

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF BORTEZOMIB SECOND-LINE IN
THE MANAGEMENT OF MULTIPLE MYELOMA**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre. The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
Alglucerase for Gaucher's disease	July 1997
Taxanes in breast cancer	July 1997
Somatropin for GHD in adults	January 1998
New drugs for Alzheimer's disease	February 1998
Atypical antipsychotics	February 1998
Dornase alfa for cystic fibrosis	July 1998
Topotecan for ovarian cancer	July 1998
Irinotecan for colorectal cancer	July 1998
Interferon alfa for haematological malignancy	July 1998
Antiretroviral therapy	July 1998
Paclitaxel in ovarian cancer	December 1998 (update)
Interferon in MS	May 1999 (update)
Octreotide	July 1999
Drug treatment of obesity	July 1999
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Ribavirin and interferon alfa for chronic hepatitis C	March 2000
Temozolomide for high grade gliomas	May 2000
New drugs for rheumatoid arthritis	May 2000
Verteporfin for age related macular degeneration	November 2000
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Atypical antipsychotics in the management of dementia	June 2001
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec [®] , STI-571), in the management of chronic myeloid leukaemia	November 2001
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Drotrecogin alfa (activated) in the management of severe sepsis	December 2002
An update on newer agents for the treatment of pulmonary hypertension	February 2004
The use of adefovir dipivoxil for the treatment of chronic hepatitis B infection	May 2004
The use of teriparatide in the management of osteoporosis	July 2004
The use of ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
The use of pegvisomant in the management of acromegaly	January 2006
The use of pemetrexed in the management of malignant pleural mesothelioma	February 2006
The adjuvant use of docetaxel or paclitaxel in the management of early stage breast cancer	March 2006
The use of erlotinib in the management of non-small cell lung cancer	March 2006
The use of ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
The use of rituximab in combination with CVP chemotherapy for the management of follicular non-Hodgkin's lymphoma	March 2006

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SUMMARY

- **Multiple myeloma (MM) is an inherently progressive malignancy of the plasma cells. It is characterised by periods of relapse and remission. Median survival from diagnosis is four years.**
- **Bortezomib is licensed as mono-therapy for the treatment of progressive MM in patients who have received at least one prior therapy and who have already undergone, or are unsuitable for, bone marrow transplantation.**
- **Bortezomib in combination with dexamethasone increases the median time to disease progression compared to dexamethasone alone, from 106 days to 189 days. In a sub-group of patients receiving treatment as second-line therapy, the median time to disease progression was 212 days compared to 169 days in the dexamethasone only control group.**
- **The incidence of adverse effects in patients receiving bortezomib is higher than observed in the dexamethasone only control group; this resulted in a greater proportion of patients ceasing treatment due to adverse effects.**
- **Bortezomib should be considered as a second-line therapy for relapsed or refractory MM only in patients for whom mono-therapy with high-dose oral steroids would otherwise be the only alternative. When deciding whether to proceed with bortezomib therapy consideration should be given to the drug's adverse effect profile and the likely benefits of treatment.**
- **Due to the administration requirements of the drug and its specialist use, prescribing should be restricted to those who are specialists in the treatment of myeloma. It is likely that treatment and monitoring will remain entirely within secondary care.**
- **The incidence of MM in the UK is estimated at 6.1 per 100,000 population per year. Using the treatment and demographical parameters as per the principle study, which assumes that 38% of patients receive the drug at first relapse and each patient receives a mean of 22 doses, the equivalent cost per 100,000 population per year would be £33,545.**
- **Patients are being actively recruited to numerous studies investigating the use of bortezomib in combination with other agents as first-line treatment and at subsequent stages of the disease.**

BACKGROUND

Myeloma, or multiple myeloma (MM), is a malignant disorder of plasma cells characterised by an excess of abnormal plasma cells within the bone marrow, lytic bone lesions and paraproteins in the serum and urine.¹ The 'multiple' descriptor stems from its tendency to occur in many parts of the skeleton simultaneously.² The condition is associated with myelosuppression, proteinaemia, proteinuria and lytic bone lesions.³ Early symptoms associated with the condition may therefore include recurrent or persistent infections, fatigue, anaemia, renal impairment, back pain and bone pain or a combination of these.⁴ Destruction of bone produces hypercalcaemia associated with thirst, nausea and kidney destruction.⁵ Some patients may develop neurological problems such as spinal cord compression.^{3,5} The disease can remain asymptomatic for many years after which multiple periods of remission and relapse can occur.³ In the symptomatic phase the most common presenting complaint is bone pain.³ MM is not curable but chemotherapy can often induce temporary remission.⁵ Typically, patients experience repeated periods of relapse, treatment and remission over the course of some years until the disease can no longer be controlled.⁵ Treatment improves the clinical situation in about 75% of patients.³

Approximately 3600 new cases of MM are diagnosed in the UK each year. This translates to an incidence of approximately 6 per 100,000 per year for men and 4 per 100,000 per year for women.² The median age at diagnosis is between 60 and 65 years.⁴ With modern treatments the median survival is approximately 4 years¹ and the 5-year survival rate is approximately 20%.⁵

The most frequently prescribed first-line treatment of MM is a combination of melphalan and prednisolone (MP).³ There are several established alternative drug regimens for MM treatment, for example vincristine, doxorubicin and dexamethasone (VAD).³ High-dose chemotherapy with stem cell rescue is increasingly used for those who can tolerate it.⁵ Bone marrow transplants may be considered for some patients, but are only suitable for younger patients (age \leq 55 years) with a very good donor genotypic match.³

In the past three to four years the evidence of the efficacy of thalidomide in relapsed disease has led to its general use, alone or with dexamethasone, as initial treatment for relapsed disease.⁶ Thalidomide alone, in combination with dexamethasone or with dexamethasone plus cyclophosphamide is also increasingly used in primary refractory disease.⁶ Thalidomide has activity both as a single agent and in combination with other therapies in newly diagnosed and advanced myeloma. The use of thalidomide is a major advance in the clinical management of myeloma⁷ although it is currently only recommended in newly diagnosed patients in the context of a clinical trial.⁶

Interferon alfa-2b is sometimes used as maintenance therapy in patients who have achieved objective remission (defined as more than 50% reduction in myeloma protein) following initial induction chemotherapy.⁸

Whole body radiotherapy or sequential hemi-body radiation is occasionally used as part of an overall strategy for high-dose therapy with transplant and/or in the management of relapsing refractory disease. In patients with refractory disease, sequential hemi-body radiation can be used temporarily for control.³

Otherwise, radiotherapy is targeted to specific severe local episodes such as bone destruction, severe pain and/or pressure on nerves or the spinal cord.³

Due to the nature of the disease virtually all patients will relapse after initial treatment;^{4,6} typically this will occur after one to three years.³

The first strategy for relapse occurring more than six months after the initial treatment is to re-utilise the therapy which produced the remission in the first place. It is estimated that approximately 50% of patients will achieve a second remission with the same therapy that induced their first, and the prognosis is even better if the period of remission was greater than one year. If the initial remission has lasted less than six months then an alternative therapy will usually be required; this is also true if relapse has occurred following a second or third use of the original induction therapy.³

The use of dexamethasone as a single agent is useful in achieving overall control of the disease; it has particular benefits to the patient due to a convenient route of administration (oral) and lack of distressing side effects such as hair loss and myelosuppression.³

Bortezomib is a novel cancer treatment that acts by inhibiting the functions of the intracellular proteasome structure. Proteasomes are involved in protein degradation and transmission of intracellular signals. Their inhibition leads to cell cycle arrest and eventually apoptosis.^{9, 10} In 2004, bortezomib was approved by the European Commission for use in patients who have already received at least two prior therapies for their MM and have demonstrated disease progression on the last therapy.¹⁰ In 2005 its licensed indications were amended and it is now licensed as mono-therapy for the treatment of progressive MM in patients who have received at least one prior therapy and who have already undergone, or are unsuitable for, bone marrow transplantation.⁹

EFFICACY

Three key trials pertaining to the use of bortezomib in MM have been published. The CREST¹¹ and SUMMIT¹² trials were open-label, non-randomised, phase II trials with 54 and 202 patients respectively. The Assessment of Proteasome inhibition for EXtending remissions (APEX)¹³ trial was a randomised, open-label, phase III multi-centre trial with a control treatment arm.

Only the APEX trial has investigated the use of bortezomib as second-line therapy in the treatment of MM although this was not a specific entry criterion. The APEX trial recruited 669 patients throughout North America, Europe & Israel, comparing the use of bortezomib as mono-therapy to high-dose oral dexamethasone, also as mono-therapy, in patients who had relapsed on at least one and no more than three previous treatments. The primary outcome measure was the time to disease progression (TTP).

Secondary endpoints included; overall survival, survival at one year, and response rate (response defined as complete or partial response) amongst other factors.

The patient populations in each group were well matched with respect to many demographic and disease characteristics and analyses although it is worth noting that the number of protocol violations was high (140 patients, 21%).¹⁴

The two treatment arms were randomly allocated but stratified, amongst other factors, with respect to the number of previous treatments (1 or >1). The trial included 251 patients who had received only one prior line of therapy (132 in the bortezomib group and 119 in the dexamethasone group). Of potential importance is the 8% (28/336) of patients in the dexamethasone group whose MM was subsequently found to have been resistant to the drug during earlier cycles.^{13, 14}

The study did not run to its intended conclusion due to the results of an interim analysis at approximately the half-way point indicating that the observed benefits in TTP and overall survival in the bortezomib group were significantly greater than the dexamethasone group.¹³ This impeded the analysis of two key patient-orientated outcomes, overall survival and one-year survival, due to a shorter follow-up period leading to censoring of survival data.^{14, 15}

The results showed that median TTP in the bortezomib group was 189 days and 106 days in the dexamethasone group (hazard ratio, HR, for the bortezomib group, 0.55; $p < 0.001$).¹³ The results for the sub-group with only one previous treatment demonstrated a median TTP in the bortezomib group of 212 days compared to the dexamethasone group with 169 days (HR for the bortezomib group 0.56; $p = 0.002$),^{9, 13} representing an absolute benefit of 43 days, or 25%.

The one-year survival data were heavily censored and are based on only 20% of the initial population. However, the results favour bortezomib, with a one-year survival rate of 80% compared to 66% in the dexamethasone group (HR for the bortezomib group, 0.57; $p = 0.001$).¹³ The one-year survival rates for the sub-group of patients receiving bortezomib as second-line therapy were 89% and 72% respectively ($p = 0.001$);¹⁶ the actual number of patients that this data relates to is likely to be very small (estimate 55 patients).

Response to treatment rates were also reported, and were consistently in favour of bortezomib. Defining the response rate as the sum of complete and partial responses using the European Blood and Marrow Transplant Group criteria, the results showed a response rate to bortezomib of 38% compared to a response rate of 18% in the dexamethasone group ($p < 0.001$). In the sub-group of patients whom had received only one prior therapy, the response rate in the bortezomib group was 45% compared to 26% in the dexamethasone group ($p = 0.004$).¹³

Although patient quality of life is not reported in the original publication of the APEX trial, data in abstract and poster format only has been made available.¹⁷ In the primary end-point of global health status from baseline and then every six weeks until 42 weeks or removal from study, patients in the bortezomib group reported significantly greater scores than patients in the dexamethasone only group. The trend was for decreasing scores in both groups over time.

ADVERSE EFFECTS

A comprehensive profile of adverse effects is now emerging primarily from the three main trials involving over 500 drug recipients.^{11, 12, 13} Due to the nature of the condition being treated, information is only available on the short-term effects of bortezomib, so comment cannot be made on any likely effects in patients who survive over the longer term.

The most common effects observed in the bortezomib group within the APEX trial were diarrhoea, nausea (57% each), fatigue, constipation (42% each), peripheral neuropathy (36%), vomiting, pyrexia, thrombocytopenia (35% each), anaemia, headache (26% each), anorexia (23%), cough, and paraesthesia (21% each). The type and frequency of adverse effects are similar to those observed in the SUMMIT and CREST trials. The most common effects observed in the dexamethasone only group were fatigue (32%), insomnia (27%), anaemia (22%), diarrhoea (21%), dyspnoea (17%) and pyrexia (16%).

The prevalence of grade 3 or 4 effects in the APEX bortezomib group was significantly greater than those observed in the dexamethasone treatment group (61% & 14% vs. 44% & 16% respectively).¹³ The most common grade 3 or 4 adverse effects observed in the bortezomib treatment group were thrombocytopenia (30%), neutropenia (14%), anaemia (10%), peripheral neuropathy (8%) and diarrhoea (7%). Again, the type and frequency of grade 3 or 4 adverse effects were broadly similar to those observed in the SUMMIT and CREST trials.

DOSAGE, ADMINISTRATION AND COST

Bortezomib (Velcade[®], Janssen-Cilag Ltd) should be administered as an intravenous bolus injection via a central or peripheral catheter.⁹ The licensed dosage regimen for MM stated in the summary of product characteristics (SPC) involves a 21-day cycle consisting of a twice weekly injection for two weeks at a dose of 1.3mg/m² body surface area (BSA) followed by a ten day rest period.⁹ The cost per 3.5mg vial is £762.38¹⁸ therefore the cost per cycle is £3,050. The Velcade[®] SPC states a maximum of eight treatment cycles per patient;^{9, 16} in the APEX study 29% of patients completed at least eight cycles (i.e. 32 doses),¹³ which, if the BSA is assumed to be 1.75m², equates to a cost of £24,396. The mean number of bortezomib doses administered to patients in the APEX trial was 22,¹⁴ equating to a cost of **£16,772** per patient, assuming a BSA of 1.75m². The mean number of treatments received by patients in whom bortezomib was being used second-line was not stated.

The incidence of MM in the UK is 6.1 per 100,000 population per year.¹⁹ The proportion of patients in the APEX trial who were treated at first relapse (i.e. second-line treatment) was 38%,¹³ this equates to a treatment rate of 2 per 100,000 per year. Using this incidence rate and assuming that the average number of treatments administered is 22, the equivalent cost per 100,000 population per year would be £33,545.

Using the one-year survival rates from the APEX trial of 80% and 66% for second-line treatment with bortezomib or high-dose dexamethasone respectively; seven patients would need to be treated with bortezomib as second-line therapy as opposed to high-dose dexamethasone to ensure one extra survivor at one year after commencing treatment. Therefore the crude cost per life year gained is £117,404.

All prices stated exclude value added tax and do not take into consideration any purchase discount that may be negotiated.

PLACE IN TREATMENT

The APEX trial could be criticised firstly because of the use of dexamethasone as the comparator treatment. Although this is often used as monotherapy in North America and Europe,¹³ this would not be standard practice in the UK, where patients are more likely to be re-challenged with their initial treatment.^{4, 6} Dexamethasone has been used as a comparator treatment in several other large studies of newly diagnosed myeloma,¹³ however the particular dose regimen used in the APEX trial is of a lower intensity than used in these other trials and in practice^{15, 20} which may serve to exaggerate potential benefits.

Secondly, the lack of statistically sound patient-orientated outcomes (survival, one-year survival, quality of life scores) for the second-line treatment sub-group is a disadvantage. The observed disease-orientated outcomes, such as TTP, may not translate to real benefits for patients, although this is considered to be a suitable endpoint when assessing the effectiveness of multiple myeloma treatments in the context of a clinical trial.^{11, 12, 20} There is no mention of quality of life scores for either treatment group in the APEX trial. Data provided by Ortho Biotech¹⁷ indicate that bortezomib patients' health-related quality of life deteriorates at a slower rate than patients on high-dose dexamethasone.

Thirdly, the clinical studies indicate that while bortezomib is undoubtedly of benefit to some patients it does also cause potentially serious side effects and may be poorly tolerated; 37% of all patients commenced on bortezomib therapy eventually discontinued treatment early due to adverse events compared to 29% in the dexamethasone arm.¹³

There are no direct comparisons providing evidence that bortezomib is more effective than other second-line cytotoxic regimens in the treatment of MM although there is some evidence that bortezomib will improve the medium-term survival of patients.^{13, 16}

Bortezomib should be considered as a second-line choice of therapy in relapsed or refractory multiple myeloma in patients for whom mono-therapy with high dose oral steroids would otherwise be the only alternative. When deciding whether to proceed with bortezomib therapy, consideration should be given to the drug's side effect profile and the likely benefits of treatment.

ARRANGEMENTS FOR PRESCRIBING

Due to the administration requirements of the drug and its specialist use, prescribing should be restricted to those who are specialists in the treatment of myeloma. It is likely that treatment and monitoring will remain entirely within secondary care.

FUTURE DEVELOPMENTS

Current research involving bortezomib is on-going in numerous studies investigating its use as first-line therapy and in combination with other cytotoxic drugs at various stages of the disease and treatment plan.²¹

The National Institute for Health and Clinical Excellence is planning to review the use of bortezomib in multiple myeloma as part of the single technology appraisal process, with publication expected in September 2006.²²

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REFERENCES

- 1 Morgan GJ, Davies FE, Cavenagh J, Jackson GH. British Committee for Standards in Haematology position statement on the use of bortezomib in multiple myeloma. British Society for Haematology June 2005.
- 2 CancerHelp UK. www.cancerhelp.org.uk. Accessed 28/10/05.
- 3 Durie BGM. Multiple myeloma – a concise review of the disease and treatment options. International Myeloma Foundation (UK) Ltd 2000, Edinburgh.
- 4 Guideline. Diagnosis and management of multiple myeloma. British Journal of Haematology 2001;115:522-40.
- 5 Improving outcomes in haematological cancers – the manual. National Institute for Clinical Excellence 2003, London.
- 6 Guidelines on the diagnosis and management of multiple myeloma. UK Myeloma Forum & The Nordic Myeloma Study Group 2005.
- 7 Guideline. Thalidomide in multiple myeloma: current status and future prospects. British Journal of Haematology 2003;120:18-26.
- 8 Schering-Plough Ltd. IntronA[®] 18, 30 or 60 million IU solution for injection, multidose pen. Summary of product characteristics. <http://emc.medicines.org.uk/>. Accessed 5/10/05.
- 9 Janssen-Cilag Ltd. Velcade[®] 3.5mg powder for solution for injection. Summary of product characteristics. <http://emc.medicines.org.uk/>. Accessed 5/10/05.
- 10 Janssen Pharmaceutica N.V. www.velcade.info. Accessed 26/10/05.
- 11 Jagannath S, Barlogie B, Berenson J et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. British Journal of Haematology 2004;127:165-72.
- 12 Richardson PG, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. New England Journal of Medicine 2003;348:2609-17.
- 13 Richardson PG, Sonneveld P, Schuster MW et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. New England Journal of Medicine 2005;352:2487-98.
- 14 Scientific discussion: Velcade (EMA/H/C/539/II/05). European Medicines Evaluation Agency 2005.
- 15 Dispenzieri A. Bortezomib for myeloma – much ado about something (editorial). New England Journal of Medicine 2005;352:2546-8.
- 16 Correspondence from Janssen-Cilag Ltd. Medical Information department 12/10/05.
- 17 Lee SJ, Richardson PG, Sonneveld P et al. Health-related quality of life of patients with relapsed multiple myeloma receiving bortezomib versus high-dose dexamethasone in the APEX trial. Poster presented at the 10th Congress of the European Haematology Association June 2005.
- 18 eMIMS. www.emims.net. Accessed 20/03/06.
- 19 Cancer Research UK. www.cancerresearchuk.org. Accessed 13/12/05.
- 20 Rajkumar SV, Blood E, Vesole D et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. Journal of Clinical Oncology 2006;24:431-6.
- 21 US National Institutes of Health. www.clinicaltrials.gov. Accessed 27/10/05.
- 22 National Institute for Health and Clinical Excellence. www.nice.org.uk/page.aspx?o=282557. Accessed 13/03/06.

APPENDICES

APPENDIX 1. SUMMARY OF TRIALS

Key: MC – multi-centre; OL – open label; RT – randomised trial; PII – phase 2; PIII – phase 3; NR – not randomised; SA – single agent; AC – active control; CO – cross over; BSA – body surface area; 90%CI – 90% confidence interval; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ORR – overall response rate; CR – complete response; MR – minimal response; PR – partial response; TTP – time to disease progression.

Summary of main clinical trials

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
APEX, Richardson ¹³ PG et al.	OL, MC, RT, AC, CO, PIII	Bortezomib 1.3mg/m ² BSA, 4 doses per 3 week cycle, eight cycles, followed by 4 doses per 5 week cycle, three cycles; or dexamethasone 40mg daily, 12 days per 5 week cycle, four cycles, followed by 4 days per 4 week cycle, five cycles. Cross over to receive bortezomib permitted after disease progression.	669. (333 in the bortezomib group, 336 in the dexamethasone group)	Measurable progressive disease after 1 to 3 previous treatments, Karnofsky score \geq 60, platelets \geq 50,000/mm ³ , haemoglobin \geq 7.5g/dL, neutrophil \geq 750/mm ³ , creatinine clearance \geq 20ml/min	Previous exposure to bortezomib, disease refractory to high-dose dexamethasone, peripheral neuropathy \geq grade 2, significant co-morbidity unrelated to myeloma. Note: 21% of all patients were subsequently found to be in violation of the selection criteria.	TTP defined using the European Blood and Marrow Transplant Group criteria.	TTP = 189 days in the bortezomib group and 106 days in the dexamethasone group. A planned sub-group analysis was performed on patients who had received only 1 prior therapy; TTP = 212 days in the bortezomib group and 169 days in the dexamethasone group.	Most common adverse effects in patients randomised to the bortezomib group; diarrhoea, nausea (57% each), constipation, fatigue (42% each), peripheral neuropathy (36%), vomiting, pyrexia, thrombocytopenia (35% each), anaemia, headache (26% each). Most common grade 3 and 4 effects in same group; thrombocytopenia (30%), neutropenia (14%), anaemia (10%), peripheral neuropathy (8%). 75% overall incidence of grade 3 and 4 effects.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
SUMMIT, Richardson PG et al. ¹²	MC, NR, OL, PII	Bortezomib 1.3mg/m ² BSA, twice weekly for 2 weeks + 1 week rest = 1 cycle. Maximum 8 cycles. Oral dexamethasone was added if suboptimal response.	202	Relapsed myeloma refractory to most recent therapy. Karnofsky performance status score of ≥ 60 . Serum AST & ALT < 3 x upper limit of normal range. Serum bilirubin < 2 x upper limit of normal range. Creatinine clearance > 10ml/min. Platelet count $\geq 30,000/\text{mm}^3$. Haemoglobin $\geq 8\text{g/dL}$. Neutrophil count $\geq 500/\text{mm}^3$. Age ≥ 18 years. Life expectancy > 3 months.	Pregnancy.	ORR to bortezomib alone, defined as CR+PR+MR.	193 patients received at least one cycle of bortezomib and made up the response population. CR in 9% PR in 18% MR in 7% No change in 24% ORR of 35%.	Most common effects were nausea (55%), diarrhoea (44%), fatigue (41%), thrombocytopenia (40%), peripheral neuropathy (31%), vomiting (27%), anorexia (25%), pyrexia (22%), anaemia (21%). Most common grade 3 or 4 effects were thrombocytopenia (31%), neutropenia (14%), peripheral neuropathy, fatigue (12% each), anaemia, vomiting (8% each)
CREST, Jagannath S et al. ¹¹	OL, SA, RT, PII, MC	Bortezomib; 1.0mg/m ² or 1.3mg/m ² BSA, twice weekly for 2 weeks + 1 weeks rest = 1 cycle; maximum eight cycles. Oral dexamethasone was permitted in patients with progressive or stable disease after 2 or 4 cycles respectively.	Fifty-four, 28 in the 1mg group and 26 in the 1.3mg group.	MM relapsed or refractory to first-line treatment, age ≥ 18 years, Karnofsky performance score $\geq 60\%$, life expectancy > 3 months, AST, ALT $\leq 3 \times$ upper normal limit, bilirubin $\leq 2 \times$ upper normal limit, creatinine clearance $\geq 10\text{ml/min}$, platelet count $\geq 30 \times 10^9/\text{L}$ haemoglobin $\geq 8\text{g/dL}$, neutrophil count $\geq 5 \times 10^8/\text{L}$	Pregnancy.	ORR to bortezomib alone, defined as CR+PR+MR.	Fifty-three patients were estimable with respect to drug response. Patients who had received bortezomib alone: ORR in the 1mg group was 33% (90%CI: 18.6 – 50.9) ORR in the 1.3mg group was 50% (90%CI: 32.7 – 67.3) Patients who had received bortezomib alone or in combination with dexamethasone: ORR in the 1mg group was 44% (90%CI 28.0 – 61.8) ORR in the 1.3mg group was 62% (90%CI 43.6 – 77.4)	Most common effects were fatigue (70%), nausea (54%), diarrhoea (44%), pyrexia (41%), peripheral neuropathy (41%) constipation (37%), arthralgia (35%), insomnia (35%), headache (31%), limb pain (31%), thrombocytopenia (30%). Most common grade 3 or 4 effects were thrombocytopenia (26%), neutropenia (17%), peripheral neuropathy, lymphopenia (11% each).