction therapy (any)	**Three arms:** Patients receive bortezomib SC on days	<u>Primary outcomes:</u> Stringent complete response

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
assignment Start date: October 2012 Expected completion date: November 2013 Estimated enrolment: 150 Study Sponsor: Mayo Clinic	and followed by autologous stem cell transplantation Less than 120 days post SCT with no evidence of relapse or progression prior to registration Measurable disease at initial diagnosis, pre-stem cell transplant (SCT) or post-SCT of multiple myeloma as defined by at least ONE of the following: Serum monoclonal protein >= 0.5 g/dL, > 200 mg of monoclonal protein in the urine on 24 hour electrophoresis, Serum immunoglobulin free light chain >= 5 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio, Monoclonal bone marrow plasmacytosis >= 30% (evaluable disease)	1 and 15 of courses 1-12 and day 1 of courses 13-24. ***Or*** Patients receive bortezomib SC as in Arm A, cyclophosphamide PO on days 1 and 15 of courses 1-12 and day 1 of courses 13-24, and dexamethasone PO on days 1 and 15 of courses 1-12 and day 1 of courses 13-24. ***Or*** Patients receive bortezomib SC as in Arm A and lenalidomide PO QD on days 1-28.	<u>Secondary outcomes:</u> Survival time Progression-free survival Adverse events

Available from: http://clinicaltrials.gov/ct2/show/NCT01706666?term=NCT01706666&rank=1

Table 15. Study NCT01685814[48]: Lenalidomide, Adriamycin, Dexamethasone (RAD) Versus Lenalidomide, Bortezomib, Dexamethasone (VRD) for Induction in Newly Diagnosed Multiple Myeloma Followed by Response-adapted Consolidation and Lenalidomide Maintenance - A Randomized Multicenter Phase III Trial by Deutsche Studiengruppe Multiples Myelom (DSMM XIV

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01685814 Open-label, randomized phase II trial, parallel assignment Start date: May 2012 Expected completion date: May 2020 Estimated enrolment: 406	Patients with newly diagnosed multiple mylenoma and no previous systemic therapy for the treatment of multiple myeloma (dexamethasone at a cumulative dose of 320 mg; plasmapheresis/dialysis	**Four arms:** Single stem cell transplant, 3-year lenalidomide maintenance ***Or*** Tandem autologous transplant, lenalidomide	<u>Primary outcomes:</u> Complete Response Progression-free survival <u>Secondary outcomes:</u> Overall response rate Complete Response Overall survival Incidence, severity relationship of SAEs Number of hospital

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study Sponsor: Wuerzburg University Hospital	without concomitant chemotherapy, local irradiation of bone lesions; and surgical intervention is accepted as pretreatment)	maintenance ***Or*** Allogeneic stem cell transplant, lenalidomide maintenance ***Or*** Tandem autologous transplant	stays and hospitalization days

Available from: http://clinicaltrials.gov/ct2/show/NCT01685814?term=NCT01685814&rank=1

Table 16. Study NCT00416273[49]: Ph. III Trial to Evaluate Safety and Efficacy of Bortezomib as Consolidation Treatment vs Observation in Patients With Multiple Myeloma Aged <= 60 After Receiving Induction Therapy Prior to Stem Cell Mobilisation and Highdose Melphalan Followed by Autologous or Allogenic Stem Cell Transplantation

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00416273 Open-label, randomized phase III trial, parallel assignment Start date: September 2006 Expected completion date: May 2013 Estimated enrolment: 217 Study Sponsor: Janssen-Cilag G.m.b.H	Patients (age < = 60 years) with multiple myeloma with prior therapy consisting of remission induction therapy and high dose chemotherapy followed by stem cell transplantation.	**Two arms:** High dose melphalan with autologous stem cell transplantation Three months after ASCT: 4 cycles of bortezomib 1.6 mg/m2 body surface intravenously once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (days 23 to 35) ***Or*** High dose melphalan with autologous stem cell transplantation	Primary outcomes: Event-free survival time Secondary outcomes: Best response Response rate Duration of response Toxicities Quality of life

Available from: http://clinicaltrials.gov/ct2/show/NCT01286077?term=NCT01286077&rank=1

Table 17. Study NCT01539083[50]: An Open-label, Randomised Trial of Bortezomib Consolidation (With Thalidomide and Prednisolone) Vs Thalidomide and Prednisolone Alone in Previously Untreated Subjects With Multiple Myeloma After Receiving Bortezomib, Cyclophosphamide, Dexamethasone (VCD) Induction and Autologous Stem Cell Transplant

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01539083 Open-label, randomized phase III trial, parallel assignment Start date: November 2011 Expected completion date: November 2017 Estimated enrolment: 220 Study Sponsor: Janssen Scientific Affairs, LLC	Patients 18 years and older who were previously diagnosed with multiple myeloma based on international myeloma working group (IMWG) criteria but have not received treatment. Have ECOG status 0-2 Meet the pretreatment laboratory criteria as specified in the study protocol at and within 21 days before baseline (Day 1 of Cycle 1, before bortezomib administration for induction).	**Two arms:** Thalidomide: Type=1, unit=mg, number=100, form=tablet, route=oral use. Oral thalidomide consolidation will be administered for a maximum of 12 months or until disease progression along with Prednisolone: Type=1, unit =mg, number=50, form=tablet, route=oral use. Prednisolone maintenance therapy will be administered on alternate days continued indefinitely or until disease progression. ***Or*** Bortezomib***:*** Type=1, unit=mg/ml, number=2.5, form= Solution for injection, route=Subcutaneous use. Bortezomib will be administered as a single subcutaneous injection at a concentration of 1.3 mg/m2 every 2 weeks for 32 weeks (16 doses) in addition to 100 mg daily oral thalidomide consolidation for a maximum of 12 months or until disease progression and 50 mg oral alternate-day prednisolone maintenance continued indefinitely or until disease progression.	<u>Primary outcomes:</u> Complete response Very good partial response <u>Secondary outcomes:</u> Complete response rate Stringent complete response Progression-free survival Disease-free survival Overall survival

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
		Thalidomide: Type=1, unit=mg, number=100, form=tablet, route=oral use. 100 mg daily oral thalidomide consolidation (administered in addition to bortezomib) will be administered for a maximum of 12 months or until disease progression and 50 mg oral alternate-day prednisolone maintenance continued indefinitely or until disease progression.	

Available from: http://clinicaltrials.gov/ct2/show/NCT01539083?term=NCT01539083&rank=1

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

The Myeloma Clinical Guidance Panel is comprised of bortezomib (Velcade) for multiple myeloma.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update from August 2012 to Present.

1. (bortezomi: or velcade: or ps?341: or ldp?341: or mln?341: or 179324-69-7:).ti,ab,rn,nm,sh,hw,ot.
2. Exp multiple myeloma/
3. (myeloma: or MM:).ti,ab,sh,hw,ot.
4. 2 or 3
5. 1 and 4

The above was limited to records entered in August 2012 or later.

Ovid EMBASE

1. exp *bortezomib/
2. (bortezomi: or velcade: or ps?341: or ldp?341: or mln?341:).ti,ab.
3. 1 or 2
4. exp *multiple myeloma/
5. (myeloma: or MM:).ti,ab.
6. 4 or 5
7. 3 and 6

The above was limited to records entered in August 2012 or later.

2. Literature Search via PubMed

PubMed

1. bortezomib* or velcade* or ps341* or ldp341* mln341*
2. publisher[sb]
3. 1 and 2

The above was limited to records entered in August 2012 or later.

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Issue 12, 2012
Search terms: (bortezomib* or velcade* or ps341* or ldp341* or mln341*) AND (myeloma*) in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: bortezomib, velcade, myeloma

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: bortezomib, velcade

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the Journal of Clinical Oncology search portal: http://jco.ascopubs.org/search
As the PEBC systematic review searched the 2005-2012 conference proceedings, the pCODR Methods Team did not search these years of ASCO.

American Society of Hematology (ASH)
via Blood (Journal of the American Society of Hematology) search portal:
http://bloodjournal.hematologylibrary.org/search
As the PEBC systematic review searched the 2005-2011 conference proceedings, the pCODR Methods Team did not search these years of ASH. The 2012 ASH conference proceedings were searched by the pCODR Methods Team.

Search terms: bortezomib, velcade

REFERENCES

1. Harousseau J-L, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010 Oct 20;28(30):4621-9.
2. Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, et al. Randomized Phase II Study of Bortezomib, Thalidomide, and Dexamethasone With or Without Cyclophosphamide As Induction Therapy in Previously Untreated Multiple Myeloma. J Clin Oncol. 2013 Oct 22 [Epub];31(2):247-55. doi: 10.1200/JCO.2011.39.5137. Epub 2012 Oct 22.
3. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011 Nov 24;118(22):5752-8.
4. Mellqvist U-H, Westin J, Gimsing P, Hjertner O, Lenhoff S, Laane E, et al. Improved response rate with bortezomib consolidation after high dose melphalan: first results of a nordic myeloma study group randomized phase III trial. Blood. 2009 Nov 20;114(22):A530.
5. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010 Dec 18;376(9758):2075-85.
6. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial. J Clin Oncol. 2012 Aug 20;30(24):2946-55.
7. Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012 Aug 23;120(8):1589-96.
8. Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, De La Rubia J, et al. Maintenance therapy after stem-cell transplantation for multiple myeloma with bortezomib/thalidomide vs. thalidomide vs. alfa2b-interferon: final results of a phase III Pethema/GEM randomized trial. Blood (ASH Annual Meeting Abstracts). 2012;120:Abstract 334.
9. Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide- dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012 05 Jul;120(1):9-19.
10. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2012. Toronto: Canadian Cancer Society; 2012.
11. Palumbo A, Anderson K. Multiple Myeloma. New England Journal of Medicine. 2011;364(11):1046-60.
12. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol. 1998 December 1, 1998;16(12):3832-42.
13. Palumbo A, Sezer O, Kyle R, Miguel JS, Orlowski RZ, Moreau P, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. Leukemia. 2009;23(10):1716-30.
14. Kouroukis CT, Reece D, Baldassarre FG, Haynes AE, Imrie K, Cheung M, et al. Bortezomib in multiple myeloma and lymphoma [In Press]. Toronto (ON): Cancer Care Ontario; 2013 Jan 8. Program in Evidence-based Care Evidence-based Series No.: 6-18 Version 2.

15. Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, et al. Improved progression free survival with bortezomib consolidation after high dose melphalan; results of a randomized phase iii trial. Haematologica. 2011;96(S1):S31.
16. Rosinol L, Cibeira MT, Mateos MV, Martinez J, Oriol A, Teruel AI, et al. A phase III PETHEMA/GEM randomised trial of posttransplant maintenance in multiple myeloma: Superiority of bortezomib. Bone Marrow Transplantation. 2012 April;47:S2.
17. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008 March 1, 2008;111(5):2521-6.
18. Durie BGM, Harousseau J-L, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.
19. Ludwig H, Durie BGM, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012 March 29, 2012;119(13):3003-15.
20. Lokhorst H, Einsele H, Vesole D, Bruno B, Miguel JS, Pérez-Simon JA, et al. International Myeloma Working Group Consensus Statement Regarding the Current Status of Allogeneic Stem-Cell Transplantation for Multiple Myeloma. J Clin Oncol. 2010 October 10, 2010;28(29):4521-30.
21. pan-Canadian Oncology Drug Review Tumour Group Submission: Velcade (bortezomib); Cancer Care Ontario: Hematology Disease Site Group. Toronto (ON); Company: Janssen Inc.; 2012 Nov 1.
22. Avet-Loiseau H, Moreau P, Mathiot C, Charbonnel C, Facon T, Attal M, et al. Use of bortezomib to overcome the poor prognosis of t(4;14), but not del(17p), in young patients with newly diagnosed multiple myeloma. J Clin Oncol. 2010;28 (Suppl 15):A8113.
23. Moreau P, Hulin C, Marit G, Caillot D, Facon T, Lenain P, et al. Stem cell collection in patients with de novo multiple myeloma treated with the combination of bortezomib and dexamethasone before autologous stem cell transplantation according to IFM 2005-01 trial. Leukemia. 2010 Jun;24(6):1233-5.
24. Moreau P, Attal M, Pegourie B, Planche L, Hulin C, Facon T, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood. 2011 Mar 17;117(11):3041-4.
25. Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, et al. Bortezomib, thalidomide, and dexamethasone (VTD) versus VTD plus cyclophosphamide as induction therapy in previously untreated multiple myeloma patients eligible for HDT-ASCT: a randomized phase 2 trial. Blood. 2009 Nov 20;114(22):A2312.
26. Moreau P, Facon T, Attal M, Doyen C, Hulin C, Marit G, et al. Comparison of reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as induction treatment prior to ASCT in de novo multiple myeloma (MM): results of IFM2007-02 study. J Clin Oncol. 2010;28(Suppl 15):A8014.
27. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. A phase III study of double autotransplantation incorporating bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) for multiple myeloma: superior clinical outcomes with VTD compared to TD. Blood. 2009 Nov 20;114(22):A351.
28. Brioli A, Perrone G, Volpe S, Pasini S, Mele A, Rossini F, et al. Autologous Peripheral Blood Stem-Cell (PBSC) collection is not impaired by Bortezomib-Thalidomide-Dexamethasone (BTD) induction therapy in newly diagnosed Multiple Myeloma (MM). Blood. 2011 18 Nov;118(21):A317.
29. Cavo M, Pantani L, Patriarca F, Petrucci MT, Galli M, Raimondo FD, et al. Superior Complete Response Rate (CR) and Progression-Free Survival (PFS) with Bortezomib-Thalidomide-Dexamethasone (VTD) Versus Thalidomide-Dexamethasone (TD) As Consolidation Therapy After Autologous Stem-Cell Transplantation (ASCT) in Multiple Myeloma (MM). ASH Annual Meeting Abstracts. 2011 December 9, 2011;118(21):1871.
30. Tacchetti P, Terragna C, Catania G, Marcatti M, Nozza A, Ferrara F, et al. Bortezomib- and Thalidomide-Induced Peripheral Neuropathy (PN) in Multiple Myeloma (MM): Clinical and Molecular Analysis of 474 Patients Treated with Thalidomide-Dexamethasone (TD) or Bortezomib-TD (VTD). ASH Annual Meeting Abstracts. 2011 December 9, 2011;118(21):1821.
31. Sonneveld P, van der Holt B, Schmidt-Wolf IGH, Bertsch U, el Jarari L, Salwender H-J, et al. First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib,

adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM). Blood. 2008;112:A653.
32. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012 Jan 26;119(4):940-8.
33. Rosinol L, Cibeira MT, Martinez J, Mateos MV, Oriol A, Terol MJ, et al. Thalidomide / dexamethasone (TD) vs. bortezomib (Velcade)/thalidomide / dexamethasone (VTD) vs. VBMCP/VBAD/Velcade as induction regimens prior autologous stem cell tTransplantation (ASCT) in multiple myeloma (MM): results of a phase III PETHEMA/GEM trial. Blood. 2009 Nov 20;114(22):A130.
34. Rosinol L, Cibeira MT, Mateos MV, Martinez J, Oriol A, Teruel AI, et al. A phase III PETHEMA/GEM randomized trial of postransplant (ASCT) maintenance in multiple myeloma: Superiority of bortezomib/thalidomide compared with thalidomide and alfa-2b interferon. Blood. 2011 18 Nov;118(21):A3962.
35. Cavo M, Galli M, Pantani L, Di Raimondo F, Crippa C, Offidani M, et al. Bortezomib-thalidomide-dexamethasone incorporated into autotransplantation is associated with more favourable outcomes after relapse in comparison with thalidomide-dexamethasone plus autotransplantation in multiple myeloma. Blood (ASH Annual Meeting Abstracts). 2012;120:Abstract 4210.
36. Gupta A, Pandey A, Sethi S. Bortezomib-induced congestive cardiac failure in a patient with multiple myeloma. Cardiovascular Toxicology. 2012 June;12(2):184-7.
37. Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, De La Guia AL, et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood. 2012 27 Sep;120(13):2581-8.
38. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review [Internet]. In: Velcade (bortezomib) injection. Company: Millennium Pharmaceuticals Inc. Application no.: 021602. Approval date 05/13/2003. Rockville (MD): The Center; 2003 [cited 2013 Feb 6]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21602_Velcade.cfm.
39. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00417911 , Efficacy of bortezomib consolidation after high-dose melphalan with stem cell support in myeloma patients; 2007 Jan 3 [Last updated 2010 Jun 17; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT00417911?term=nct00417911&rank=1.
40. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00461747 , GEM05 for patients with multiple myeloma under 65 years; 2007 Apr 17 [Last updated 2009 Sep 17; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT00461747?term=NCT00461747&rank=1.
41. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library Medicine (US); 2000 Feb 29-. Identifier NCT01208766. A randomized phase III study to compare bortezomib, melphalan, prednisone (VMP) with high dose melphalan followed by bortezomib, lenalidomide, dexamethasone, (VRD) consolidation and lenalidomide maintenance in patients with newly diagnosed multiple myeloma; 2010 Sep 23 [Last updated 2011 Jun 16]. Available from: http://clinicaltrials.gov/ct2/show/NCT01208766?term=nct01208766&rank=1
42. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00416208 , Consolidation therapy with bortezomib in elderly patients with multiple myeloma; 2006 Dec 22 [Last updated 2012 Nov 16]. Available from: http://clinicaltrials.gov/ct2/show/NCT00416208?term=NCT00416208&rank=1.
43. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01286077 , A Phase 2, multicentre, randomised, open-label, parallel group study to evaluate the effect of velcade on myeloma related bone disease; 2011 Jan 27 [Last updated 2012 Nov 28; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01286077?term=NCT01286077&rank=1.

44. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01191060 , Study comparing conventional dose combination RVD to high-dose treatment with ASCT in the initial myeloma up to 65 years; 2010 Apr 16 [Last updated 2012 Jun 6; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01191060?term=NCT01191060&rank=1.
45. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01109004 , Stem cell transplant with lenalidomide maintenance in patients with multiple myeloma ; 2010 Apr 21 [Last updated 2012 Mar 28; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01109004?term=NCT01109004&rank=1.
46. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01208662 , Randomized trial of lenalidomide, bortezomib, dexamethasone vs high-dose treatment with SCT in MM patients up to age 65; 2010 Sep 23 [Last updated 2011 Jul 20; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01208662?term=NCT01208662&rank=1.
47. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01706666 , Bortezomib based consolidation in multiple myeloma patients completing stem cell transplant; 2012 Oct 11 [cited 212 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01706666?term=NCT01706666&rank=1.
48. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01685814 , Lenalidomide, adriamycin, dexamethasone (RAD) versus lenalidomide, bortezomib, dexamethasone (VRD) for induction in newly diagnosed multiple myeloma followed by response-adapted consolidation and lenalidomide maintenance; 2012 Jun 27 [Last updated 2012 Sep 11; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01685814?term=NCT01685814&rank=1.
49. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00416273 , Bortezomib as consolidation therapy in patients with multiple myeloma age < 60 years; 2006 Dec 22 [Last updated 2012 Nov 14; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT00416273?term=NCT00416273&rank=1.
50. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01539083 , Velcade (bortezomib) consolidation after transplant (VCAT); 2011 Nov 23 [Last updated 2012 Nov 14; cited 2012 Dec 5]. Available from: http://clinicaltrials.gov/ct2/show/NCT01539083?term=NCT01539083&rank=1.