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The clinical and cost-effectiveness of bortezomib and thalidomide for the first-line treatment of multiple myeloma: a systematic review and economic evaluation

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

J Picot (Research Fellow) developed the research protocol, drafted the background section, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted and edited the final report, and project managed the study; K Cooper (Senior Research Fellow) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation, drafted the report; J Bryant (Principal Research Fellow) developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted the report; AJ Clegg (Professor) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted the report.

Table of contents

APPENDICES

TABLES

FIGURES

EXECUTIVE SUMMARY

Background

Multiple myeloma (MM) is the second most common haematological cancer in the UK, characterised by unregulated plasma cell proliferation. In England and Wales there are approximately 3600 new diagnoses recorded annually and in 2007 most diagnoses were recorded in people aged 75-79 years. Symptoms and clinical features of MM include fatigue, bone pain and/or fracture, anaemia, the presence of M-protein in serum and/or urine, and hypercalcaemia. The aetiology of MM is unknown and malignant cells display a variety of cytogenetic abnormalities. Myeloma is not curable, but can be treated with a combination of supportive measures and chemotherapy. The aim is to extend the duration and quality of survival by alleviating symptoms and achieving disease control whilst minimising the adverse effects of the treatment. Survival of patients from diagnosis can vary from months to over a decade. Factors affecting prognosis include burden of disease, type of cytogenetic abnormality present, patient-related factors such as age and performance status, and treatment response factors.

In England and Wales the choice of first-line treatment depends on a combination of factors. The majority of patients are not able to withstand intensive treatment, such as high-dose chemotherapy with autologous stem-cell transplantation, because of age, specific problems or poor performance status. These patients are therefore offered single agent or combination chemotherapy which is less intensive. Typically combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid (such as prednisolone or dexamethasone). More recent treatment options may also include combination therapies that incorporate drugs such as thalidomide and bortezomib (Velcade®).

Objectives

To assess the clinical and cost-effectiveness of bortezomib or thalidomide in combination chemotherapy regimens with an alkylating agent and a corticosteroid for the first-line treatment of MM.

Methods

Data Sources: Electronic bibliographic databases, including MEDLINE, EMBASE, and The Cochrane Library, were searched from 1999 to 2009 for English language articles. Bibliographies of articles, grey literature sources, and manufacturers' submissions were also

searched. Experts in the field were asked to identify additional published and unpublished references.

Study Selection: Titles and, where available, abstracts were screened for eligibility by two reviewers independently. The inclusion criteria specified in the protocol were applied to the full text of retrieved papers by one reviewer and checked independently by a second reviewer. The inclusion criteria were as follows:

Interventions: Bortezomib in combination with an alkylating agent and a corticosteroid for first-line treatment of MM. Thalidomide in combination with an alkylating agent and a corticosteroid for first-line treatment of MM.

Comparators: (i) The interventions compared with each other or (ii) Melphalan or cyclophosphamide in combination with prednisolone/prednisone or dexamethasone.

Population: People with previously untreated MM who are not candidates for high-dose chemotherapy with stem cell transplantation.

Outcomes: Studies had to report one or more of the following outcomes - overall survival (OS); progression-free survival (PFS); time-to-progression (TTP); response rates; health-related quality of life (HRQoL); cost-effectiveness (such as incremental cost per quality adjusted life year (QALY) gained).

The study types that were eligible for inclusion in the systematic review of clinical effectiveness were:

- randomised controlled trials (RCTs). Good-quality observational studies could be considered if the data from available RCTs were incomplete

and for the systematic review of cost-effectiveness eligible study types were:

- full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved through discussion at each stage.

Data synthesis

Studies were synthesised through a narrative review with full tabulation of the results of all included studies.

Economic Modelling

A cost utility decision analytic model was used to compare the cost-effectiveness estimates of bortezomib in combination with melphalan and prednisolone/prednisone (VMP), thalidomide

in combination with cyclophosphamide and attenuated dexamethasone (CTDa), and thalidomide in combination with melphalan and prednisolone/prednisone (MPT) versus melphalan and prednisolone/prednisone (MP). The model used a survival analysis approach to estimate the OS and PFS for each of the interventions for a patient with newly diagnosed MM. The model consisted of cycles of six weeks in length to be consistent with the cycle lengths used for chemotherapy treatment. The model survival curves were derived using trial data for the duration of trial follow-up and an exponential distribution was used to extrapolate beyond the length of the trial. Second-line treatment costs were included. The perspective of the analysis was that of the National Health Service (NHS) and Personal Social Services (PSS). The model estimated the lifetime costs and benefits of treatment with discount rates of 3.5%. The intervention effect in terms of improvement in OS and PFS was derived from the systematic review of effectiveness. The outcome of the economic evaluation is reported as cost per QALY gained.

Results

Number and quality of studies

A total of 1436 records were screened and 40 references were retrieved for consideration for the systematic review of clinical effectiveness. Five RCTs met the inclusion criteria for the clinical effectiveness systematic review. One RCT evaluated VMP, three evaluated MPT, and one evaluated CTDa. The comparator in all the included trials was MP. Study quality was uncertain for most RCTs because details needed to judge study quality were incompletely reported. All studies stated that the analyses followed intention to treat (ITT) principles but none adequately reported the amount and pattern of data censoring. Two RCTs, one of the MPT versus MP trials and the CTDa versus MP trial, had a maintenance phase with thalidomide which did not meet the inclusion criteria. This meant that some results from these trials were not eligible for inclusion in the systematic review.

Summary of benefits and risks

The evidence from one RCT indicated that combination chemotherapy with VMP was more effective than MP in terms of the primary outcome TTP, and the secondary outcomes of OS and the proportion of participants achieving complete response, or achieving a partial response or better (response outcomes not ITT). Adverse events (AEs) occurred in both trial arms. The use of bortezomib was associated with a statistically significant increase in grade 3 AEs.

Evidence from two RCTs indicated that MPT was more effective than MP in terms of these trials' primary outcome of OS, and the secondary outcome of PFS. Three trials provided

evidence indicating a statistically significant greater proportion of participants receiving MPT achieved complete response. [redacted]

Limited evidence on HRQoL was provided by the single trial of VMP versus MP. This indicated that after the onset of best response, participants treated with VMP had a higher sustained HRQoL improvement rate in 14 of the 15 European Organisation for Research and Treatment of Cancer QoL questionnaire C-30 (EORTC QLQ-C30) scores than those participants receiving therapy with MP.

Summary of cost-effectiveness

The systematic review of published economic evaluations identified five abstracts which did not contain enough information for critical appraisal. The systematic review of QoL studies did not find any generic preference-based QoL studies that assessed QoL in the population of interest. However two studies that used the EORTC QLQ-C30 questionnaire were identified and a mapping algorithm was available to map the EORTC QLQ-C30 to the European Quality of Life – 5 Dimensions (EQ-5D).

Two manufacturers submitted evidence to be considered for this review. Janssen-Cilag, the manufacturer of bortezomib, constructed a survival model that estimated OS and PFS based on treatment effects from a mixed treatment comparison (MTC) of the trials. They included second and third-line treatment. The base-case results from the submission found all treatments to be cost-effective. The incremental cost-effectiveness ratio (ICER) for VMP versus MP is estimated to be £10,498. Furthermore the ICERs of VMP versus MPT and VMP versus CTDa were estimated to be £11,907 and £10,411 respectively.

Celgene, the manufacturer of thalidomide, constructed a Markov model with health states for pre-progression (with or without AEs), post progression and death. They assumed that survival after disease progression was the same irrespective of first-line treatment. Treatment

effects for disease progression were calculated using a random-effects MTC. The base-case results from the submission estimated an ICER of £23,381 per QALY gained for MPT versus MP and £303,845 per QALY for VMP versus MPT.

SHTAC developed an independent survival model. From this independent model, the incremental cost-effectiveness versus MP for MPT, VMP and CTDa was £9,174, £29,837 and £33,216 per QALY gained respectively. However MPT dominated VMP as it was cheaper and more effective.

Sensitivity analyses

The effect of a range of parameter values in the economic model were evaluated in deterministic and probabilistic sensitivity analyses. The model results were robust to changes in the parameter values tested. The model results were most sensitive to changes in the values of the hazard ratios for OS. The PSA estimated the probability of each of the treatments to be cost effective at the £20,000 and £30,000 willingness to pay thresholds. MPT has the highest probability of being cost-effective with probabilities of 0.95 at both the thresholds tested.

Discussion

A systematic review and economic evaluation have been carried out independent of any vested interest but both are associated with some limitations. Only one RCT contributed data on VMP and the published peer-reviewed follow-up data are immature. For MPT OS data from two trials were eligible for inclusion but the doses of thalidomide differed between the trials and the treatment period was not reflective of current UK practice so the generalisability of the findings is uncertain. No evidence on OS or PFS following treatment with CTDa met the inclusion criteria for the systematic review because of the use of thalidomide maintenance therapy for some participants in the single RCT that assessed this intervention.

No head-to-head trials were identified which compared bortezomib in combination with an alkylating agent and a corticosteroid, with thalidomide in combination with an alkylating agent and a corticosteroid.

Assessment of the impact of treatment on quality of life was very limited. Data on HRQoL could only be included from one RCT, the study of VMP versus MP. The single RCT that assessed CTDa versus MP reported HRQoL outcomes but these did not meet the inclusion criteria of the systematic review.

An MTC was not carried out because of doubts about the validity of doing so due to potential differences in participant characteristics, delivery of MP treatment in the comparators arms, and differences in length of follow-up. Furthermore, CTDa could not have been included in such an analysis because the single trial that assessed CTDa included randomisation to maintenance therapy for some participants. The systematic review of clinical effectiveness was therefore unable to determine whether any of three interventions, VMP, MPT or CTDa, was more clinically effective than the others.

The review of QoL found that the only HRQoL studies for the population of interest had used a disease-specific HRQoL measure. Therefore EQ-5D utility estimates used in the SHTAC model had to be derived using a mapping algorithm. The OS outcome from the single trial of CTDa versus MP did not meet the inclusion criteria for the systematic review of clinical effectiveness but CTDa was included in the cost-effectiveness analysis because it is a relevant comparator. As some patients in this trial received thalidomide maintenance therapy and [redacted]

The results from the cost-effectiveness analyses submitted by the two manufacturers and the results from the SHTAC cost-effectiveness model varied considerably. These variations arise because of differences in the modelling approaches taken and the data used to population each model. Costs vary substantially between the analyses. Key contributors to the variation in costs were differences in costs included for subsequent treatments, and differences in assumptions made about the mean number of vials of bortezomib used. Incremental QALY estimates for MPT versus MP also varied widely.

Conclusions

A review of clinical effectiveness has found that VMP and MPT can both be considered more clinically effective than MP for the first-line treatment of MM in people for whom high dose therapy and stem cell transplantation would not be appropriate. [redacted] Cost-effectiveness analysis indicates that MPT has a greater probability of being cost effective than either VMP or CTDa. Results for CTDa however should be treated with caution because this trial included maintenance therapy with thalidomide for some patients and [redacted]

Uncertainties therefore remain and further research is needed. In particular head to head trials of bortezomib containing, and thalidomide containing combination regimens are desirable. These trials should include assessments of patient HRQoL in response to treatment. It is not known whether the choice of second-line treatment or the sequence of treatments affects patient outcomes.

List of abbreviations

ABSCS	Autologous blood stem cell support
AE	Adverse event
CEAC	Cost-effectiveness acceptability curve
CR	Complete response
CRD	Centre for Reviews and Dissemination
CTDa	Cyclophosphamide, thalidomide and attenuated dexamethasone
CTRU	Clinical Trials Research Unit
DS	Durie-Salmon staging system
EBMT	European Group for Blood and Marrow Transplantation
EORTC QLQ C-30	European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30
EQ-5D	European quality of life 5-Dimensions
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto **(**Italian Group for Adult Hematologic Diseases)
HDD	High dose dexamethasone
HDM	High dose melphalan
HDT	High-dose chemotherapy
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IFM	Intergroup Francophone du Myelome
IQR	Inter-quartile range
ISS	International staging system
ITT	Intention to treat
KM	Kaplan-Meier
MM	Multiple myeloma
MMIX	Myeloma IX
MP	Melphalan + prednisolone/prednisone
MPT	MP + Thalidomide
MR	Minimal response
MRC	Medical Research Council
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OLS	Ordinary Least Squares
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PBPCT	Peripheral blood progenitor cell transplantation
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSCT	peripheral stem cell transplantation
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratios

SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SPC	Summary of product characteristics
SUHT	Southampton University Hospitals Trust
TAR	Technology Assessment Report
TTP	Time-to-progression
VAD	Vincristine, doxorubicin, and dexamethasone
VAD/VAMP	Vincristine, adriamycin and dexamethasone / vincristine, adriamycin and methyl prednisone
VAS	Visual analogue scale
VMCP-IFN∞2b	Vincristine, melphalan, cyclophosphamide, prednisolone, interferon-∞2b
VMP	Bortezomib (Velcade®) + MP

1 BACKGROUND

1.1 Description of underlying health problem

Multiple Myeloma (MM) is a type of cancer. The cancer (myeloma) tends to be located at more than one site where there is bone marrow, such as the pelvis, spine, and ribs, which is why it is known as multiple myeloma.[1] MM occurs when a plasma cell begins to proliferate in an unregulated way. Plasma cells are a specialised component of the bone marrow and immune system and they normally produce specific antibodies to fight infection. In MM the myeloma cells produce large quantities of one type of abnormal antibody, monoclonal immunoglobulin protein (M-protein).[2] As the abnormal myeloma cells build in number, the normal functions of bone marrow become impaired to varying degrees of severity because the abnormal myeloma cells may disrupt the function of normal cells, and because the space available for normal bone marrow may be reduced.

In the early stages of MM there may not be any symptoms or a range of symptoms may be present that are not specific to MM such as fatigue, weight loss, and increased infections. A common presenting symptom of MM is bone pain, and/or bone fracture due to lytic bone lesions. Lytic bone lesions are a typical feature of MM and are caused because the malignant plasma cells impair normal bone repair functions. MM cells both produce and influence chemokines and cytokines which causes bone resorption to become uncoupled from bone formation such that resorption predominates.[3]

The most common finding on clinical investigation is anaemia.[4] This occurs because the presence of proliferating myeloma cells in the bone marrow negatively impact on the ability of the bone marrow to produce red blood cells leading to a reduction in red blood cells in the circulation which contributes to the symptom of fatigue. Likewise, circulating numbers of other cells produced in the bone marrow are also reduced. The reduction in normal white blood cells, and the antibodies these produce (hypogammaglobulinemia), leads to an increased risk of infection, whilst the reduction in platelets contributes to easy bruising and other bleeding.

Other common findings on clinical investigation are M-protein which is secreted by the myeloma cells and an excess of calcium in the blood (hypercalcaemia) which occurs as a result of bone destruction.[5] The presence of M-protein in serum may increase blood viscosity which is associated with an increased risk of thrombosis. A high level of serum protein (hyperproteinaemia), M-protein and light chains may also contribute to renal failure. The

aetiology of this is generally multifactorial, and hypercalcaemia is another common contributing factor.

MM is one of a number of lymphoproliferative diseases classified by the World Health Organisation (WHO) International Classification of Diseases 10th revision (ICD-10) as malignant neoplasms of lymphoid, haematopoietic and related tissue.[6] The exact aetiology of MM is unknown but it is clear that the malignant cells arise from a single plasma cell. Therefore research has focussed on gaining an understanding of the chain of events that occur between hematopoietic stem cells giving rise to B lymphocytes in the bone marrow, and these B-cells subsequently differentiating to form plasma cells.[7,8]

Normally plasma cells would contain a pair of each of the 22 autosomal (non-sex) chromosomes. Myeloma cells however display a variety of genetic abnormalities. Common abnormalities of MM cells include aneuploidy (an abnormal number of chromosomes), and translocations (exchange of material between two different chromosomes). When aneuploidy is present, monosomies (one copy of a chromosome) are more common than trisomies (three copies of a chromosome). One of the most common monosomies is the loss of one copy of chromosome 13 which is associated with a shorter survival and lower response rate to treatment.[9,10] Of the translocations t(11;14)(q13;q32) and t(4:14)(p16.3;q32) are the most common. The former is associated with improved survival whereas the latter is an indication of an unfavourable prognosis.[9,10] The genetic abnormalities underlying cases of MM can be identified by cytogenetic techniques such as conventional karyotype analysis and fluorescence in situ hybridisation.

Prognosis

Myeloma is not curable, but can be treated with a combination of supportive measures and chemotherapy to improve survival and quality of life. A range of factors affect prognosis. These include factors related to burden of disease (e.g. $beta_2$-microglobulin (β2-microglobulin)); characteristics of the myeloma cells biology (e.g. the type of cytogenetic abnormality present); the microenvironment surrounding the myeloma cells (e.g. bone marrow microvessel density); patient-related factors (e.g. age and performance status); and treatment response factors (e.g. whether complete response is achieved with initial therapy).[5] Because of the number of factors that affect prognosis survival of patients from the point of diagnosis varies from months to over a decade.[4] In the UK and Ireland median survival increased from around two years in the 1980s and early 1990s to around four years in the late 1990s.[11] There is evidence from some cohorts of patients that novel therapies can extend median survival time to eight years.[12]

Epidemiology

MM is the second most common haematological cancer after lymphoma in the UK. In 2007 there were 3357 new diagnoses of MM in England,[13] with the highest incidence among those aged 75-79 years (Table 1). In Wales in the three years from 2004 to 2006 an average of 252 new MM diagnoses were recorded.[14] MM is rare before the age of 40 years. The average incidence rates were higher in men than in women, and higher for both sexes in Wales compared to England (Table 2). There are ethnic differences in incidence rates which have been observed in data from the USA; in black people (African American and other black people, but not Hispanic people) the incidence of MM is about twice that of white people, whereas in Asian people the incidence is lower than that of white people.[15] The statistical information team at Cancer Research UK has used incidence and mortality data for 2001-2005 to estimate the lifetime risk of developing MM, which is 1 in 148 for men and 1 in 186 for women in the UK.[16] There are currently approximately 10,000-15,000 people living with MM in the UK.[17]

Table 1: Newly diagnosed cases of multiple myeloma in England in 2007[13]

Age group	**Numbers[a]**		**Rates[b]**	
	Males	Females	Males	Females
20-24	2	1	0.1	0.1
25-29	3	4	0.2	0.2
30-34	9	4	0.5	0.2
35-39	11	7	0.6	0.4
40-44	26	17	1.3	0.9
45-49	47	31	2.7	1.7
50-54	96	51	6.3	3.3
55-69	158	91	10.3	5.7
60-64	214	174	15.1	11.7
65-69	239	176	22.2	15.2
70-74	300	217	32.7	20.9
75-79	324	248	44.8	26.8
80-84	256	238	53.2	32.3
85+	173	240	50.2	31.7

[a] New cases of cancer diagnosed in England, 2007, by age group and sex

[b] Rates per 100,000 population of newly diagnosed cases of cancer in England 2007, by age group and sex

Table 2: Age standardised incidence rates[a] of multiple myeloma per 100,000 population[14]

	Men	Women
England	**6.0**	**3.9**
Wales	**6.8**	**4.9**

[a] Rate calculated as three-year averages for 2004-2006 and age standardised using the European standard population.

The risk factors for developing MM are not well defined but there is evidence for involvement of genetic factors because the first degree relatives of people with MM are at greater risk of developing MM and related conditions than the first degree relatives of people without MM.[8,18] Epidemiological studies have looked for evidence of a causal link between a range of potential environmental risk factors and MM, but in general these have not produced consistent results.[4,8]

Diagnosis and Staging

MM is typically diagnosed in secondary care using a combination of tests such as urine tests, blood tests, bone marrow examination, imaging, plain x-ray and/or magnetic resonance imaging results. If necessary further tests can be conducted to find out the stage of disease.[1] There are two systems for staging MM. The Durie-Salmon[19] (DS) staging system which has been in use since 1975 is one of the systems but this is gradually being replaced by an updated system, the International Staging System (ISS).[20] This new system is based on measurement of two serum proteins, β2-microglobulin and albumin (Table 3). A patient with stage 1 disease will not necessarily proceed linearly through disease stages. Stage 3 disease can be reached without a requirement to pass through stage 2 first. It is also noteworthy that staging does not have a significant influence on treatment. If MM is symptomatic, treatment is required irrespective of disease stage.

Table 3: Staging systems for multiple myeloma

Stage	Durie-Salmon[19] criteria	ISS[20] criteria
I	All of the following: ▪ Haemoglobin value > 10g /100ml ▪ Serum calcium value normal (≤ 12 mg/100ml) ▪ Normal bone structure or solitary bone plasmacytoma only ▪ Low M-component production rates: a) IgG value < 5g/100ml; b) IgA value < 3g/100ml; c Urinary light chain M-component (Bence-Jones protein) on electrophoresis <4g/24 hours	▪ Serum β2-microglobulin < 3.5 mg/L ▪ Serum albumin ≥ 3.5g/dL
II	Fitting neither Stage I nor Stage III	Not stage I or III: ▪ Serum β2-microglobulin < 3.5 mg/L but Serum albumin <3.5g/dL ▪ or ▪ Serum β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.
III	One or more of the following: ▪ Haemoglobin value < 8.5g /100ml ▪ Serum calcium value > 12 mg/100ml) ▪ Advanced lytic bone lesions ▪ High M-component production rates: a) IgG value >7g/100ml; b) IgA value > 5g/100ml; c Urinary light chain M-component (Bence-Jones protein) on electrophoesis > 12 g/24 hours	▪ Serum β2-microglobulin ≥ 5.5 mg/L
Subgroup for each stage	**A** if relatively normal renal function (serum creatinine value < 2.0 mg/100ml) **B** if abnormal renal function (serum creatinine value ≥ 2.0 mg/100ml.	

1.2 Current service provision

The aim of treatment for MM is to extend the duration and quality of survival by alleviating symptoms and achieving disease control whilst minimising the adverse effects of the treatment.[21] First-line treatment aims to achieve a period of stable disease (plateau phase) for as long as possible, prolonging survival and maximising quality of life. In England and Wales the choice of first-line treatment depends on a combination of factors including age, comorbidity, social factors and performance status of the patient. High-dose chemotherapy (HDT) with autologous stem-cell transplantation (SCT) will be offered if appropriate for the

patient. However, the British Society for Haematology (BSH) guidelines on the diagnosis and management of MM 2005[22] state that (page 428) "Although high-dose is recommended where possible, the majority of patients will not be able to receive such therapy because of age, specific problems or poor performance status." For those patients who are not able to withstand such an intensive type of treatment, single agent or combination chemotherapy which is less intensive may be offered as a first-line treatment. Patients eligible for HDT will get initial chemotherapy to reduce disease burden before transplant.

Typically combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid (such as prednisolone or dexamethasone). The treatment recommended by the 2005 guidelines for patients unable to receive intensive treatment was either melphalan or cyclophosphamide given either with or without prednisolone.[22] More recent treatment options may also include drugs such as thalidomide[23-25] and bortezomib.[26] Such drugs are being investigated in ongoing clinical trials, such as the Medical Research Council (MRC) funded Myeloma IX study[27] which has compared thalidomide in combination with cyclophosphamide and dexamethasone (CTDa) against the standard drug combination of melphalan with prednisolone (MP).

The BSH guideline on the diagnosis and management of MM is being revised and updated. The draft of these revised guidelines[28] contains a recommendation that for older and/or less fit patients in whom high-dose therapy is not planned, the initial therapy should consist of either a thalidomide-containing regimen in combination with an alkylating agent and steroid (such as thalidomide in combination with MP (MPT) or CTDa) or bortezomib in combination with melphalan and prednisolone (VMP). The draft revised guideline indicates that the choice of first-line therapy should take into account patient preference, comorbidities and the toxicity profile of the treatments.[28]

After first-line treatment most patients will show a response. Response is usually assessed based on changes in serum levels of M-protein and/or urinary light chain excretion and ranges from partial to complete remission, but almost all patients will eventually relapse. A minority of patients will have disease that proves resistant to primary treatment.

In addition to chemotherapy patients also require concomitant supportive therapy to control the symptoms of the disease, including bisphosphonates to treat bone disease, erythropoietin to treat anaemia, antibiotics to treat infections and various types of pain medication. Prophylaxis against thrombosis is recommended in the thalidomide summary of product characteristics (SPC) for the first five months that patients receive thalidomide.[29] In UK this

recommendation for prophylaxis against thrombosis is followed, but there is less agreement about whether to continue with prophylaxis for the entire duration of thalidomide therapy. Therefore clinical practice is likely to vary. Side effects of treatment may result in discontinuation or change of chemotherapy treatment.

UK clinical experts have indicated that the most common combination therapy used as a first-line treatment for patients who are not able to withstand high-dose therapy is CTDa. The second most common therapy is MPT, with the ratio of patients on CTDa to those on MPT being approximately 2:1 although in some areas the ratio may be nearer 3:1. Tolerance to thalidomide limits it use in some patients, and occurrence of peripheral neuropathy limits the duration of treatment in some patients (clinical opinion expert advisor). VMP is not widely used as a first-line treatment, but may be used in the subgroup of patients who have renal impairment or failure at presentation. Use of MP is declining, but this is still used in patients who cannot tolerate thalidomide or where the use of thalidomide is contraindicated (clinical opinion expert advisor).

As noted in section 1.1 there is some evidence that myeloma characterised by a high risk cytogenetic abnormality can demonstrate a poor response to conventional treatment. However, whilst there is interest in the use of cytogenetic data as a prognostic indicator, the incorporation of cytogenetic data into decisions about treatment choice is not currently supported in the UK.[22,28]

When patients relapse after first-line treatment most will receive a second-line treatment. The choice of second-line treatment is individualised to the patient and in theory a patient could receive the same therapy that they received as a first-line treatment, particularly if this had been effective and the remission had lasted a long time. However, in current UK practice many patients will receive bortezomib monotherapy as a second-line treatment because, as noted below, this has been recommended by the National Institute for Health and Clinical Excellence (NICE). Similarly when patients relapse after second-line treatment the treatment recommended by NICE for this patient group is lenalidomide.

In addition to the British Society for Haematology guidelines on the diagnosis and management of MM,[22] two NICE technology appraisals have been completed for MM. NICE has previously recommended bortezomib monotherapy for relapsed MM as a possible treatment for progressive MM for people (TA129[30]):

- whose MM has relapsed for the first time after having one treatment, and
- who have had a SCT, or who are unsuitable to receive one.

NICE has also recommended lenalidomide (a structural derivative of thalidomide) when used in combination with dexamethasone as a possible treatment for MM when people have already received at least two other treatments (TA 171[31]). Neither of these NICE appraisals considered first-line therapy for MM.

One technology appraisal is in development; denosumab for the treatment of bone metastases from solid tumours and MM, but the scope of this appraisal is not available at the time of writing (January 2010) and the expected date of issue is not until January 2012.

NICE has also published Guidance on Cancer Services – Improving Outcomes in Haematological Cancers – The Manual.[32] This document covers all haematological cancers, including MM, and makes recommendations for service delivery and organisation. Some information about current service costs are included but these relate to the haematological cancer service as a whole.

1.3 Description of technology under assessment

Two interventions are being considered in this assessment,[21] bortezomib in combination therapy with an alkylating agent and a corticosteroid, and thalidomide in combination therapy with an alkylating agent and a corticosteroid. The scope of this review allows for the inclusion of bortezomib or thalidomide when used in combination with any alkylating agent and any corticosteroid. This may therefore include drug combinations that are not covered by the licences for bortezomib and thalidomide; for example CTDa.

Place of the interventions in the treatment pathway

In this assessment bortezomib and thalidomide are being considered for use in combination therapy with an alkylating agent and a corticosteroid as a first-line treatment for MM in patients who are not eligible for HDT with autologous SCT.

Bortezomib

Bortezomib (Velcade®, manufacturer Janssen-Cilag) is a proteasome inhibitor which is specific for the 26S proteasome of mammalian cells and it has been designed to inhibit the chymotrypsin-like activity of this proteasome. Inhibition of the proteasome by bortezomib affects cancer cells in a number of ways resulting in cell cycle arrest and apoptosis which causes a reduction in tumour growth.[33]

Bortezomib is given by injection. It was initially granted a marketing authorisation in the European Union in 2004 as a therapy for patients with MM who had received at least two prior lines of treatment. Subsequently, in 2005, the indication was extended to enable treatment, earlier in the course of the disease, for relapsed MM in patients who have progressed after receiving at least one previous line of treatment.[34]

In 2008 the marketing authorisation for bortezomib was extended further for the following indication "Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant" (page 2).[34]

The SPC for bortezomib[33] recommends nine 6-week treatment cycles for combined therapy with VMP. During these treatment cycles bortezomib is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter at a dose of 1.3 mg/m^2 body surface area, followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. In the first four cycles of treatment bortezomib is administered twice weekly. For cycles 5-9, bortezomib is administered once weekly. Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both administered orally on days 1, 2, 3 and 4 of the first week of each cycle. The dose and total number of cycles may change depending on the patient's response to treatment and on the occurrence of certain side effects. Because the licence for bortezomib does not cover its use in combination with agents other than melphalan and prednisone the SPC does not provide dosage information for any other alkylating agents or corticosteroids.

The net price for a 3.5-mg vial of bortezomib is £762.38.[35] Full details of the estimated drug costs associated with the use of bortezomib as a first-line treatment for MM are described within our independent economic evaluation (Section 5.5.3.5).

Thalidomide

Thalidomide is an immunosuppressive agent with antiangiogenesis and other activities that are not fully characterised. It is also a non-barbiturate centrally active hypnotic sedative. Although the precise mechanism of action is unknown and under investigation, the effects of thalidomide are immunomodulatory, anti-inflammatory and anti-neoplastic.[29]

Thalidomide (Thalidomide Celgene, formally known as Thalidomide Pharmion, and now manufactured by Celgene) is taken orally. It was granted a marketing authorisation in 2008 for use in combination with melphalan and prednisone as first-line treatment of patients with

untreated MM, aged≥ 65 years or ineligible for HDT. Because thalidomide is a known human teratogen it must be prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

The SPC for thalidomide[29] recommends an oral dose of 200 mg per day, taken as a single dose at bedtime to reduce the impact of somnolence. However the advisory group for this review has indicated that treatment usually starts with a lower dose which is gradually increased if the patient can tolerate this. In the UK most patients ineligible for HDT and SCT are likely to receive a 100mg dose. A maximum number of 12 cycles of 6 weeks is recommended. Thromboprophylaxis should also be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The dose and total number of cycles may change depending on the patient's response to treatment and on the occurrence of certain side effects.

The SPC does not recommend particular doses or dosing schedule for melphalan and prednisone when administered in combination with thalidomide (licensed indication). Because the licence for thalidomide does not cover its use in combination with agents other than melphalan and prednisone the SPC does not provide dosage information for any other alkylating agents or corticosteroids.

The net price of a 50mg x 28 capsule pack of thalidomide is £298.48.[35] Full details of the estimated drug costs associated with the use of thalidomide as a first-line treatment for MM are described within our independent economic evaluation (Section 5.5.3.5).

2 DEFINITION OF THE DECISION PROBLEM

This section states the key factors that will be addressed by this assessment, and defines the scope of the assessment in terms of these key factors in line with the definitions provided in the NICE scope.[21]

2.1 Decision problem

Two interventions are included within the scope of this assessment. These are bortezomib in combination with an alkylating agent and a corticosteroid, and thalidomide in combination with an alkylating agent and a corticosteroid. In both cases the focus of this assessment is the use of these combination chemotherapies for the first-line treatment of MM.

The population that is being considered by this assessment is people with previously untreated MM, for whom HDT with SCT is not appropriate. If sufficient evidence is available consideration will be given to specific patient subgroups. For example patients with different prognostic factors such as β2-microglobulin, performance status and stage, patients whose MM has different cytogenetic features, and patients that have a comorbidity such as renal impairment. Additionally, if the evidence allows, consideration will be given to the number of treatment cycles and continuation rules for treatment.

The interventions will be assessed when compared to melphalan or cyclophosphamide in combination with prednisolone or dexamethasone. The NICE scope also allows for the interventions to be compared with one another. In this assessment we will include interventions using prednisone as well as prednisolone. Prednisone, which is not used in the UK, is converted into the biologically active steroid prednisolone by the liver.[36] Prednisone and prednisolone are equally effective, they are used in the same manner, and doses are largely equivalent.

The clinical outcomes of interest include overall survival (OS), progression-free survival (PFS), time-to-progression (TTP), response rates, health-related quality of life (HRQoL), and adverse effects (AEs) of treatment. Other outcomes of interest, such as duration of treatment, or second-line treatments received may also be reported. Outcomes for the cost-effectiveness assessment will include direct costs based on estimates of health care resources associated with the interventions as well as consequences of the interventions, such as treatment of AEs.

2.2 Overall aims and objectives of assessment

The aim of this health technology assessment is to systematically assess the evidence on the clinical and cost-effectiveness of bortezomib or thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of MM.[21]

3 METHODS

The *a priori* methods for systematically reviewing the evidence of clinical- and cost-effectiveness are described in the research protocol (Appendix 1), which was sent to our expert advisory group for comment. None of the comments we received identified specific problems with the methods of the review. The methods outlined in the protocol are briefly summarised below.

Search strategy

The search strategies were developed and tested by an experienced information specialist. The strategies were designed to identify studies reporting clinical-effectiveness, cost-effectiveness, HRQoL, resource use and costs, epidemiology and natural history.

The following databases were searched for published studies and ongoing research from 1999 (earliest use of thalidomide for MM[37] and earliest description of bortezomib as a potential cancer therapy[38]) to December 2009: Medline, MEIP, Embase, Web Of Science, BIOSIS, CRD (DARE, HTA, and NHSEED), Cochrane Central register of controlled trials. Bibliographies of articles and grey literature sources were also searched. Reference lists within drug manufacturers' submissions to NICE were searched for any additional studies which met the inclusion criteria. Our expert advisory group was asked to identify additional published and unpublished references. Searches were restricted to English language. Further details, including an example search strategy, can be found in Appendix 2.

Inclusion and Exclusion Criteria

Study design

- For the systematic review of clinical effectiveness randomised controlled trials (RCTs) were eligible for inclusion. In addition, evidence from good-quality observational studies was also eligible for consideration if the data from available RCTs were incomplete (e.g. absence of data on outcomes of interest).
- For the systematic review of cost-effectiveness economic evaluations (such as cost-effectiveness studies, cost utility studies, cost benefit studies) were eligible for inclusion.
- Abstracts or conference presentations of studies were eligible for inclusion only if sufficient details were presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- Case series, case studies, narrative reviews, editorials and opinions were excluded, as were non-English language studies. Systematic reviews and clinical guidelines were used only as a source of references.

Intervention(s)

- Bortezomib in combination with an alkylating agent and a corticosteroid for first-line treatment of MM.
- Thalidomide in combination with an alkylating agent and a corticosteroid for first-line treatment of MM.

- Studies of treatment with either bortezomib or thalidomide as a single agent were excluded.

Comparator(s)

- Interventions described above compared with each other.
- Melphalan or cyclophosphamide in combination with prednisolone/prednisone or dexamethasone.
- Other chemotherapy regimens or SCT were excluded.

Population

- People with previously untreated MM who are not candidates for HDT with SCT.
- Studies of MM patients who had received previous treatment(s) were excluded.

Outcomes

- Studies were included if they reported on one or more of the following outcomes:
  - OS
  - PFS (deaths counted as events)
  - TTP (deaths are excluded from the calculation of this outcome)
  - response rates
  - HRQoL
  - cost-effectiveness (such as incremental cost per quality adjusted life-year (QALY) gained)
- AEs of treatment were reported when available within the trials that met the inclusion criteria.

Response Definitions

- Response to treatment is usually assessed based on changes in serum levels of M-protein and/or urinary light chain excretion. Two different systems for categorising response are included in this report, the EBMT criteria[39] and the IFM criteria.[23] Where there are differences in the two systems, in general the EBMT criteria require a slightly greater improvement. For example in the definition of partial response one of the IFM requirements is more than a 75% reduction in 24-hour urinary light chain excretion, whereas one of the EBMT criteria for partial response is a 90% decrease urinary light chain excretion. The EBMT and IFM criteria for judging response are provided in Appendix 3.

AE definitions

- Two slightly different National Cancer Institute's (NCI) criteria have been used to grade AEs, the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4, and the NCI Common Toxicity Criteria (CTC) version 2. The NCI CTCAE v4 grades AEs on a five point scale (1 to 5) and the NCI CTC v2 grades AEs on a six point scale as 0 is included (0 = No adverse event or within normal limits). Events of a higher grade are more serious than those at a lower grade with a grade 1 event described as mild, grade 2 moderate, a grade 3 event would be considered severe, whilst a grade 4 event could be life threatening. Grade 5 is reserved for deaths related to an AE.

Inclusion and data extraction process

Studies were selected for inclusion in the systematic reviews of clinical-effectiveness and cost-effectiveness through a two-stage process. Literature search results (titles and abstracts) were screened independently by two reviewers to identify all the citations that might meet the inclusion criteria. Full manuscripts of selected citations were then retrieved and assessed by one reviewer against the inclusion/exclusion criteria and checked independently by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

Data from included studies were extracted by one reviewer using a standardised data extraction form and each data extraction was checked for accuracy by a second reviewer. Again discrepancies in the extracted data were resolved by discussion, with involvement of a third reviewer when necessary.

Critical appraisal strategy

The quality of included clinical effectiveness studies were assessed using The Centre for Reviews and Dissemination criteria (CRD).[40] Quality criteria were applied by one reviewer and checked by a second reviewer with any disagreements resolved by consensus and involvement of a third reviewer where necessary.

Methods of data synthesis

Clinical and cost-effectiveness studies were synthesised through a narrative review with tabulation of results of included studies. Results of included RCTs were meta-analysed if appropriate (more than one trial with populations, interventions and outcomes believed to be sufficiently similar) and possible (adequate data reported). For time to event analyses (OS and PFS) the log hazard ratio and its standard error (SE) for each outcome were used to

calculate a summary hazard ratio and 95% confidence interval using the Cochrane Collaboration Review Manager 5.0.23 software. However since the SEs of the log hazard ratios were not reported by the RCTs, these had to be estimated using the methods and MS Excel spreadsheet of Tierney and colleagues.[41]

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

4 CLINICAL EFFECTIVENESS

4.1 Results of the systematic review of clinical effectiveness

4.1.1 Quantity and quality of research available

Titles and, where available, abstracts of a total of 1436 records were screened and full copies of 40 references were retrieved. Of these, six were excluded after inspection of the full article (Appendix 4). Two of these articles were excluded because they were not clinical trial reports, two were abstracts excluded because they described maintenance therapy with thalidomide, another abstract was excluded because it did not report on any of the outcomes of interest, and a sixth abstract described a systematic review with meta-analysis. Five full papers described four RCTs that met the inclusion criteria of the review (Table 4). Each RCT was described by at least one full paper with linked abstracts also being available. As the full papers provided the most complete data these were the primary source of information for the review.

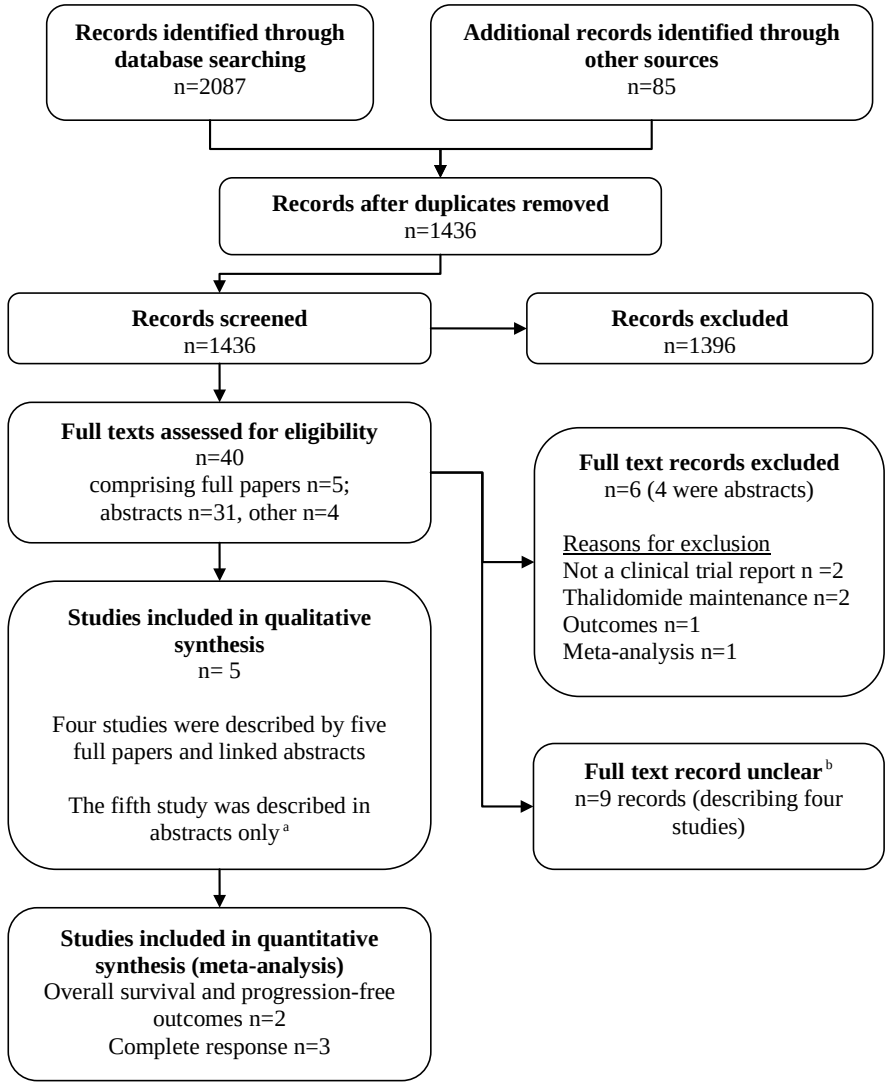
One ongoing RCT, the Myeloma IX (MMIX) trial which is a UK based MRC collaborative RCT with two treatment pathways, appeared to meet the inclusion criteria of the review and was described in conference abstracts. The search for studies of clinical effectiveness identified three abstracts for this RCT,[42-44] with a further three abstracts identified in the manufacturers submissions.[45-47] Four of the abstracts,[42-44,46] were excluded because they described the intensive pathway or thalidomide maintenance treatment which did not meet the inclusion criteria for this review. Two abstracts[45,47] described the non-intensive pathway which met the inclusion criteria. The final results from the three year median follow up have not yet been published. However because of this RCT's potential relevance to our inclusion criteria, the Clinical Trials Research Unit (CTRU) at the University of Leeds, who are coordinating the RCT, provided the trial protocol,[48] additional background information,[49,50]

trial baseline data,[51] and have also made the results from the non-intensive treatment pathway[52-57] available to NICE and the authors of this report in academic confidence. As the trial protocol and results provided directly by the CTRU provided the most complete and up to date data these were used as the primary source of information for the review.

Four additional ongoing RCTs were described in conference abstracts but it was unclear whether these met the inclusion criteria for this review. These 'unclear' studies are briefly described in section 4.3. The total number of records assessed at each stage of the systematic review screening process is shown in the flow chart in Figure 1.

One of the included RCTs evaluated VMP (VISTA trial)[26] whilst three RCTs evaluated MPT (Intergroup Francophone du Myelome (IFM) trial 01/01 trial,[58] IFM 99/06 trial,[23] and the Italian Group for Adult Hematologic Diseases (GIMEMA) trial[24]). The fifth RCT, the MMIX trial (non-intensive pathway), evaluated the CTDa. The comparator in all five of the included RCTs was MP.

Figure 1: Flow diagram of reference screening processes



[a] additional information was received from the trialists providing details for one RCT only described in conference abstracts. The additional details allowed us to appraise the study methodology and make judgements about study quality. Results from this RCT could therefore be considered for inclusion in the systematic review of clinical effectiveness.

[b] Outcomes from these studies could not be included because of insufficient details about study methodology and insufficient details about study quality. These studies, which are all ongoing, are briefly summarised in section 4.3.

Bortezomib in combination with melphalan and prednisone (VISTA trial)

The RCT investigating VMP was a randomised (1:1), open-label, phase 3 trial conducted in 151 centres in 22 countries in Europe, North and South America, and Asia. The RCT enrolled 682 participants and was funded by two industry sponsors (Table 4).

Patients received nine 6-week cycles of melphalan (at a dose of 9 mg per square metre of body surface area) and prednisone (at a dose of 60 mg per square metre) on days 1 to 4, alone or in combination with bortezomib (at a dose of 1.3 mg per square metre), by intravenous bolus on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. The dose of bortezomib or melphalan was reduced if there was any prespecified haematologic toxic effect or grade 3 or 4 nonhaematologic effect. Patients with myeloma-associated bone disease received bisphosphonates unless such therapy was contraindicated.

Patients were eligible if they had newly diagnosed, untreated, symptomatic, measurable myeloma and were not candidates for HDT plus SCT because of age (≥65 years) or coexisting conditions. Measurable disease was defined as the presence of quantifiable M-protein in serum or urine, or measurable soft-tissue or organ plasmacytomas. Over 80% of patients had ISS stage II or III disease, about a third had a Karnofsky performance score of ≤70%, and over 60% had lytic bone lesions. Most participants were white. No exclusion criteria for study entry were stated.

During the 54 week treatment period blood and urine samples were collected every three weeks. After completion of treatment, samples were collected every eight weeks until disease progression. Patients were followed after disease progression at least every 12 weeks for survival and subsequent myeloma therapy.

The primary outcome measure was time to disease progression. The study was powered at 80% for the primary outcome but no power calculations were reported for patient subgroups. Secondary outcomes were rate of complete response, duration of response time, time to subsequent myeloma therapy, OS and PFS. Disease progression was defined by European Group for Blood and Marrow Transplantation (EBMT) criteria and assessed by investigators. The sponsors also determined progression with the use of a computer algorithm that applied EBMT criteria. Data are presented in the published paper from the assessment by investigators and from the algorithmic analysis. TTP, time to subsequent myeloma therapy and OS were analysed from randomisation to the event of interest.

Thalidomide in combination with melphalan and prednisone (IFM and GIMEMA trials)
All three of the included RCTs investigating MPT were multi-centre trials. The number of centres ranged from 44 to 73 and all were located in one or more European countries (France, Belgium, Switzerland, Italy). The IFM RCT by Facon and colleagues[23] was the largest, recruiting 447 patients; however only 321 participants are reported on here because this trial had a third arm (reduced-intensity SCT) which is not relevant to this review as the intervention does not meet the inclusion criteria. The GIMEMA group RCT by Palumbo and colleagues[24] enrolled 331 participants, and the remaining IFM RCT, Hulin and colleagues,[58] enrolled 232 participants (Table 4). All of the RCTs received free thalidomide for the study from the drug manufacturers but other funding costs were met by grants from other sources (Appendix 5).

The dosing schedules of the RCTs varied in terms of overall length and the drug doses used. Hulin and colleagues[58] and Facon and colleagues,[23] the two IFM RCTs, had 72 week treatment periods consisting of 12 six-week treatment cycles. The treatment period in the GIMEMA group RCT by Palumbo and colleagues was shorter, lasting for 24 weeks and consisting of six four-week treatment cycles. The intervention in each RCT was MPT. Thalidomide was prescribed as a set 100mg daily dose in the RCTs by Hulin and colleagues[58] and Palumbo and colleagues,[24] while a 400mg daily dose was the goal of Facon and colleagues (if this could be tolerated).[23] In the two IFM RCTs[23,58] doses were described according to body weight. The dosing schedule of MP (on days 1-4 of each six-week treatment cycle) and prednisone dose (2mg/kg prednisone) was the same in both RCTs, whilst the melphalan doses differed slightly (Hulin and colleagues[58] 0.2mg/kg melphalan; Facon and colleagues[23] 0.25mg/kg melphalan). Palumbo and colleagues[24] described drug doses according to body surface area. Melphalan (4mg/m^2) and prednisone (40mg/m^2) were taken on days 1-7 of each 4-week treatment cycle. All RCTs allowed thalidomide dose adjustments. In each RCT the comparator was MP alone (no thalidomide prescribed) provided in the same manner as in the MPT arms as described (also see Table 4). Only one RCT, Hulin and colleagues[58] included a placebo in place of thalidomide in the comparator arm.

As mentioned earlier, to be included in this systematic review, RCTs had to report on treatment of participants with MM who were not eligible for HDT with SCT and who had not been previously treated. All participants in each RCT met these criteria. The two IFM RCTs differed in the target age range of participants: Hulin and colleagues[58] focussed on people aged at least 75 years, whereas Facon and colleagues[23] focussed on people aged between 65 and 75 years, with younger patients being eligible for inclusion providing they were not

eligible for HDT. Palumbo and colleagues[24] focused on people older than 65 years of age without specifying any upper age limit, and like Facon and colleague[23] did include participants younger than 65 years providing they were unable to undergo SCT. All RCTs included people whose MM was at DS stage II or III, and the two IFM RCTs[23,58] also included patients with DS stage I MM if they met the criteria for high-risk stage I disease. The percentage of participants in the IFM[23,58] and GIMEMA[24] RCTs with a WHO performance status score of 3 or 4 ranged from 4% to 8%. Over three quarters of the participants in the IFM RCTs had bone lesions but this information was not reported by Palumbo and colleagues[24] (Table 4). None of the RCTs reported on the ethnicity of the participants.

All three RCTs specified their exclusion criteria. In the two IFM RCTs[23,58] these were almost identical, the only difference being that Hulin and colleagues[58] excluded anyone with a history of venous thrombosis during the previous 6 months in addition to the other exclusions (any one with previous neoplasms (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or higher, if unrelated to MM; substantial renal insufficiency with creatinine serum concentration of 50mg/L or more; cardiac or hepatic dysfunction; peripheral neuropathy; HIV infection, or hepatitis B or C infections). Palumbo and colleagues[24] listed fewer exclusion criteria. Two were similar to those of the IFM RCTs (exclusion of people with another cancer; or any grade 2 peripheral neuropathy) and one was novel to this RCT (exclusion of people with psychiatric disease). Palumbo and colleagues[24] also stated that abnormal cardiac function, chronic respiratory disease, and abnormal liver or renal functions were not criteria for exclusion.

The timing of clinic visits during the RCTs varied. Palumbo and colleagues[24] monitored response to treatment every 4 weeks, whereas visits were scheduled every 6 weeks for the RCT by Hulin and colleagues[58] until treatment completion or study withdrawal. Facon and colleagues[23] saw participants after inclusion at three months, six months and then every six months thereafter until withdrawal from the RCT. When scheduled clinic visits ended (after withdrawal or end of treatment), Palumbo and colleagues[24] continued to assess participants every two months, and the two IFM RCTs[23,58] continued to assess participants every 6 months.

OS was the primary outcome measure for the two IFM RCTs.[23,58] Both RCTs were powered at 80% for the primary outcome but recruitment was stopped early in both RCTs because interim analyses had demonstrated a clear survival advantage. The secondary outcomes of these RCTs were response rates,[23,58] PFS,[23,58] survival after progression,[23] toxicity,[23] and

safety.[58] Facon and colleagues[23] report some of their outcomes for more than one follow-up period. OS, PFS, and survival after progression analyses were reported for a data point of January 8th 2007, these outcomes were also reported along with all other outcomes for the earlier date point of October 8th 2005. In contrast the primary outcome of the RCT by Palumbo and colleagues[24] was stated as response rates and PFS. A power calculation was reported for the response outcome. The secondary outcomes of this RCT were OS, time to first evidence of response, prognostic factors, and frequency of any grade 3 or higher AEs.

Thalidomide in combination with cyclophosphamide and attenuated dexamethasone (MMIX trial)

The MMIX RCT non-intensive pathway evaluated CTDa in comparison to MP. Participants were randomised in 1:1 ratio to receive either CTDa or MP. Within each treatment arm participants were also randomised to bisphosphonate treatment either with sodium clondronate or zoledronic acid. This multi-centre RCT was conducted [redacted] in the UK [redacted] (Table 4). The RCT was funded by a core grant from the MRC, with some other funding provided by five industry sponsors and one charitable sector sponsor (Appendix 5).

The treatment period with CTDa in the intervention arm was designed to be between 24 and 36 weeks, equivalent to a minimum of six, or a maximum of nine four-week treatment cycles. Thalidomide was prescribed as a daily starting dose of 50mg with the aim that this would be increased every 4 weeks by 50mg to a maximum of 200mg. During each four-week treatment cycle 500mg cyclophosphamide was taken once a week on days 1, 8, 15 and 22, and dexamethasone 20mg was taken daily on days 1-4 and days 15-18 of each cycle. Participants in the comparator arm received MP (melphalan 7mg/m^2 and prednisolone 40mg) on days 1-4 of each 4 week cycle. Dose adjustments were permitted in both RCT arms.

In common with the other included RCTs, patients were eligible if they were newly diagnosed with symptomatic MM or non-secretory MM and had not received previous treatment for myeloma (other than local radiotherapy). The MMIX non-intensive pathway was designed for older (generally ≥ 70 years of age) or less fit patients (who could be younger than 70) but strict age restrictions were not in place to ensure that fit older patients were not excluded from the intensive therapy arm. [redacted]

Exclusion criteria included asymptomatic MM, solitary plasmacytoma of bone and

extramedullary plasmacytoma (without evidence of myeloma). People with acute renal failure were excluded but those with a history of ischaemic heart disease or psychiatric disorder could be considered for inclusion at the discretion of the clinician. Further details of exclusion criteria can be found in Appendix 5.

OS, PFS, and response were the co-primary outcomes and power calculations were provided for both survival and response. Secondary outcomes were quality of life (QoL), skeletal-related events, height loss, toxicity (thromboembolic events; renal toxicity; haematologic toxicity; graft versus host disease), and proportion receiving bortezomib-dexamethasone as 'early rescue' on induction chemotherapy, or at relapse.

Table 4: Overview of characteristics of included studies

Study details [a]	San Miguel et al.[26,59,60] VISTA Trial Multicentre RCT at 151 centres in 22 countries in Europe, North and South America, Asia 682 enrolled	Facon et al.[23] 2007 IFM 99/06 Trial Multicentre RCT at 73 centres in France, Belgium, and Switzerland 447 enrolled to all three groups	Hulin et al.[58] 2009 IFM 01/01 Trial Multicentre RCT at 44 centres in France & Belgium 232 enrolled	Palumbo et al.[24] 2006 GIMEMA network Multicentre RCT at 54 centres in Italy 331 enrolled (255 followed up)	MMIX Trial: Non-intensive pathway[48,51] Multicentre RCT [redacted] in the UK [redacted]
Median follow-up	Full paper 16.3 months[26] [b] Abstract 25.9 months[59] Abstract 36.7 months[60]	51.5 months [b]	47.5 months [b]	38.4 months MPT [c] 37.7 months MP	[redacted] [d]
Intervention	VMP: n= 344 9 x 6-week cycles of bortezomib (1.3 mg/m^2) on days 1,4,8,11,22,25,29, and 32 during cycles 1 to 4 and on days 1,8,22 and 29 during	MPT: n= 125 thalidomide < 400mg daily for 12 MP cycles (i.e. 72 weeks) + MP 12 x 6	MPT: n= 115 thalidomide 100mg daily for 72 weeks + MP 12 x 6 week cycles of melphalan 0.2mg/kg and prednisone 2	MPT: n=167 (129 followed up) thalidomide 100mg daily for six MPT cycles (i.e. for 24 weeks) + MP 6 x 4	CTDa: [redacted] thalidomide: 50mg daily for 4 weeks, increasing every 4 weeks by 50mg increments to 200mg daily. + Cyclophosphamide: 500mg once a week, on days 1,8,15 and 22 of each cycle Dexamethasone: 20mg daily on days 1-4 and 15-18 of each cycle Cycle length 4 weeks, to maximal response, but with a min-max number of cycles of 6-9.

	cycles 5 to 9 + MP melphalan ($9mg/m^2$) plus prednisone ($60mg/m^2$) on days 1 to 4 of each cycle	week cycles of melphalan 0.25mg/kg and prednisone 2 mg/kg on 4 days per cycle	mg/kg on days 1 to 4 of each cycle	week cycles of melphalan $4mg/m^2$ and prednisone $40mg/m^2$ on days 1 to 7 of each cycle	
Comparator	MP: n= 338 MP 9 x 6-week cycles melphalan ($9mg/m^2$) plus prednisone ($60mg/m^2$) on days 1 to 4 of each cycle	MP: n= 196 MP 12 x 6 week cycles of melphalan 0.25mg/kg and prednisone 2 mg/kg on 4 days per cycle Third arm did not meet inclusion criteria.	MP + placebo: n= 117 placebo daily for 72 weeks + MP 12 x 6 week cycles of melphalan 0.2mg/kg and prednisone 2 mg/kg on days 1 to 4 of each cycle.	MP: n= 164 enrolled (126 followed up) MP 6 x 4 week cycles of melphalan $4mg/m^2$ and prednisone 40 mg/m^2 on days 1 to 7 of each cycle	MP: [redacted] MP 6-9 cycles of melphalan $7mg/m^2$ and prednisolone dose 40mg on days 1 to 4 of a 4-week cycle
Key attributes of participants	Not candidates for HDT with SCT because of age 65 years or over, or co-existing conditions. Newly diagnosed and previously	Aged between 65 and 75 years Previously untreated MM at DS Stage II or III Patients	Aged at least 75 years Newly diagnosed MM at DS stage II or III Patients with DS stage I MM who met	Older than 65 years of age Younger participants included if unable to undergo transplantation Previously	Aged at least 18 years Newly diagnosed symptomatic MM or non-secretory MM

	untreated Measurable disease	younger than 65 years were included if they were ineligible for high-dose treatment. Patients with DS stage I MM who met criteria of high-risk stage I disease	criteria of high-risk stage I disease Patients with nonsecretory or oligosecretory MM allowed	untreated DS stage II or III MM Measurable disease	
Selected baseline characteristics	Median age, years (range): VMP 71 (57-90) MP 71 (48-91)	Age ≥ 70 years: MPT 50/125 (40%); MP 84/196 (43%)	Age ≥ 80 years: MPT 43/113 (38%); MP + placebo 40/116 (34%)	Median age, years: MPT 72 MP 72	[redacted]
Gender (m:f)	VMP 175:169 (51%:49%); MP 166/172 (49%:51%)	MPT 63:62 (50%:50%); MP 109/87 (56%:44%)	MPT 43:70 (38%:62%); MP + placebo 61:55 (53%:47%)	not reported	[redacted]

Disease stage (DS or ISS criteria)	ISS stage: Stage 1 VMP 19%, MP 19% Stage 2 VMP 47%, MP 47% Stage 3 VMP 35%, MP 34%	DS stage II or III MPT 112/125 (90%); MP 177/196 (91%)	DS stage II or III MPT 100/113 (89%); MP + placebo 107/116 (93%)	DS stage II or III MPT 129/129 (100%) MP 126/126 (100%) calculated by reviewer	[redacted]
Performance status [e]	Karnofsky performance status ≤70 VMP 122 (35%) MP 111 (33%)	WHO performance index 3-4 MPT 10/125 (8%) MP 13/196 (7%)	WHO performance index 3-4 MPT 9/113 (8%); MP 7/116 (6%)	WHO performance index 3-4 MPT 9/129 (7%) MP 6/126 (4%)	WHO performance index 3 [redacted] WHO performance index 4 [redacted]
Bone lesions present	VMP 224/343 (65%); MP 222/336 (66%)	MPT 90/125 (76%); MP 154/196 (79%)	MPT 87/113 (78%); MP + placebo 93/116 (82%)	Not reported	[redacted]
Primary outcome	Time to disease progression	Overall survival	Overall survival	Response rates and progression-free survival	Overall survival, progression-free survival, response
Secondary outcomes	Rate of complete response, duration of response, time to subsequent myeloma therapy, overall survival, progression-free survival	response, progression-free survival, survival after progression, and toxicity	safety, response rates, progression-free survival.	overall survival, time to first evidence of response, prognostic factors, frequency of any grade 3 or higher adverse events.	Quality of life, Skeletal-related events, Height loss, Toxicity, Proportion receiving bortezomib-dexamethasone as ‘early rescue’ on induction c

[a] Detailed data extraction forms for each RCT are available in Appendix 5.

[b] RCTs reported median follow up for the RCT as a whole and not for each RCT arm separately.

[c] After 6 x 4 week cycles of MPT, thalidomide was continued at 100mg per day as maintenance therapy. This does not meet the inclusion criteria of the review therefore only outcomes to 24 weeks follow up are data extracted here.

[d] After completion of induction chemotherapy, eligible patients entered a second randomisation to thalidomide maintenance or no maintenance. The initial randomisation to chemotherapy was not maintained, although initial chemotherapy was a stratification factor. As maintenance therapy does not meet the inclusion criteria of the review only outcomes from the induction chemotherapy period (6-9 months follow up) are reported on in this systematic review.

[e] Performance status definitions are provided in Appendix 6.

Quality assessment of included studies

The outcome of the quality assessment of included RCTs is summarised in Table 5.

Bortezomib in combination with melphalan and prednisone

The VISTA study of VMP versus MP was an RCT, with randomisation stratified according to baseline levels of β_2-microglobulin, serum albumin and region. However, no details are given on the methods used to generate random numbers or conceal allocation to treatment group, and therefore it is not possible to know whether the RCT is at risk of selection bias due to unbalanced confounding factors and failure to adequately conceal allocation. Baseline demographics and disease characteristics are reported to be well balanced between the two groups but no *p*-values are given. The RCT is described as open label which suggests that researchers and/or participants were not blinded. As bortezomib is administered intravenously the researchers may have felt blinding was not possible. However, for objective outcomes, such as OS, risk of bias is low regardless of lack of blinding. There is no evidence that more outcomes were measured than reported by study authors. The authors did not report whether there were any unexpected imbalances in drop-outs between the groups. TTP, time to subsequent myeloma therapy, and OS from randomisation were analysed in the intention to treat (ITT) population (all randomised patients). For TTP analyses data from patients for whom there was no disease progression were censored at the last assessment, or at the start of subsequent therapy. Although not explicitly stated it is assumed that deaths without disease progression were not included in the outcome of TTP. Details of censoring in terms of number of patients with censored data and reasons for censoring in each group are not given. The response analysis was not ITT as seven patients in each group could not be evaluated for a response: 5 did not receive the study drug; 3 patients in the VMP arm and 6 patients in the MP arm had no measurable disease at baseline on the basis of assessment by a central laboratory (although the patients met the eligibility criteria of measurable disease according to evaluation by a local laboratory).

Thalidomide in combination with melphalan and prednisone

All the included studies were RCTs of MPT versus MP. However one of the three RCTs, Facon and colleagues,[23] did not report on the methods used to generate random allocations or how the allocations were concealed. Without this information we cannot be certain that the randomisation method balanced out confounding factors or that allocation bias has been avoided in this RCT. Hulin and colleagues[58] did not report on the method used to generate the randomisation sequence but the central allocation of patients should have provided adequate allocation concealment. Palumbo and colleagues,[24] were the only authors to report

sufficient information about randomisation and allocation concealment allowing this RCT to be judged at low risk from unbalanced confounding factors and low risk of allocation bias.

All three MPT RCTs reported on the baseline characteristics of participants according to treatment group. Hulin and colleagues[58] provided an indication that statistical testing had been used to test the similarity of the groups at baseline and reported that the only statistically significant difference was for sex (more female participants in MPT group, p=0.03). However Facon and colleagues[23] did not report on whether the groups had been judged to be similar at baseline. Palumbo and colleagues[24] stated that baseline demographics and other characteristics of the two groups were balanced but they did not report whether this had been tested statistically.

One of the three MPT RCTs, Palumbo and colleagues[24] was not blinded, and this was clearly stated by the authors. One of the RCTs, Hulin and colleagues,[58] involved the use of a placebo in the comparator arm which suggests blinding may have been in place although this was not explicitly stated. The third MPT RCT did not report whether blinding was in place or not. In each RCT some of the outcomes were objective (e.g. survival) and therefore the risk of bias for these would be low, regardless of whether blinding was in place or not.

There was no evidence in any of the MPT RCTs that more outcomes were measured than were reported. But for each of the three MPT RCTs it was unclear whether there were any unexpected imbalances in drop-outs between groups because none of the RCT authors commented on this.[23,24,58]

All the MPT RCTs stated that an ITT analysis had been conducted but the details of these analyses and methods used to account for missing data were unclear due to poor reporting. Hulin and colleagues[58] stated that an ITT analysis was conducted but in this case the ITT analysis appears to have excluded three randomised participants who discontinued before study treatment (two in the MPT group and one in the MP group). Facon and colleagues[23] stated that an ITT analysis was conducted and from the numbers provided in the results for OS and PFS but not response their ITT analysis appears to have included all patients randomised, including those who were not treated as assigned. Palumbo and colleagues[24] stated an ITT analysis had been conducted at six months (the only outcome point eligible for inclusion in this review) but at the time of analysis not all randomised participants had been enrolled for six months. Therefore 76 out of the 331 randomised participants (38 in each arm) were not included in the analysis of six month data. As these RCTs reported time to event data such as OS and PFS it was expected that some data would be censored. However, only

one RCT, Hulin and colleagues[58] stated when data on patients who were alive were censored in the survival analysis and when data on patients without disease progression were censored for the analysis of PFS. One of the MPT RCTs, Facon and colleagues,[23] marked the position of censored data on the survival plots but none of the RCTs reported details of how many participants' data were censored, and for what reason (e.g. censored due to withdrawal, censored due to death from an unrelated cause such as a car accident, or censored as event of interest not experienced). It is not possible to determine whether the amount and pattern of censoring was comparable between the groups and whether this had any effect on outcomes.

Thalidomide in combination with cyclophosphamide and attenuated dexamethasone

The MMIX study of CTDa versus MP was an RCT, with randomisation, that used a minimisation algorithm, stratified by centre; haemoglobin; corrected serum calcium; serum creatinine; and platelets.[48,51] No details are reported on the methods used to generate random numbers however allocation to treatment groups was adequately concealed by the use of an automated 24 hour telephone system. The RCT is therefore at a low risk of selection bias. [redacted] The RCT was not a blinded RCT, but as already noted for the other included RCTs, the risk of bias is low for the objective outcomes. There is no evidence that more outcomes have been measured during the RCT than are reported. The authors did not report whether there were any unexpected imbalances in drop-outs between the groups. All summaries and analyses were by ITT unless stated otherwise and ITT was defined as all patients randomised, with the exception of those misdiagnosed. For the QoL data the analysis includes all patients who agreed to take part in the QoL study. Patients with missing follow-up data or who had not experienced progression were censored on the last date they were known to be alive and progression-free. OS was calculated from initial randomisation to death. Patients with missing follow-up data, or not known to have died at time of analysis were censored on the last date they were known to be alive. It was not reported whether the amount and pattern of censoring was comparable between the groups. PFS was calculated from random assignment to progression or death. There was no other censoring of data.

Table 5: Quality assessment of included studies.

Study	Randomisation sequence	Allocation concealment	Balanced baseline characteristics	Blinding	Drop out imbalance	More outcomes than reported	Intention-to-treat analysis	Missing data accounted for
San Miguel et al.[26,59]	NR	NR	Yes	No	?	No	Y	?
Facon et al.[23]	NR	NR	?	NR	?	No	Y	?
Hulin et al.[58]	NR	Yes	Yes	?	?	No	Y	?
Palumbo et al.[24]	Yes	Yes	Yes	No	?	No	Y	?
MMIX[48,49,51]	Yes	Yes	Yes	No	NR	No	Y	?

'?' = unclear (uncertain risk of bias), 'NR' = not reported.

4.1.2 Assessment of effectiveness

4.1.2.1 Overall Survival

OS was a secondary outcome in the VISTA RCT of VMP versus MP (Table 6) and was calculated from randomisation. A statistically significant survival benefit for VMP compared with MP is reported in an abstract[59] after a median follow-up of 25.9 months (Hazard ratio (HR) =0.64, p=0.0032). Three year survival rates in a more recent abstract[60] after a median follow up of 36.7 months were 68.5% versus 54% respectively. At the earlier median follow up of 16.3 months, reported in the published paper,[26] median OS had not been reached. However San Miguel and colleagues stated that a survival benefit was associated with bortezomib because 45 patients (13%) in the VMP group had died in comparison to 76 patients (22%) in the MP group (HR 0.61, p=0.008) (despite 44%[59] of MP patients receiving subsequent bortezomib therapy after disease progression) (Table 21). The most recent abstract reports that median OS is 43.1 months in the MP group but not estimable in the VMP group.[60]

Two[23,58] of the three RCTs investigating MPT versus MP alone reported OS as their primary outcome. Both RCTs calculated OS from randomisation but only one of them, Hulin and colleagues,[58] explained that data on patients who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. For the third RCT,[24] OS was a secondary outcome and was not eligible for inclusion in this systematic review because participants received maintenance therapy with thalidomide after the six four-week cycles of MPT were completed.

A statistically significant difference in OS in favour of the MPT group was found by both RCTs (Table 6). Facon and colleagues[23] reported their results after median follow up of 51.5 months. In the MPT group there were 62 events (deaths) and median survival was 51.6 months (Inter-quartile range (IQR) 26.6 to not reached) whereas in the MP group, where there were 128 events, median survival was 33.2 months (IQR 13.8 to 54.8). The difference in OS was statistically significant with an estimated hazard ratio for median OS in favour of MPT of 0.59 (95% CI 0.46-0.81, p=0.0006). When adjusting for prognostic factors (e.g. WHO performance index; β_2 microglobulin, albumin etc) the results showed that MPT remained the superior treatment in terms of the specified outcome OS (HR 0.49, 95% CI 0.33-0.73, p=0.0002) (Appendix 5). Similarly Hulin and colleagues,[58] reporting after a slightly shorter median follow up of 47.5 months, found that the median survival of 44 months (95% CI 33.4 to 58.7) in the MPT group was statistically significantly longer than in the MP + placebo group where median survival was 29.1 months (95% CI 26.4 to 34.9). In this RCT the reported hazard ratio for median OS in favour of MPT was 0.68 (95% CI for the hazard ratio not reported, p=0.028).

As noted above, neither RCT reported on the amount of censored data, or the reasons for this. It is therefore not possible to determine whether censored data had any impact on the outcome of OS.

The MMIX RCT[48] OS outcome was not eligible for inclusion in this systematic review because participants were entered into a second randomisation to receive either maintenance therapy with thalidomide or no maintenance therapy after they had completed first-line treatment with either CTDa or MP.

Table 6: Overall Survival

Study	**Median follow-up**	**Treatment arms**		
San Miguel et al.[26,59] VISTA		**VMP (n=344)**	**MP (n=338)**	**HR and *p*-value**
Overall survival (abstract[60])	*36.7 months*	Not estimable	43.1 months	Not reported
Overall survival (abstract[59])	25.9 months	Not reported	Not reported	HR 0.64 p=0.0032
Overall survival[26]	16.3 months	Median survival not reached	Median survival not reached	HR 0.61 p=0.008
Deaths[26]		45/344 (13%)	76/338 (22%)	
Three year survival rate (abstract [60])		68.5%	54.0%	Not reported
Three year survival rate (abstract [59])		72%	59%	Not reported
Facon et al.[23] IFM 99/06		**MPT (n=125)**	**MP (n=196)**	**HR and *p*-value**
Overall Survival, [a] Median (SE, IQR)	51.5 months (IQR 34.4 – 63.2)	51.6 months (4.5, 26.6 to not reached)	33.2 months (3.2, 13.8 to 54.8)	HR 0.59 (95% CI 0.46-0.81) p=0.0006
Deaths		62/125 (50%)	128/196 (65%)	
Hulin et al.[58] IFM 01/01		**MPT (n=113)**	**MP + placebo (n=116)**	**HR and *p*-value**
Overall Survival, Median (95% CI)	47.5 months	44.0 months (33.4 to 58.7)	29.1 months (26.4 to 34.9)	HR 0.68 (95% CI not reported) p=0.028
Deaths [b]		58/113 (51%)	76/116 (65.5%)	p=0.03

[a] At the initial analysis (median follow up 36.8 months) no difference in OS was recorded as a function of initial thalidomide dose (≤200 mg per day vs >200 mg per day, p=0.93).

[b] Myeloma progression was considered to be the major cause of the majority of deaths in both study arms (36/58 deaths in the MPT group; 54/76 deaths in the MP + placebo group).

Two MPT versus MP RCTs[23,58] reported OS outcome data that met the inclusion criteria of the review. A fixed effects meta-analysis was conducted and as can be seen in Figure 2 the I^2 test suggests there is little or no heterogeneity between the two RCTs for this outcome. The summary OS HR was 0.62 (95% CI 0.50 to 0.77) in favour of MPT.

Figure 2: MPT versus MP Overall Survival

The Facon study confidence intervals shown in Figure 2 obtained from Review Manager are slightly different to those reported by the published paper and shown in Table 6. The difference arises from the use of the estimating method[41] used to obtain the standard errors for the log hazard ratios needed to undertake the meta-analysis.

4.1.2.2 Deaths during treatment

In the VISTA RCT[26] of VMP versus MP, death rates during treatment were similar for the VMP group and the MP group (5% and 4% respectively). San Miguel and colleagues also report that treatment-related deaths were similar in the two groups, but the time at which these deaths occurred is not reported (treatment related deaths VMP 1% and MP group 2%).

The two RCTs of MPT that report OS[23,58] also provide some information about the deaths that occurred. Facon and colleagues[23] provided very limited information, only commenting on toxic deaths (no definition is provided but the term toxic death usually refers to a treatment-related death) and deaths within the first three months of treatment (Table 7). In the MPT group there were no toxic deaths and only three deaths in the first three months of treatment. In the MP group there were both more toxic deaths (four deaths all due to infection) and more early deaths (13 deaths) but as no statistical comparison between the arms is reported it is not known whether these differences were statistically significant.

Hulin and colleagues[58] reported only one toxic death in the MPT group and one in the MP + placebo group. Both of these toxic deaths were caused by intestinal perforation. The number of early deaths was also very similar between the groups. In the MPT group three deaths were reported after one month of treatment, and five deaths after three months of treatment. In the MP + placebo group three deaths were reported after one month of treatment and six after three months of treatment. For both study arms it is not clear whether the number of deaths reported after three months is a cumulative value, i.e. including the deaths reported after one month of treatment, or whether these are additional deaths that have occurred in months two and three.

[redacted]

Table 7: Deaths during treatment

Study	Treatment arms	
San Miguel et al.[26] VISTA	**VMP (n=344)**	**MP (n=338)**
Deaths during treatment	5%	4%
Treatment related deaths	1%	2%
Facon et al.[23] IFM 99/06	**MPT (n=124)**	**MP (n=193)**
Toxic death	n=0	n=4 (2%), all due to infection
Early death – in first 3 months of treatment	3/124 (2%)	13/193 (7%)
Hulin et al.[58] [a] IFM 01/01	**MPT (n=113)**	**MP + placebo (n=116)**
Toxic death (intestinal perforation)	n=1	n=1
Early death – after 1 month of treatment	n=3	n=3
Early death – after 3 months of treatment	n=5	n=6
MMIX[48,52,53]	**CTDa** [redacted]	**MP** [redacted]

[a] Withdrawals due to death are reported in Table 18.

4.1.2.3 Response to treatment

Various response to treatment rates are reported as secondary outcomes in the VISTA RCT of VMP (Table 8),[26] although the analysis is not ITT as previously explained. The time at which response was assessed is not reported. Rates of partial response (PR) or better (according to EBMT criteria, Appendix 3) were 71% in the VMP group and 35% in the MP group ($p<0.001$), and the complete response (CR) rates were 30% and 4% respectively ($p<0.001$). The rate of partial response was 40% in the VMP group and 31% in the MP group and minimal response (MR) rates were 9% and 22% respectively. Stable disease rates were 18% in the VMP group and 40% in the MP group, and progressive disease rates were 1% and 2% respectively.

All three RCTs investigating MPT reported on response to treatment (Table 8).[23,24,58] The two IFM RCTs[23,58] reported the response at 12 months as a secondary outcome and response was judged according to their own criteria. These criteria are very similar, but not identical to, the EBMT criteria which were used in the RCT by Palumbo and colleagues[24] to assess response

at six months which was the primary outcome of this RCT (Appendix 5). Facon and colleagues[23] stated that all analyses were done on an ITT basis, it is therefore unclear why response to treatment outcomes are reported for only 60% of the MPT group (75 of the 125 participants enrolled to this group) and 84% of the MP group (165 of 196 enrolled). Hulin and colleagues[58] did not indicate that all analyses were ITT (only survival analyses were clearly stated to be ITT) but response to treatment is reported for 93% of the MPT group and 96% of the MP + placebo group. Palumbo and colleagues[24] reported on all of those who contributed to the six month follow-up results. However as noted earlier, not all of the randomised participants contributed data to this outcome because some participants had not achieved six months of follow up when these data were analysed.

At 12 months statistically significant differences in complete response in favour of the MPT group were observed in both the IFM RCTs.[23,58] Facon and colleagues[23] reported 13% of 75 participants in the MPT group had achieved complete response at 12 months in comparison to just 2% of 165 participants in the MP group (p=0.008). Caution must be applied in interpreting these results however which appear to be based on a small proportion of the participants. The difference between the groups reported by Hulin and colleagues[58] was less marked but still statistically significant (MPT 7% of 107 participants complete response versus 1% of 112 participants in MP + placebo group, p<0.001). Palumbo and colleagues[24] reported an absolute difference in complete response MPT-MP at six months of 13% (95% CI 6.3 to 20.5).

When response categories were combined, the percentage of participants in the IFM RCT MPT groups achieving at least a partial response at 12 months was double the percentage achieving this level of response in the MP group (Facon and colleagues[23] MPT 76% versus MP 35%, p<0.0001; Hulin and colleagues[58] MPT 62% versus MP + placebo 31%, p<0.001). At six months in the RCT by Palumbo and colleagues there was a difference in favour of the MPT group of 28.3% (95% CI 16.5 to 39.1) for participants achieving either a complete or partial response.

Each MPT RCT reported on a sub-category of participants with a partial response. In the two IFM RCTs only one sub-category of participants was reported on who were described as having a very good partial response.[23,58] These participants had more than a 90% decrease in monoclonal protein in serum and urine. Palumbo and colleagues reported on three sub-categories of participants with partial response.[24] Those with a near complete response had disappearance of M-protein from serum and urine but still detectable by immunofixation (immunofixation positive) the remaining participants with a partial response were divided into

those with a 90% to 99% M-protein reduction and those with a 50% to 89% M-protein reduction. Facon and colleagues[23] reported at least a very good partial response at 12 months in 35 of 75 participants (47%) which was statistically significantly better than in the MP group where only 7% (11/165) of participants met the criteria ($p<0.001$). Hulin and colleagues[58] also reported a statistically significant difference in favour of the MPT group at 12 months when 21% (23/107) met the criteria for at least very good partial response, in comparison to 7% (8/112) in the MP group ($p<0.001$). Palumbo and colleagues[24] report greater proportions of participants in the MPT group than in the MP group at each sub-category of partial response after six months of follow up. Of the 78 participants (60.4%) in the MPT group with a partial response most (n=51) had experienced a 50% to 89% M-protein reduction, 11 participants had a 90% to 99% M-protein reduction, and 16 participants had a near complete response. In contrast only 57 (45.2%) of MP group participants achieved a partial response with the majority (n=45) having a 50% to 89% M-protein reduction, six participants having a 90% to 99% M-protein reduction, and six participants achieving a near complete response.

Facon and colleagues[23] and Hulin and colleagues[58] gave no details about participants who achieved less than a partial response at 12 months. Palumbo and colleagues[24] however provided information on each of the remaining three EBMT categories, minimal response at 6 months, no response at 6 months, and progressive disease at 6 months, as well as indicating the proportion of data that was not available (Table 8). There were greater proportions of participants from the MP group than the MPT group in the final three categories.

The MMIX RCT[48,52,53] assessed maximal response after induction chemotherapy with either CTDa or MP. Response was categorised using EBMT definitions (Appendix 3). Response was one of the three co-primary outcomes of this RCT. [redacted]

[redacted]

Table 8: Response to treatment

Study	
San Miguel et al.[26] VISTA	**VMP**
Rate of PR or better	238/3
Rate of CR	102/3
Rate of PR	136/3
Minimal response	32/33
Stable disease	60/33
Progressive disease	3/337
Facon et al.[23] IFM 99/06	**MPT**
Complete response at 12 months	10/75
At least partial response at 12 months	57/75
At least very good partial response at 12 months	35/75
Hulin et al.[58] IFM 01/01	**MPT**
Complete response at 12 months	7/107
At least partial response at 12 months	66/10
At least very good partial response at 12 months	23/10

Palumbo et al.[24] GIMEMA	**MPT**
Complete response at 6 months	20/12
Complete or partial response at 6 months	98/12
Partial response	78/12
- Near complete response	16/12
- 90% to 99% M-protein reduction	11/12
- 50% - 89% M-protein reduction	51/12
Minimal response at 6 months	7/129
No response at 6 months	7/129
Progressive disease at 6 months	10/12
Not available	7/129
MMIX[48,52,53]	**CTD**
[redacted]	[redacted]

Risk ratios for complete response

Three MPT versus MP RCTs[23,24,58] reported complete response outcome data that could be meta-analysed. A fixed effects meta-analysis was conducted and as can be seen from Figure 3 the I^2 test suggests there is little or no heterogeneity between the three RCTs for this outcome. The outcome is reported as a risk ratio (RR) because a summary relative risk was required for the cost-effectiveness model (Section 5.5.3.3). The Facon results were entered using the original group sizes to generate a conservative estimate of overall treatment effect for use in the cost-effectiveness model. The overall effect for the outcome of complete response favours MPT (RR 5.49, 95% CI 2.55 to 11.38).

Figure 3: MPT versus MP Complete Response

Risk ratios for the outcome of complete response were also obtained for the single RCTs for the VMP versus MP comparison and the CTDa versus MP comparison using the data reported in Table 8 and Review Manager software. These risk ratios were needed for the cost-effectiveness model (complete response VMP vs MP RR 8.35 95% CI 4.68 to 14.89).

4.1.2.4 Other time to event data

The VISTA RCT[26] of VMP was the only included RCT to report time to disease progression (TTP) and this was the primary outcome of this RCT. TTP was calculated from randomisation to disease progression. Data from patients in whom there was no disease progression were censored at the last assessment or at the start of subsequent therapy. Although not explicitly stated it is assumed that this outcome does not include deaths where there was no disease progression (these events would be included in the outcome of PFS section 4.1.2.5). Median TTP was significantly longer in the VMP group than in the MP group (VMP group 20.7 months versus MP group 15.0 months, HR=0.54, p<0.001). The median time to first response (partial or better) was 1.4 months in the VMP group and 4.2 months in the MP group, (p<0.001), and 4.2 months and 5.3 months for complete response (p<0.001), respectively (Table 9). The median duration of response (according to EBMT criteria) was 19.9 months in the VMP group and 13.1 months in the MP group; the median

duration of response among patients who had a complete response was 24 months in the VMP group and 12.8 months in the MP group. Time to subsequent myeloma therapy and treatment-free interval was reported in the published paper[26] as 20.8 months and 9.4 months respectively in the MP group; these times were not reached for the VMP group. In the abstracts reporting longer follow-up,[59,60] time to next therapy was 28.1 months in the VMP group and 19.2 months in the MP group ($p<0.000001$, HR 0.53); the treatment-free intervals were 16.6 months and 8.4 months ($p<0.00001$, HR 0.54) respectively after a median follow up of 25.9 months.[59] After median follow up of 36.7 months[60] treatment-free interval was 17.6 months in the VMP group and 8.4 months in the MP group (HR 0.54, $p<0.0001$).

Of the MPT RCTs only Palumbo and colleagues[24] reported on the length of time it took to observe a partial response to treatment (Table 9). In the MPT treatment arm the median time to partial response was 1.4 months (range 22-200 days) but in the MP arm it took longer to reach the median time to partial response of 3.1 months but responses occurred within a very similar range of 25-210 days.

The MMIX RCT[48] TTP outcome was not eligible for inclusion in this systematic review because participants were entered into a second randomisation to either maintenance therapy with thalidomide or no maintenance therapy after they had completed first-line treatment with either CTDa or MP.

Table 9: Other time to event outcomes

Study	**Treatment arms**		
San Miguel et al.[26a] VISTA	**VMP (n=344)**	**MP (n=338)**	**HR and *p*-value**
TTP median (from computer algorithm analysis)	20.7 months	15.0 months	p<0.001 HR=0.54
Median time to first response (partial response or better)	1.4 months	4.2 months	p<0.001
Median time to CR	4.2 months	5.3 months	p<0.001
Median duration of CR or PR	19.9 months	13.1 months	Not reported
Median duration of CR	24 months	12.8 months	Not reported
Median time to subsequent myeloma therapy	Not reached	20.8 months	HR=0.52, p<0.001
Treatment-free interval	Not reached	9.4 months	Not reported
Time to next therapy from abstracts[59,60]	28.1 months (n not reported)	19.2 months (n not reported)	HR=0.53, p<0.000001
Treatment free interval from abstract[59]	16.6 months (n not reported)	8.4 months (n not reported)	HR=0.54, p<0.00001
Treatment free interval from abstract[60]	17.6 months	8.4 months	HR = 0.543 p<0.0001
Palumbo et al.[24] GIMEMA	**MPT**	**MP**	
Time to partial response, median (range)	1.4 months (22-200 days)	3.1 months (25-210 days)	Not reported

[a] time to event data determined by computer algorithm applying EBMT criteria. TTP from trial investigators data also available (Appendix 5)

4.1.2.5 Progression-free survival

PFS, in the VISTA RCT VMP was defined by San Miguel and colleagues[26] as the time between randomisation and either disease progression or relapse from complete response by EBMT criteria, or death due to any cause, whichever occurred first. Median PFS by investigator assessment based on central laboratory data and applying EBMT criteria was 21.7 months in the VMP group and 15.2 months in the MP group (HR 0.56, p<0.001). See Table 10.

The two included IFM RCTs[23,58] reported on PFS and both calculated PFS from randomisation to either progression, or death without progression (Table 10). Hulin and colleagues[58] censored data on patients who had not experienced progression to the last day

that they were known to be alive and progression-free. Facon and colleagues[23] did not comment on methods for censoring data.

After a median follow up of 51.5 months 92 of the 125 participants in the MPT group of the Facon and colleagues[23] RCT had either experienced disease progression or they had died. The median PFS of the MPT group was 27.5 months (SE 2.1). In comparison, in the MP group 171 of 196 participants had disease progression or had died and the median PFS was 17.8 months (SE 1.4). The difference in PFS was statistically significant (p=0.001) with a hazard ratio for median PFS in favour of MPT of 0.51 (95% CI 0.39-0.66).

Hulin and colleagues[58] also found that the difference in PFS between MPT and MP + placebo groups after a median follow up of 47.5 months was statistically significant with a hazard ratio of 0.62 (p=0.001). In the MPT group median PFS was 24.1 months (95% CI 19.4 to 29.0) in comparison to 18.5 months (95% CI 14.6 to 21.3) in the MP + placebo group.

The event-free[24] and progression-free[48] survival outcomes reported by Palumbo and colleagues[24] and the MMIX RCT[48] were not eligible for inclusion in this systematic review because participants received maintenance therapy with thalidomide after first-line treatment had been completed.

Table 10: Progression-free survival

Study	**Median follow-up**	**Treatment arms**		
San Miguel et al.[26] VISTA		**VMP (n=344)**	**MP (n=338)**	**HR and *p*-value**
Progression-free survival, Median	16.3 months [a]	21.7 months	15.2 months	HR 0.56, p<0.001
Facon et al.[23] IFM 99/06		**MPT (n=125)**	**MP (n=196)**	**HR and *p*-value**
Progression-free Survival, Median (SE)	51.5 months	27.5 (2.1) months	17.8 (1.4) months	HR 0.51 (95% CI 0.39-0.66) p=0.0001 [b]
Hulin et al.[58] IFM 01/01		**MPT (n=113)**	**MP + placebo (n=116)**	**HR and *p*-value**
Progression-free Survival, Median (95% CI)	47.5 months	24.1 (19.4 to 29.0) months	18.5 (14.6 to 21.3) months	HR 0.62, p=0.001

[a] Median follow up not explicitly stated, assumed to be the same as that for OS.

[b] At the initial analysis (median follow up 36.8 months) no difference in PFS was recorded as a function of initial, maximum or average thalidomide doses (p=0.22, p=0.75, p=0.92 respectively).

Two MPT versus MP RCTs[23,58] reported PFS outcome data that was included in a fixed effects meta-analysis. As can be seen in Figure 4 the I^2 test suggests there is little or no heterogeneity between the two RCTs for this outcome. The summary PFS HR was 0.56 (95% CI 0.46 to 0.67) in favour of MPT.

Figure 4: MPT versus MP Progression-free survival

The Facon study confidence intervals shown in Figure 4 obtained from Review Manager are slightly different to those reported by the published paper and shown in Table 10. The

difference arises from the use of the estimating method used to obtain the standard errors for the log hazard ratios needed to undertake the meta-analysis.

4.1.2.6 Quality of Life

The VISTA RCT included a QoL assessment which has only been reported in an abstract.[61] The abstract states that the aim of the study was to describe the rate of patients who experienced a sustained HRQoL improvement after best response and the overall HRQoL impact of best response. A sustained HRQoL improvement was defined as a change in score of at least 5 points for at least 2 consecutive cycles after best response (CR, PR or MR). After best response onset, patients in the VMP arm had a higher sustained HRQoL improvement rate than those in the MP arm in 14 of the 15 European Organisation for Research and Treatment of Cancer QoL questionnaire C-30 (EORTC QLQ-C30) scores.

Table 11: Quality of life

Study	**Treatment arms**		
San Miguel et al.[60] VISTA	**VMP (n=344,number analysed not reported)**	**MP (n=338, number analysed not reported)**	***p*-value**
Sustained response in QLQ-C30 domains[a]			
- cognitive functioning	27%	28%	not reported
- nausea/vomiting	not reported	not reported	p=0.0095[b]
- appetite loss	not reported	not reported	p=0.0170
- diarrhoea	not reported	not reported	p=0.0082
- Global health	49%	40%	not statistically significant
- Pain	40%	32%	not statistically significant
- Insomnia	32%	24%	not statistically significant

[a] The rate of sustained improvement was calculated in the population of patients who were followed for at least 2 cycles after best response (n=363). The number of patients in each arm contributing data was not reported.

[b] The differences for Nausea and Diarrhea remained significant in the Cox models when adjusted for baseline score, score at best response, and type of response (CR, PR or MR).

The MMIX RCT[48] assessed QoL but it was not possible to include data in this systematic review because some of the participants were entered into a second randomisation to either maintenance therapy with thalidomide or no maintenance therapy after they had completed first-line treatment with either CTDa or MP.

4.1.2.7 Adverse events

This section summarises AEs reported by RCTs, concentrating on the events that require active management, and/or have the greatest impact on patient QoL. The AEs that have been omitted from each table are listed in the table footnotes and the complete AE data for each RCT can be found in the data extraction forms in Appendix 5.

AEs reported by San Miguel and colleagues in the VISTA RCT[26] of VMP were graded with the use of the NCI CTCAE (version 3). Occurrence of any AE and grade 4 AE was similar in the two groups although grade 3 events were more common in the VMP group (53% vs 44%, p=0.02) (see Table 12). Haematologic toxic events were the most frequently reported AEs and were also similar in the two groups. Peripheral sensory neuropathy was reported more frequently in the VMP group but by the data cut-off point, 74% of peripheral neuropathy events had either resolved (56%) or decreased by at least one toxicity grade (18%) within a median of two months. All grade 3 and grade 4 gastrointestinal events were more frequent in the VMP group than in the MP group (19% vs 5%, no *p*-value given). Incidence of deep vein thrombosis was low and similar in the two groups.

Table 12: Adverse events reported in the VISTA trial, No (%)

Study	**Treatment arms**		
San Miguel et al.[26,59] VISTA	**VMP (n=340)**	**MP (n=337)**	***p*-value**
Any event [a]	338 (99%)	326 (97%)	Not reported
- grade 3	181 (53%)	148 (44%)	p=0.02
- grade 4	96 (28%)	92 (27%)	Not reported
Serious adverse events	46%	36%	Not reported
Haematologic events [b]			
- thrombocytopenia	178 (52%)	159 (47%)	Not reported
- neutropenia	165 (49%)	155 (46%)	Not reported
- anaemia	147 (43%)	187 (55%)	Not reported
- leucopenia	113 (33%)	100 (30%)	Not reported
- lymphopenia	83 (24%)	58 (17%)	Not reported

Gastrointestinal events of grade 3 and grade 4 [c]	19%	5%	Not reported
Infections			
- pneumonia	56 (16%)	36 (11%)	Not reported
- herpes zoster	45 (13%)	14 (4%)	Not reported
Nervous system disorders			
- peripheral sensory neuropathy	151 (44%)	16 (5%)	Not reported
- neuralgia	121 (36%)	5 (1%)	Not reported
- dizziness	56 (16%)	37 (11%)	Not reported
Other conditions [c]			
- fatigue	98 (29%)	86 (26%)	Not reported
- deep vein thrombosis	4 (1%)	6 (2%)	Not reported

[a] Listed AEs were reported in at least 15% patients and the median dose intensities of MP were the same in both groups. Patients could have more than one AE.

[b] rates of red cell transfusion were 26% in the VMP group, 35% in the MP group; rates of erythropoiesis-stimulating agents for treatment-related anaemia were 30% and 39% respectively.

[c] Gastrointestinal AEs detail on nausea, diarrhoea, constipation and vomiting omitted. Details of other conditions, pyrexia, anorexia, asthenia, couth, insomnia, peripheral oedema, rash ,back pain, dyspnea, hypocalaemia and arthralgia also omitted. Full details available in Appendix 5

The two IFM RCTs[23,58] did not report which system was used to grade toxic effects and AEs to treatment and therefore caution must be applied when comparing the results of these two RCTs with each other, and with the RCT reported by Palumbo and colleagues.[24] Neither IFM RCT describes whether all AEs that occurred have been reported, or whether only a subset of AEs is reported in the trial publication. Palumbo and colleagues used the NCI CTC (version 2) to grade AEs and all grade 3-4 events reported by patients or observed by investigators were reported. However, only AE reporting of infections from Palumbo and colleagues can be included here as the majority of AEs were reported for the whole trial period which included administration of thalidomide maintenance therapy in the MPT group. AEs are summarised in Table 13. Facon and colleagues[23] analysed safety at the October 2005 date point after 36.8 months of follow up, a shorter follow-up than for the outcomes of OS, PFS, and survival after progression.

Four types of haematological event (at grade 3 and 4) were reported by Facon and colleagues.[23] There were no statistically significant differences in the occurrence of anaemia (14% both groups, p=0.94) or thrombocytopenia (MPT group 14%, MP group 10%, p=0.29). A statistically significant difference was reported for neutropenia which occurred in a greater

proportion of MPT patients than MP patients (48% versus 26%, p<0.0001). Hulin and colleagues[58] also reported a statistically significantly greater proportion of participants in the MPT group experienced neutropenia (grade 3 and 4) than those in the MP group (23% versus 9%, p=0.003) but did not report on any other haematological events.

Both IFM RCTs[23,58] reported the occurrence of grade 3 and 4 thrombosis or embolism. Facon and colleagues[23] found the greater proportion of patients with grade 3 and 4 thrombosis or embolism in the MPT group was a statistically significant difference in comparison to the MP group (MPT 12% versus MP 4%, p=0.008). In contrast there was no statistically significant difference in this AE in the Hulin and colleagues RCT[58] (MPT 6% versus MP 3%, p=0.33).

Peripheral neuropathy occurred statistically significantly more frequently in the MPT groups of both IFM RCTs but the reporting of this differed. Facon and colleagues[23] reported on the occurrence of grade 3 and 4 peripheral neuropathy in both groups (MPT 6% versus zero events in the MP group, p=0.01). Facon and colleagues[23] also stated that peripheral neuropathy was observed in 69 (55%) patients in the MPT group, with the majority of cases (n=62) being grade 1 or 2, and the remainder grade 3 (n=7), with no grade 4 events. The equivalent data for the MP group were not provided. In contrast, Hulin and colleagues[58] reported on each grade of peripheral neuropathy separately for each group. The proportion of patients with peripheral neuropathy was reported to be statistically significantly greater in the MPT group than the MP group (p=0.003) although it was not clear whether the p-value related to peripheral neuropathy in general or grade 1 peripheral neuropathy in particular. Most cases of peripheral neuropathy were of grade 1 or grade 2 (grade 1 peripheral neuropathy MPT 18%, MP 16%, grade 2 peripheral neuropathy MPT 19%, MP 3%). Severe peripheral neuropathy was less common with 2% of both groups experiencing grade 3 peripheral neuropathy, and no grade 4 events reported.

Facon and colleagues[23] report what appears to be a composite outcome described as somnolence/fatigue/dizziness (grade 3 and 4). This occurred in 8% of the MPT group, statistically significantly more than the MP group where no one had these symptoms at this grade (p<0.0001). In contrast, Hulin and colleagues[58] reported on the single outcome of somnolence but over a wider severity range (grade 2 to 4) and found no statistically significant difference between the groups (MPT 6% versus MP 3%, p=0.19).

The incidence of grade 3 and 4 infections was reported by two RCTs[23,24] and details of the infections contributing to this outcome were provided. Facon and colleagues[23] reported no statistically significant difference in the number of patients with infections of grade 3 and 4

(MPT n=16 patients, 13%; versus MP n=18 patients, 9%; p=0.32). However, it is clear, although not explicitly stated, that some patients must have experienced more than one grade 3 or 4 infection, because the reported numbers of individual infections sum to 20 (Appendix 5). In the six month period of treatment in the Palumbo and colleagues RCT[24] eligible for inclusion in the review, there were statistically significantly more infections in the MPT group than the MP group (MPT 10% all within the first four months versus MP 2%, p=0.01). Hulin and colleagues[58] did not report this outcome, other than stating that the higher incidence of neutropenia in the MPT group did not translate into more frequent severe infections.

Gastrointestinal events of nausea and vomiting when reported were also infrequent events (Table 13). Constipation was the most commonly reported gastrointestinal AE. Facon and colleagues[23] reported that only participants in the MPT group experienced constipation at grade 3 and 4 which was a statistically significant difference (p<0.0001) in comparison to the MP group where no grade 3 and 4 constipation AEs were reported. Hulin and colleagues[58] reported on constipation AEs of grade 2 to grade 4, and the difference between the groups was not statistically significant (MPT 17% versus MP 10%, p=0.16).

Overall, Facon and colleagues[23] found that non-haematological toxic effects of grade 3 or higher were statistically significantly more likely in the MPT group than the MP group (MPT 42% versus MP 16%, p<0.0001).

Table 13: Adverse events reported by trials investigating MPT

Study	**Treatment arms**		
Facon et al.[23ab] IFM 99/06	**MPT (n=124)**	**MP (n=193)**	***p*-value**
Grade 3 and 4 AEs, numbers of patients (%) after 36.8 months of follow up			
Haematological			
- anaemia	17 (14%)	27 (14%)	p= 0.94
- neutropenia	60 (48%)	51 (26%)	p<0.0001
- thrombocytopaenia	17 (14%)	19 (10%)	p= 0.29
Thrombosis or embolism	15 (12%)	8 (4%)	p= 0.008
Peripheral neuropathy	7 (6%)	0	p= 0.001
Somnolence/fatigue/dizziness	10 (8%)	0	p<0.0001

Infection	16 (13%)	18 (9%)	p= 0.32
Gastrointestinal			
- nausea	1 (1%)	2 (1%)	
- constipation	13 (10%)	0	p<0.0001
Any grade ≥3 non-haematological toxic effect	52 (42%)	30 (16%)	p<0.0001
Hulin et al.[58bc] IFM 01/01	**MPT (n=113)**	**MP + placebo (n=116)**	***p*-value**
Peripheral neuropathy grade 1	20 (18%)	19 (16%)	p=0.003
Peripheral neuropathy grade 2	21 (19%)	4 (3%)	
Peripheral neuropathy grade 3	2 (2%)	2 (2%)	
Neutropenia grade 3 or 4	26 (23%)	10 (9%)	p=0.003
Thrombosis or embolism grade 3 or 4	7 (6%)	4 (3%)	p=0.33
Somnolence grade 2 to 4	7 (6%)	3 (3%)	p=0.19
Constipation grade 2 to 4	19 (17%)	12 (10%)	p=0.16
Nausea/vomiting grade 2 to 4	3 (3%)	5 (4%)	p=0.5
Palumbo et al.[24d] GIMEMA	**MPT**	**MP**	***p*-value**
Grade 3-4 Infections	12/129 (10%) within the first 4 months of treatment	2/126 (2%) Timing of occurrence unknown:	p = 0.01

[a] In the MPT group 15 patients experienced 17 episodes of thrombosis or pulmonary embolism. Thalidomide was resumed in eight of the 15 patients with thrombosis after full anticoagulation, and without recurrent in seven patients (one patient had three episodes). In the MPT group 62 patients had grade 1 or 2 peripheral neuropathy and 7 patients had grade 3 peripheral neuropathy (these are the 7 noted above).

[b] For Facon et al the AEs of severe haemorrhage, cardiac AEs, and the gastrointestinal AEs of mucositis and bleeding have been omitted. Details on the infections that occurred have also been omitted. For Hulin et al AEs of Depression and Oedema have been omitted.

[c] There is contradictory information in text and table 3 of this paper. For peripheral neuropathy grades 1 and 2 text states 21 (19%) grade 1 and 20 (18%) grade 2 in MPT group but table has these the other way around (as shown here). For the MP + placebo group table states 17% with peripheral neuropathy whereas text states 16%. Text appears correct as 19/116 is 16.4%. For neutropenia (grade 3 or 4) text states 25 (22%) for MPT group but table has 26 (23%).

[d] Full AE reporting not data extracted because period that this covered and timing of the occurrence of the events was not reported (therefore unable to distinguish between events occurring during the first 6 months of treatment and those occurring later during thalidomide maintenance). Details on the infections that occurred can be found in Appendix 5

The MMIX IX protocol[48] does not indicate which system would be used to AEs. It is also not clear whether all AEs that occurred related to induction chemotherapy are presented in the results that have been made available.[53] AEs are summarised in Table 14.

[redacted]

Table 14: Adverse events reported by trials investigating CTDa

Study	Treatment arms		
MMIX[53]	CTDa (safety population)	MP (safety population)	*p*-value
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

[redacted]

[redacted]

4.1.2.8 Discontinuation or withdrawal due to adverse events

In addition to the reporting of AEs in general above (Section 4.1.2.7, Table 12 to Table 14) some of the included RCTs also reported on the patients who discontinued study medication, or withdrew from the study as a consequence of AEs (Table 15 and Table 16).

In the VISTA RCT[26] 50 patients (15%) in the VMP group and 47 patients (14%) in the MP group discontinued treatment due to AEs (Table 15), including 37 patients (11%) and 35 patients (10%), respectively, who had treatment-related events. San Miguel and colleagues[26] provide no further details. Bortezomib alone was discontinued in an additional 63 patients (19%).

Table 15: Discontinuations from the VISTA trial due to adverse events

Study	**Treatment arms**		
San Miguel et al.[26] VISTA	**VMP (n=340)**	**MP (n=337)**	***p*-value**
Discontinued treatment due to AEs	50 (15%)	47 (14%)	Not reported
Discontinued treatment due to treatment-related events	37 (11%)	35 (10%)	Not reported
Discontinuations of bortezomib alone	63 (19%)	-	

For the MPT RCTs it was not clear from the study reports how many of the AEs that led to discontinuation or withdrawal had already been included in the general reporting of AEs (Table 13). It also seemed clear from data reported that some discontinuations and withdrawals were due to events not specified in the general reporting of AEs (Table 13), for example discontinuation of thalidomide due to cutaneous effects,[23] and withdrawals due to cardiac events,[58] and rash[58] (Table 16).

Two of the RCTs, Hulin and colleagues[58] and Palumbo and colleagues,[24] reporting on withdrawals due to AEs/toxicity and inability to complete six cycles of treatment due to AEs respectively, reported the outcome for both study groups. AEs led to more withdrawals from treatment in the MPT group than the MP group but the differences were not tested statistically

(Hulin and colleagues MPT 42.5% versus MP plus placebo 12.9%; Palumbo and colleagues MPT 13.2% versus MP 3.2%). Palumbo and colleagues[24] also report that discontinuation of thalidomide was required by 43 patients (33.3%) after a median of 2.1 months. It is not clear, but presumably these 43 patients included the 17 in the MPT group who were unable to complete the six treatment cycles. Facon and colleagues[23] report discontinuation of thalidomide in the MPT group among 45% of the participants who discontinued because of toxic effects, but do not report on discontinuations in the MP arm due to AEs.

In addition to discontinuation of thalidomide due to AEs, two RCTs reported that reductions in the dose of study drug were required by 17.7% of the MPT group versus 2.6% of the MP group in the Hulin and colleagues RCT[58] and in 28.7% of the MPT group after a median of 4 months of treatment in the Palumbo and colleagues RCT[24] where dose reductions required in the MP arm were not reported.

Table 16: Discontinuation or withdrawal due to adverse events in trials of MPT

Study	**Treatment arms**		
Facon et al.[23a] IFM 99/06	**MPT**	**MP**	***p*-value**
Discontinuation of thalidomide because of toxic effects	56/124 (45%)	Not reported	Not reported
- peripheral neuropathy	n=23	Not reported	Not reported
- thrombosis	n=7	Not reported	Not reported
- somnolence, dizziness, or fatigue	n=8	Not reported	Not reported
- cutaneous toxic effects	n=4	Not reported	Not reported
- psychiatric complications	n=1	Not reported	Not reported
Withdrawn because of other reasons	n=13	Not reported	Not reported
- haematological toxic effects	n=5	Not reported	Not reported
- infection	n=7	Not reported	Not reported
- stroke	n=1	Not reported	Not reported

Hulin et al.[58b] IFM 01/01	**MPT (n=113)**	**MP + placebo n=116)**	***p*-value**
Withdrawals due to adverse events/toxicity	n=48 (42.5%) [c]	n=15 (12.9%) [c]	Not reported
- peripheral neuropathy	n=12	n=3	Not reported
- neurological events (nonperipheral)	n=10	n=1	Not reported
- thrombosis/embolism	n=7	n=1	Not reported
- haematological events	n=7	n=6	Not reported
- digestive events	n=4	n=2	Not reported
- cardiac events	n=3	n=1	Not reported
- rash	n=2	n=0	Not reported
- other	n=3	n=1	Not reported
Dose reduction required because of AEs	n=20 (17.7%) [c]	n=3 (2.6%) [c]	Not reported
Palumbo et al.[24] GIMEMA	**MPT**	**MP**	***p*-value**
Unable to complete six cycles due to AEs	17/129 (13.2%) [c]	4/126 (3.2%) [c]	Not reported
Thalidomide discontinuation required	43 (33.3%) [c] patients after a median of 2.1 months		
Thalidomide dose reduction to 50mg required	37 (28.7%) [c] patients after a median of 4 months		

[a] Outcomes reported after a median follow up of 36.8 months.

[b] There is contradictory information in text and Fig1 of the study report. Text states 9 MPT group participants withdrew due to neurological events (nonperipheral) whereas Fig1 shows 10 participants. Data provided on timing of withdrawal due to toxicity but appears to be for study overall, not by group: within 3 months 9 patients; within 6 months 23 patients; within 12 months 38 patients.. Also unclear which patients are included as patient numbers given with timing of withdrawals sum to 70, but only 63 patients (48 MPT and 15 MP + placebo) withdrew due to toxicity.

[c] Percentages calculated by reviewer

4.1.2.9 Withdrawals from study due to any reason

A supplementary appendix to the VISTA RCT publication[26] reports on the numbers of patients withdrawn from the study with reasons (Table 17). Numbers are similar in the two

groups overall and for treatment-related events, death and other non-specified reasons. Withdrawal due to patient choice and maintenance of CR is higher in the VMP group, whilst withdrawal due to progressive disease is higher in the MP group (no *p*-values are given).

Table 17: Patient withdrawal from the VISTA study

Study	**Treatment arms**		
San Miguel et al.[26] VISTA	**VMP (n=340)**	**MP (n=337)**	***p*-value**
Patients still receiving assigned protocol at data cut off point	47 (14%)	33 (10%)	Not reported
Total discontinued treatment	139 (41%)	166 (49%)	Not reported
Discontinued due to progressive disease	24 (7%)	72 (21%)	Not reported
Discontinued due to treatment related events	37 (11%)	35 (10%)	Not reported
Discontinued due to patient choice	32 (9%)	18 (5%)	Not reported
Discontinued due to death	14 (4%)	17 (5%)	Not reported
Discontinued due to maintenance of CR	9 (3%)	1 (<1%)	Not reported
Other reasons for discontinuation	10 (3%)	11 (3%)	Not reported

The IFM RCTs report on the proportion of participants withdrawn from the study, and provide some information on the reasons for the withdrawals. It is not clear whether withdrawal data in Facon and colleagues[23] are reported for the initial analysis date of October 2005 (median follow up 36.8 months), or the later date of 2007 (median follow up of 51.5 months). Hulin and colleagues,[58] report withdrawals for the median follow up of 47.5 months. The majority of participants from both RCTs had been withdrawn from study treatment arms at the point of data analysis. In Facon and colleagues' RCT[23] 93 participants (75%) were withdrawn from the MPT arm, and 151 participants (78%) from the MP arm. Facon and colleagues do not report the reasons for these withdrawals but do indicate what proportion of withdrawn participants went on to receive a second-line treatment, and of those who had not received another treatment, how many had died and how many were still alive (Table 18). Hulin and colleagues[58] had 88.5% of participants withdraw from the MPT arm and 93.1% withdraw from the MP + placebo arm of their RCT. Most withdrawals in the MPT arm were due to toxicity (48 of 100 withdrawals) whereas in the MP + placebo arm most withdrawals were due to disease progression (69 of 108 withdrawals) (Table 18). A similar pattern was reported by Palumbo and colleagues[24] for the initial six treatment cycles (before the introduction of thalidomide maintenance therapy) where the most common reason for participants in the MPT group being unable to complete the six treatment cycles was AEs, but

in the MP group progressive disease was the main reason. No statistical comparisons of the data are reported within any of the RCTs.

Table 18: Withdrawals overall from trials of MPT

Study	**Treatment arms**		
Facon et al.[23] [a] IFM 99/06	**MPT**	**MP**	***p*-value**
Not withdrawn [b]	31/124 (25%)	42/193 (22%)	not reported
Withdrawn and not receiving second-line treatment	38/124 (31%)	25/193 (13%)	not reported
- up to death	11/38 (29%)	24/25 (96%)	not reported
- still alive	27/38 (72%)	1/25 (4%)	not reported
Withdrawn and having received second-line treatment	55/124 (44%)	126/193 (65%)	not reported
Hulin et al.[58] [c] IFM 01/01	**MPT**	**MP + placebo**	
Withdrawals overall	n = 100/113 (88.5%)	n = 108/116 (93.1%)	not reported
- due to disease progression	n=37	n=69	not reported
- due to death	n=6	n=16	not reported
- due to consent withdrawal	n=9	n=8	not reported
- due to toxicity (details above)	n=48	n=15	not reported
Palumbo et al.[24] GIMEMA	**MPT**	**MP**	***p*-value**
Unable to complete six cycles	32/129 (25%)	31/126 (25%)	not reported
- due to AEs (as noted above)	17/32	4/31	not reported
- due to progressive diseases	9/32	16/31	not reported
- because withdrew consent	3/32	2/31	not reported
- because lost to follow-up	3/32	7/31	not reported
- due to protocol violations	0/32	2/31	not reported

[a] Outcomes reported after a median follow-up of 36.8 months.

[b] either still on first-line treatment; or first-line ceased as planned and no further treatment, or alive without progression, or not withdrawn for another reason

[c] percentages calculated by reviewer

[redacted]

Table 19: Withdrawals from the MMIX trial of CTDa

Study	Treatment arms		
MMIX[51]	CTDa	MP	Total
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4.1.2.10 Duration and intensity of first-line treatment

San Miguel and colleagues reported that in the VISTA RCT[26] treatment lasted for a median of eight cycles in the VMP arm and seven cycles in the MP arm (Table 20). This is equivalent to approximately 11.5 months, and 10 months respectively.

The median duration of treatment in the MPT arm of 11 months in one of the MPT RCTs, Facon and colleagues[23] was similar to that of the VISTA RCT. The duration of treatment was not reported for the MP trial arm. Facon and colleagues also reported on the intensity of treatment with thalidomide. The aim was for participants to achieve a 400mg daily dose of thalidomide if it could be tolerated. Although not explicitly reported, it appears unlikely (see Table 20) that many participants received 400mg for the majority of the treatment period. Approximately 29% (36/124 participants) received less than 200mg/day for the duration of first-line treatment, and 47/124 of participants had their dose reduced during treatment. Only 11 participants were able to tolerate having their thalidomide dose increased during treatment.

Hulin and colleagues[58] had a treatment period of 72 weeks (about 18 months) but whilst the median duration of treatment in the MP group was 18 months, the median duration of treatment in the MPT group was only 13.5 months (Table 20). The trial authors do not comment on this.

[redacted]

Table 20: Median duration and intensity of first-line treatment

Study	**Treatment arms**		
San Miguel et al.[26] VISTA	**VMP (n=340)**	**MP (n=337)**	***p*-value**
Median number of treatment cycles	8 (46 weeks)	7 (39 weeks)	Not reported
Facon et al.[23] IFM 99/06	**MPT**	**MP**	***p*-value**
Median duration of treatment (IQR)	11 months (5-15)	Not reported	Not reported
Initial daily dose[a] of T 200mg or less	n=64/124 (52%) (includes 9 participants receiving initial dose of 100mg)	Not reported	Not reported
Initial daily dose of T more than 200mg	n=60/124 (48%) (includes 5 participants receiving initial dose of 300mg)	Not reported	Not reported
No change of dose throughout first-line treatment	n=66/124 (36 at ≤ 200 mg/day; 30 at >200 mg/day)	Not reported	Not reported
Dose increased during first-line treatment	n=11/124	Not reported	Not reported
Dose reduced during first-line treatment	n=47/124	Not reported	Not reported
Hulin et al.[58] IFM 01/01	**MPT**	**MP + placebo**	***p*-value**
Median duration of treatment	13.5	18	Not reported

	months	months	
MMIX[51,52]	**CTDa**	**MP**	***p*-value**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

[a] The initial daily dose was defined as the greatest dose used in the first 4 weeks of treatment.

[redacted]

4.1.2.11 Second-line treatments received by trial participants

San Miguel and colleagues[26] reported that in the MP group 57% of participants started second-line therapy within two years, in comparison to 35%[26] (updated to 38% in a more recent abstract[59]) in the VMP group. It is not clear what the denominator in these calculations is, the total number of randomised participants or the number of surviving participants. Over half of the participants in each group received either thalidomide, or lenalidomide as a second-line therapy (Table 21).

Two of the three RCTs of MPT versus MP provided data on second-line treatment that could be included in the review[23,58] (as participants in the RCT by Palumbo and colleagues[24,25] received maintenance therapy with thalidomide second-line treatment data has not been included here). Second-line treatment was administered to 65% of the MP group in comparison to 44% of the MPT group in the RCT reported by Facon and colleagues.[23] Hulin and colleagues[58] reported disease progression occurrence in 156 participants overall, with more participants with disease progression in the MP + placebo group than the MPT group (72% versus 64%). Second-line treatment was administered to a similar proportion of participants with disease progression in each arm. In both RCTs thalidomide (alone or in combination) was the most commonly administered second-line treatment in the MP group, with about a fifth of participants in the MPT groups of these RCTs receiving thalidomide again as second-line therapy. The most commonly administered second-line treatment in the MPT group reported by Facon and colleagues[23] was a combination of vincristine, doxorubicin, and dexamethasone (VAD). Only 13% of MPT arm participants received bortezomib. In contrast, Hulin and colleagues[58] reported that 31% of participants in the MPT arm received bortezomib as a second-line treatment (Table 21).

Table 21: Second-line therapy received by trial participants

Study	**Treatment arms**			
San Miguel et al.[26] VISTA	**VMP**		**MP**	
Started second-line treatment within 2 years[26]	35%		57%	
Outcomes from abstract[60] at median follow-up of 36.7 months	**VMP (n=178)**		**MP (n=233)**	
Received subsequent therapy containing:				
- bortezomib	43 (24%)		116 (50%)	
- thalidomide	81 (46%)		110 (47%)	
- lenalidomide	57 (32%)		30 (13%)	
Overall response rate to subsequent therapy				
- bortezomib	47%		59%	
- thalidomide	41%		53%	
- lenalidomide	59%		52%	
Outcomes from abstract[59] at median follow-up of 25.9 months	**VMP (n=129)**		**MP (n=194)**	
Required subsequent therapy[59]	38%		57%	
Received bortezomib[59]	16%		43%	
Received thalidomide[59]	49%		44%	
Received lenalidomide[59]	19%		6%	
Subsequent therapy and number of patients who received it[59 a]	CR (%)	PR (%)	CR (%)	PR (%)
Bortezomib or bortezomib combination (n=105)	6%	33%	10%	45%
Thalidomide combination (n=149)	4%	44%	3%	52%
Lenalidomide combination (n=37)	4%	52%	0	55%
Facon et al.[23 b] IFM 99/06	**MPT**		**MP**	
Second-line treatment administered	55/124 (44%)		126/193 (65%)	
Second-line treatment thalidomide alone or in combination	10/55 (18%)		55/126 (44%)	
Second-line treatment VAD	15/55 (27%)		42/126 (33%)	
Second-line treatment dexamethasone	7/55 (13%)		12/126 (10%)	
Second-line treatment alkylating agent-based regimens	14/55 (25%)		13/126 (10%)	
Bortezomib	7/55 (13%)		3/126 (2%)	
Other	2/55 (4%)		1/126 (1%)	

Hulin et al.[58] IFM 01/01	MPT	MP + placebo
Disease progression occurrence	72/113 (64%)	84/116 (72%)
Second-line treatment administered [c]	61/72 (85%)	70/84 (83%)
Thalidomide	16/72 (22%)	53/84 (63%)
Bortezomib	22/72 (31%)	28/84 (33%)
Lenalidomide	11/72 (15%)	9/84 (11%)
Thalidomide &/or lenalidomide	25/72 (35%)	59/70 (83%)
Thalidomide &/or lenalidomide &/or Bortezomib	38/72 (53%)	68/81 (83%)

[a] other agents were used as subsequent therapy such as dexamethasone; patient could receive multi-agent regimens.

[b] Reported after a median follow-up of 36.8 months

[c] Second-line treatment administered to 156 patients (combined total both groups) presenting with disease progression.

4.1.2.12 Survival time after disease progression

Median survival time after disease progression was longer by approximately two months in participants in the MPT groups, than for those in the MP groups in the two RCTs that reported this outcome.[23,58] However, in the one RCT that reported a statistical comparison this difference was not statistically significant (MPT 11.5 months versus MP 9.9 months, p=0.89) (Table 22).

Table 22: Survival time after disease progression

Study	Treatment arms		
Facon et al.[23] IFM 99/06	**MPT** (n=83)	**MP** (n=154)	***p*-value**
Survival time after progression, Median (SE), after median follow up of 51.5 months	13.4 months (2.3) 52 events/83 patients	11.4 months (1.9) 111 events/154 patients	
Hulin et al.[58] IFM 01/01	**MPT**	**MP**	***p*-value**
Survival time after progression, Median (95% CI)	11.5 months	9.9 months	p=0.89

4.1.2.13 Subgroup analysis

Subgroup analysis in the VISTA RCT took place between VMP and MP participant subgroups defined by participant baseline characteristics. Results were presented only for the

outcome of time to disease progression. These results showed that for each of the seven prespecified subgroups (age, sex, race, baseline β2-microglobulin level, baseline albumin level, region, and disease stage) and single *post-hoc* subgroup (baseline creatinine clearance) the risk of disease progression in the VMP arm was lower than for participants in the equivalent subgroups in the MP arm (i.e. time to disease progression was shorter in the MP subgroups than the VMP subgroups). It is not clear whether the RCT was powered for these subgroup analyses and therefore caution should be applied when interpreting the results.

No subgroup analysis data were eligible for inclusion in this review from the RCTs of MPT versus MP. Facon and colleagues[23] state in the discussion section of their paper that *post-hoc* analyses for three subgroups were conducted but the results of these are not presented. No subgroup analyses are reported by Hulin and colleagues[58] and the subgroup analyses for PFS and OS reported by Palumbo and colleagues[24,25] are not eligible for inclusion due to the use of thalidomide maintenance in the MPT group of this RCT.

The MMIX trial protocol[48] states that "Subgroup analysis may by chance generate false negative/positive results. Those carried out will be interpreted with caution and treated as hypothesis-generating" (page 57).

[redacted]

4.2 SHTAC review of clinical effectiveness in manufacturers' submissions

Celgene Ltd (thalidomide manufacturer) and Janssen-Cilag Ltd (bortezomib manufacturer) submitted reports to NICE. The clinical effectiveness evidence presented in these reports has been briefly appraised (Appendix 7). A discussion of the economic models and cost-effectiveness results included in the manufacturers' submissions (MSs) can be found in section 5.3 and section 5.4.

The manufacturers both conducted systematic reviews of the clinical effectiveness evidence, however only Janssen-Cilag presented this within the main body of the MS. Celgene reported

a systematic review only as part of the appendix which described the meta-analysis they had undertaken. Both manufacturers supplied search strategies and reported on the details of the searches undertaken. Neither manufacturer appeared to have searched for ongoing studies although conference proceedings were included in their searching.

The MSs differ in the clinical effectiveness evidence that has been included, and the evidence in each submission also differs to that included in the SHTAC systematic review (Section 4.1). These differences can be seen in Table 23 which shows which studies have been included. In addition to the available published evidence Janssen-Cilag included data from the clinical study reports of the bortezomib RCT.

The conclusions on the clinical effectiveness of MPT and VMP of the two MSs and the SHTAC systematic review (based on narrative summaries of trial outcomes) are broadly similar. Due to the differences in the trials included and the different methodologies employed between the SHTAC meta-analyses and the manufacturers mixed treatment comparison (MTCs), it has not been possible to draw meaningful comparisons between them.

Table 23: Clinical effectiveness evidence included in the systematic reviews conducted by Janssen-Cilag, Celgene and SHTAC

Trial	Janssen-Cilag	Celgene[c]	SHTAC
San Miguel et al. VISTA	✓	✓	✓
Facon et al. IFM 99/06	✓	✓	✓
Hulin et al. IFM 01/01	✓	✓	✓
Palumbo et al. GIMEMA	✓	in sensitivity analysis only	Only data prior to the start of thalidomide maintenance therapy
Nordic myeloma study group[a]	✓	in sensitivity analysis only	X – ongoing study, designated unclear
Hovon 49[a]	✓	in sensitivity analysis only	X – ongoing study, designated unclear
MMIX[a]	✓	X	✓

[a] Reported in abstract form only at the time these systematic reviews were conducted

[b] SHTAC had access to additional information on methodology and additional results data which was provided by the MMIX trialists at the request of NICE. Janssen-Cilag and Celgene only had access to the information reported in the published abstracts.

4.3 Ongoing studies

The clinical effectiveness search for studies identified seven abstracts and two ClinicalTrials.gov records which described four ongoing studies, each comparing MPT with MP. It is not clear whether these studies meet the inclusion criteria of this systematic review.

Two abstracts[62,63] and a ClinicalTrials.gov record (identifier NCT00218855) describe an ongoing study which recruited participants in Norway, Sweden and Denmark between 2002 and 1st May 2007. This study has not been reported on in detail because insufficient details about study were provided (e.g. drug doses for MP unknown, number of participants in each study arm unknown), and there were also insufficient details presented to allow judgements about study quality to be made. Some information presented differed between the two abstracts, and the ClinicalTrials.gov description of the study indicates that patients receive

thalidomide maintenance treatment so it is therefore unclear whether this study meets the inclusion criteria of this review.

The second ongoing study, Hovon 49, is described in three abstracts[64-66] and again it is unclear whether this study meets the inclusion criteria for this review because patients could receive thalidomide maintenance treatment. The study recruited participants in The Netherlands starting in 2002 but participant accrual was stopped early (date not reported) due to the publication of other RCTs showing a positive outcome for thalidomide treated participants.

The third ongoing study, described in a single abstract,[67] compares MP with MPT but also includes a second randomisation at the end of induction therapy to maintenance therapy with either dexamethasone, or dexamethasone plus thalidomide.

If the full publications describing the three studies above report outcome data for participants at a time point prior to maintenance therapy then these data would be eligible for inclusion. Similar data have already been included in this review from the study by Palumbo and colleagues[24] and the MMIX study[48,52,53] which both incorporated maintenance therapy.

The fourth ongoing RCT described in a conference abstract and a ClinicalTrials.gov record (identifier NCT00934154)[68] is an RCT initiated by the Turkish Myeloma Study Group that allows participants from the MP arm to cross-over to the MPT arm if insufficient response to MP is obtained, with response being evaluated at every other cycle. It is not clear whether this cross-over RCT will meet the inclusion criteria of the review.

4.4 Summary of clinical effectiveness

- Five RCTs[23,24,26,48,58] met the inclusion criteria of the systematic review, four[23,24,26,58] have been published in full papers, one has only been reported in abstracts but additional information has been provided by the trialists.[48] One RCT[26] examined the effectiveness of bortezomib in combination with MP, three RCTs[23,24,58] examined the effectiveness of MPT, and one RCT[48] examined CTDa. The comparator in all five RCTs was MP, the comparator of one RCT also included a placebo in place of thalidomide.
- Four further trials, published only in abstract form,[62-68] provided insufficient details to allow a judgement about whether they are likely to meet the inclusion criteria of this review (so these were excluded from the systematic review).

VMP versus MP alone

- The quality of the RCT[26] was difficult to determine. Risk of allocation bias and of unbalanced confounding factors could not be judged because details on these aspects were not reported. Most, but not all, analyses had followed the ITT principle but the methods used to account for any missing data were not described. It was not possible to determine whether the amount and pattern of censored data was similar between trial arms.
- Time to disease progression was the primary outcome of the RCT and a statistically significant effect in favour of the VMP group was reported.
- OS was a secondary outcome. A survival advantage for the VMP arm in comparison to the comparator MP was reported.
- Statistically significantly more participants in the VMP group achieved complete response, or achieved a partial response or better. This outcome was not analysed by ITT principles.
- Median PFS was statistically significantly longer in the VMP group than in the MP group.
- Limited data on HRQoL was available. This indicated that after the onset of best response, participants treated with VMP arm had a higher sustained HRQoL improvement rate in 14 of the 15 EORTC QLQ-C30 scores than those participants receiving therapy with MP.
- AEs occurred in both trial arms. Although the occurrence of any AE and any grade 4 AE was similar in the two groups, there was a statistically significant increase in grade 3 AEs in the VMP group.
- Subgroup analyses were conducted. The RCT may not have been powered for these analyses so the results, which indicate that the reported benefits of bortezomib for TTP apply to each of the seven sub-groups of participants assessed, should be interpreted with caution.

MPT versus MP alone

- The quality of the three RCTs[23,24,58] was variable. Risk of allocation bias could not be judged for one RCT and the risk of allocation bias and of unbalanced confounding factors could not be judged for another RCT because the necessary details were not reported. Although all RCTs stated that ITT analyses had been conducted the details of these analysis and the methods used to account for missing data were in general poorly described. It was not possible to determine whether the amount and pattern of censored data was similar between trial arms for any of the included RCTs.

- OS was a primary outcome in two of the RCTs.[23,58] Both reported a survival advantage for the MPT arm in comparison to the comparator MP alone. Meta-analysis of the OS data from two RCTs confirmed the superiority of MPT in comparison to MP for the OS outcome. The third RCT of MPT included maintenance therapy with thalidomide and therefore OS, which was a secondary outcome of this RCT, was not eligible for inclusion in the review.
- Response to treatment was the primary outcome of one RCT[24] (at a six month time point) and a secondary outcome in two RCTs[23,58] (both at a 12 month time point). At six months more participants in the MPT group achieved complete response or achieved a partial response or better, but a *p*-value for the comparison is not reported. At 12 months, two RCTs reported that a statistically significant greater proportion of participants had achieved complete response or had achieved at least a partial response. However, it was noteworthy that in one of these RCTs the numbers of participants contributing data to this outcome was low. Outcomes for complete response from three RCTs were combined by meta-analysis which confirmed that MPT was superior in comparison to MP in terms of the proportion of patients achieving complete response.
- Two RCTs[23,58] reported a statistically significant advantage in the MPT group in comparison to the MP group for the outcome of PFS. The PFS data were combined by meta-analysis which confirmed that MPT was superior in comparison to MP for this outcome.
- AEs were reported in different ways so it was difficult to summarise the results across the RCTs. Because one RCT had included maintenance therapy with thalidomide few AE data could be included so the majority of the data come from just two RCTs. AEs with a statistically significant greater occurrence in the MPT arm that was reported by two RCTs included neutropenia and peripheral neuropathy. One RCT found that overall non-haematological toxic effects were statistically significantly more likely in the MPT group. For the outcomes of thrombosis or embolism, somnolence, constipation and infections, the results were inconsistent between RCTs (no significant difference in incidence reported by one RCT, but statistically significantly more in the MPT arm reported by the other RCT). This inconsistency may be a consequence of the different methods of reporting AEs. Some outcomes were only reported by one RCT, such as anaemia and thrombocytopenia (no statistically significant differences).

CTDa versus MP

- This RCT[48] was judged to be at low risk from allocation bias and bias due to unbalanced confounding factors. Analyses had been conducted by ITT principles and some information was provided on the methods used to handle missing data. It was not reported whether the amount and pattern of censoring was comparable between the groups.
- Response was one of three co-primary outcomes of this RCT. [redacted]. The remaining two co-primary outcomes, OS and PFS, and also the HRQoL outcomes were not eligible for inclusion, because participants were randomised to maintenance therapy with thalidomide after induction chemotherapy and this treatment did not meet the inclusion criteria of the systematic review.
- AEs occurred in both RCT arms. [redacted]
- Subgroup analyses were conducted although numerical data were not presented. [redacted]

5 ECONOMIC ANALYSIS

Introduction

The aim of this section is to assess the cost effectiveness of first-line treatments for people with MM, who are ineligible for HDT with SCT compared to existing treatments. The economic evaluation comprises:

- a systematic review of the cost effectiveness of either bortezomib or thalidomide in combination with an alkylating agent and a corticosteroid (Section 5.1);
- a systematic review of studies of the HRQoL of people with MM (Section 5.2);
- a critical appraisal of the submissions from manufacturers received as part of the NICE appraisal process (Section 5.3 and Section 5.4); and,

- a *de novo* economic model and cost effectiveness evaluation developed by SHTAC (Section 5.5).

5.1 Systematic review of existing cost-effectiveness evidence

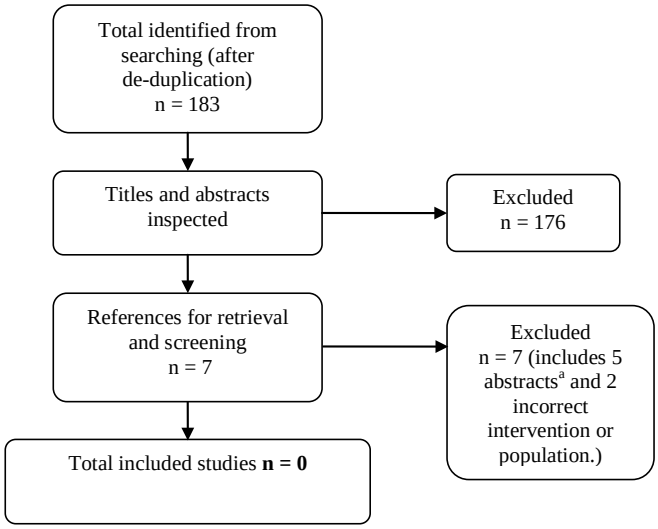
5.1.1 Methods for the systematic review of cost-effectiveness

A systematic literature search was undertaken to identify economic evaluations for first-line treatment with either bortezomib or thalidomide in combination with an alkylating agent and a corticosteroid in people with MM, who are ineligible for HDT with SCT, compared to existing treatments. The details of the search strategy and the methods for the systematic review of cost effectiveness studies are outlined in Section 3 and Appendix 1.

5.1.2 Results of the systematic review of cost-effectiveness

Searches for economic evaluations identified the titles and abstracts of 183 potentially relevant studies. The full text of seven papers was retrieved for further consideration, with none of the studies meeting the *a priori* inclusion criteria. A summary of the selection process and the reasons for exclusion are presented in Figure 5 and a list of excluded studies in Appendix 8. Two studies were excluded as they assessed a different intervention and/or population group from that specified in the research protocol.[69,70] Although five studies reported as abstracts appeared to meet the *a priori* inclusion criteria,[71-75] they did not contain sufficient information on the methods used and the results to justify formal data extraction or critical appraisal. Given the apparent relevance of these five studies, a brief summary of the abstracts is presented below.

Figure 5: Flow chart of identification of studies for inclusion in the review of cost effectiveness



[a]The five abstracts provided insufficient details of methods and results to allow inclusion in a formal systematic review. However as the abstracts met other inclusion criteria they are discussed for information.

Deniz and colleagues[71] estimated the life-time health and cost consequences of MPT compared to MP in people in Scotland with previously untreated MM. They developed a Markov model for a cohort of patients receiving a course of MPT or MP, conceptualizing the disease by four health states: pre-progression without AE, pre-progression with AE, progressive disease and death. Progression between health states as well as treatment duration, dose and AE risks were derived from a long-term RCT (see section 4.1).[23] Patient cohorts received a maximum of twelve 6-week cycles of treatment, until progression or treatment-limiting toxicity. The abstract indicates that health state utilities associated with disease states and AEs were obtained from the literature, but no sources are provided. Thalidomide costs were from UK list prices and routine disease management costs reflected current practice in Scotland. Costs and health outcomes were discounted at 3.5% per annum. The model estimated improvements in health outcomes with MPT with a median TTP of 25 months versus 12 months with MP. Estimated median OS was 4.03 years with MPT versus 2.88 years with MP. These translated to a gain of 0.91 QALYs for MPT (3.24 QALYs) compared with MP (2.32 QALYs). There were increased costs with MPT of £25,199 per patient compared to £8,935 per patient for MP, leading to an incremental cost-effectiveness ratio (ICER) of £17,847 per QALY and £14,803 per life year gained. The authors state that

sensitivity analyses showed that these results were consistent through changes in model parameters, although no information is presented. The authors conclude that MPT improves PFS and OS compared to MP and the results are cost effective. A similar study comparing life-time health and cost consequences of MPT compared with MP was completed for untreated MM patients in Wales.[73] Whilst this evaluation employed the same clinical outcomes for OS and PFS, it used slightly different QALY gains (0.9 QALYs) and life-time costs specific to managing the disease in Wales (£16,937 per patient for MPT versus £1524 per patient for MP). The study produced a slightly more favourable ICER of £17,002 per QALY and £13,346 per life year gained. It was reported that sensitivity analyses showed that findings were robust with 95% of outcomes between £12,750 and £26,500 per QALY gained. Both studies were funded by the manufacturer of thalidomide.

De Abreu Lourenco and colleagues[74] assessed whether MPT was cost effective compared to MP for people in Australia newly diagnosed with MM as part of an application to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. They extrapolated Kaplan Meier (KM) survival curves from an unspecified phase III study to a lifetime horizon to estimate the mean survival time. Costs included drugs, medical services and treatment for thalidomide related AEs. These data were incorporated into a cost effectiveness analysis adopting an Australian health care system perspective, with costs and benefits discounted at 5% (Australian $ 2008). The modelled analysis estimated an incremental gain in average survival of 1.47 years and 1.14 QALYs with an associated average incremental cost of AUS$23,953. This results in an ICER of AUS$20,998. The authors concluded that the analysis had resulted in a positive recommendation from PBAC to fund thalidomide for the treatment of patients newly diagnosed with myeloma.

Yoong and colleagues[72] estimated the cost effectiveness of bortezomib in combination with MP (VMP) compared to MP and MPT in previously untreated people with MM in Canada who are unsuitable for SCT. Clinical outcomes originated from the VISTA study[26] for VMP compared to MP and from an unspecified indirect comparison of VMP and MPT. The economic model projected OS over a 10 year horizon for VMP, MP and MPT using data from relevant studies and survival hazard ratios. Resource use data included costs of drugs, outpatient cancer clinic, managing of AEs, supportive care and subsequent lines of treatment, although sources were not specified. The discounted QALYs were 3.51 for VMP, 2.84 for MP and 3.29 for MPT. The total cost of treatment per patient were CAN$59,117 for VMP, CAN$27,026 for MP and CAN$52,226 for MPT. The ICER for VMP versus MP was CAN$48,294 per QALY gained and CAN$31,975 per QALY gained for VMP versus MPT. The study states that sensitivity analyses showed that survival difference was the most

influential factor. The authors concluded that the VMP regimen indicates good value for money, and it is being adopted by public cancer agencies in Canada.

Wang and colleagues[75] also compared the cost effectiveness of VMP, MPT and MP as first-line therapy for people with MM in the US who were ineligible for autologous SCT. A lifetime (20 years) Markov model from the US payer's perspective was developed with seven health states respresenting periods of treatment response (stable disease / minimal response, partial response, or complete response), treatment-free interval, progressive disease, second-line treatment and death. Monthly transition probabilities were estimated from the VISTA trial data for VMP and MP[26] and from the IFM 99-06 trial for MPT.[23] Costs included drug and medical costs, treatment-related AEs, second-line treatment and resource utilisation during treatment free intervals and progressive disease. All costs were adjusted to 2009 and presented in US dollars. State-specific utility estimates were derived from patient-level EQ-5D data from the VISTA RCT.[26] Cost and health outcomes were discounted at 3%. The discounted QALY was 2.99 for VMP, 2.09 for MP and 2.95 for MPT. The total costs were US$110,870 for VMP, US$57,864 for MP and US$129,902 for MPT. The ICER of VMP versus MP was US$56,109 per QALY gained. VMP was dominant compared to MPT (greater benefit and lower cost). One-way sensitivity analyses were reported to show that the ICERs were robust, with the key drivers being the hazard ratio for VMP versus MP for the transition between second-line treatment and and the hazard ratios for MPT versus MP for treatment discontinuation. The authors concluded that VMP is cost effective compared to MP in the United States.

SUMMARY

The systematic review of cost effectiveness showed that there were no fully published economic evaluations assessing the use of either bortezomib or thalidomide in combination with an alkylating agent and a corticosteroid as first-line treatment for people with MM who are ineligible for HDT. Five economic evaluations published as abstracts only were identified.[71-75] Of these evaluations, three compared MPT with MP[71,73,74] and two compared VMP with MPT and MP. [72,75] All three studies showed additional benefits from MPT compared with MP at additional cost with cost per QALY gained ranging from £17,002 to £17,847[71,73]in the UK and AUS$20,998 in Australia.[74] The two economic evaluations assessing VMP, MPT and MP showed that additional benefits were provided by VMP compared to MPT and by VMP and MPT compared to MP. The studies showed that ICERs ranging from CAN$48,294[72] to US$56,109[75] per QALY gained for VMP compared to MP and CAN$31,975 per QALY gained[72] and dominance[75] for VMP compared to MPT. All of the studies had the involvement of the manufacturer of the interventions.

5.2 Systematic Review of Health-Related Quality of life studies

A systematic review was undertaken to assess the HRQoL of people suffering from and/or treated for MM. The aim was to provide data to populate the lifetime economic model with utilities to calculate QALYs. Although the methods used, and the process for their application, were similar to those described in Section 3 and Appendix 1, there were some variations. The selection criteria used to assess the titles and abstracts of studies and the full papers of those retrieved were modified. Although the primary focus of the review was on people with previously untreated MM who were not candidates for HDT with SCT, it was thought that there would be limited HRQoL data available. As a consequence, the selection criteria were broadened. Studies were included if they assessed the HRQoL of people with previously untreated MM who were not candidates for HDT with SCT using either a generic preference-based utility measure (e.g. the European Quality of Life-5 Dimension (EQ-5D)) or the EORTC-QLQ-C30 disease-specific measure. Although the EORTC QLQ-C30 is a disease-specific, rather than a generic preference-based measure, it is commonly used to assess HRQoL in cancer and mapping studies are available to convert this measure to other HRQoL utility values (i.e. EQ-5D). In addition, studies were included if they assessed the HRQoL of people with MM irrespective of treatments received as long as a generic preference-based measure was used.

Generic preference-based methods generate a HRQoL score using a choice based method, such as time trade off or standard gamble, which values patients HRQoL on a scale between 0 (death) and 1 (perfect health).[76] These measures use a generic questionnaire which can be used for most health conditions or diseases. The EQ-5D is the preferred measure of HRQoL in adults by NICE[77] and has been used and validated in many different patient populations. The EQ-5D consists of five dimensions of health: mobility, self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. HRQoL utility values are generated for patients' responses using an algorithm derived from a large UK population study.

The search strategy identified 208 papers that were potentially relevant. The titles and abstracts were screened with the full text of 18 papers retrieved for further inspection. After checking the retrieved papers six studies met the inclusion criteria, five full papers and one abstract. A summary of the selection process and the reasons for exclusion are presented in Figure 6 and a list of excluded studies in Appendix 9. The nine studies excluded were due to the use of an inappropriate measure of QoL,[78-86] with two studies also assessing a different

population group.[79,81] The six studies included in the systematic review are summarised in Table 24. No generic preference-based QoL studies were found for newly diagnosed and untreated patients who were ineligible for HDT. Three studies focused on newly diagnosed and untreated patients, however they either were assessed on the EORTC QLQ-C30 non generic preference-based measure[87,88] and/or received treatment not included in the current evaluation.[88,89]

Generic preference-based measures of HRQoL (i.e EQ-5D) were assessed in four studies.[89-92] These four studies evaluated the EQ-5D among people with MM who were either receiving second-line or subsequent treatment,[90,92] where treatment status was unclear[91] or patients received or were receiving treatment not included in this evaluation.[89,91,92] Two studies reported HRQoL for patients receiving interventions included in this evaluation,[87,90] using the EORTC QLQ-C30 to assess patients newly diagnosed with MM receiving MP[87] and patients with relapsed and refractory MM receiving bortezomib.[90] The remainder of this section examines the six studies in more detail, providing an indication of the HRQoL of people with MM at different stages during their treatment.

Figure 6: Flow chart of identification of studies for inclusion in the review of quality of life studies

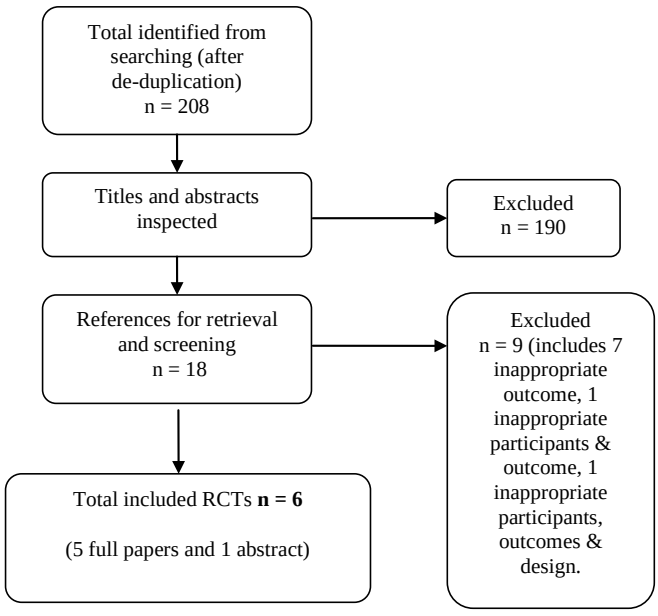


Table 24: Characteristics of included quality of life studies

Author	**Gulbrandsen et al.**[87]	**Mujica-Mota et al.**[90]	**Slovacek et al.**[91]	**Strasser-Weippl and Ludwig**[88]	**Uyl-de Groot et al.**[92]	**Van Agthoven et al.** [89]
Publication Year	2004	2004	2008	2008	2005	2004
Country	Denmark, Sweden and Norway.	USA	Czech Republic	Austria	The Netherlands	Belgium and The Netherlands.
Study type	2 prospective studies using QoL questionnaire with comparison to reference population through regression.	Utility mapping study.	QoL observational cohort study.	QoL sub-study within an RCT.	Prospective, longitudinal cohort study.	Cost utility study based on an RCT.
Study population	424 patients with newly diagnosed MM.	202 patients with relapsed and refractory MM.	32 patients with MM.	92 patients with recently diagnosed and previously untreated MM (ECOG performance status ≤3).	51 patients newly diagnosed with MM either untreated or undergoing first-line treatment.	261 patients with undiagnosed and untreated MM
Study population age	<60 yrs for people treated with high dose melphalan (HDM) with autologous blood stem cell support (ABSCS), >60 yrs for those treated with MP and 18-93 yrs for reference population.	Not reported.	Mean age 60 yrs (range 53-67 yrs).	Median age 66 yrs (range 43-84 yrs).	Mean (sd) 53 yrs (7.2).	Median age: Intensive chemotherapy group 55 yrs (range 38-65); Myeloablative therapy group 56 yrs (range 32-65).

Comparator population	Randomly selected Norwegian adults as a reference population (n=3000).	No comparator.	No comparator.	Age and gender-adjusted reference population (no details provided).	No comparator.	UK general public (no details provided).
Intervention(s)	HDM with ABSCS (n=221) and MP (n=203).	Bortezomib (Velcade).	High dose chemotherapy (melphalan) followed by autologous transplantation of blood stem cells (PBPCT).	Continuous or intermittent prednisolone plus vincristine, melphalan, cyclophosphamide, prednisolone, interferon-∝2b (VMCP-IFN∝2b) for induction therapy.	Vincristine, adriamycin and dexamethasone / vincristine, adriamycin and methyl prednisone (VAD/VAMP) chemotherapy, followed by HDM and then peripheral stem cell transplantation (PSCT).	Intensive chemotherapy compared with intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue.
Included QoL instrument used	EORTC QLQ-C30	Elements of the EORTC QLQ-C30 and MY24, FACT-Fatigue and FACT/GOG-Ntx were mapped to the EQ-5D.	EQ-5D and EQ-5D visual analogue scale (VAS).	EORTC QLQ-C30	EORTC QLQ-C30 and EQ-5D	EQ-5D

Time period where HRQoL instruments administered	QoL was assessed at baseline, 1, 6, 12, 24, and 36 months.	Not reported.	Not reported.	Baseline only.	Baseline (2 weeks post induction therapy), day of hospital discharge after HDM (T2), 1 month post discharge after HDM (T3), day of hospital admission for PSCT (T4), day of discharge following PSCT (T5), 6 months (T6) and 12 months (T7) post discharge for PSCT.	6, 12, 18 and 24 months.
Methodology of collecting QoL data	The 30 item questionnaire was administered within the 2 studies and by postal questionnaire to the reference population.	Not reported.	Postal questionnaire with voluntary and anonymous response.	Patients in the RCT were invited to take part and provided with the questionnaires at their first study visit of the trial.	Questionnaires were either handed to patients in hospital wards or mailed to their homes. Reminders were sent where not returned within a month.	Not reported.

Results	At diagnosis MM patients had significantly impaired QoL on all scores compared to the reference population, except for diarrhoea. Pain and fatigue, reduced physical functioning, limitations in role functioning and reduced overall QoL were the most distressing problems. After start of treatment, small to moderate improvements in mean QoL scores were observed in most domains.	Utility scores appeared similar across patient groups as defined by serological response to Bortezomib, with an overall utility score of 0.65.	For people treated with HDT and PBPCT the global QoL was 0.689 on EQ-5D and 0.666 on EQ-5D VAS. By age group the EQ-5D was 0.815 for people aged 40-49 yrs, 0.742 for those 50-59 yrs, 0.642 for those 60-69 years and 0.615 for those 70-79 yrs.	Study showed low levels of functional QoL scores and increased symptom scores in patients with active disease at start of first-line therapy. It was felt that measures such as pain, fatigue, physical functioning were important. Patients have significant impairment of physical and psychosocial dimensions at baseline compared to the health reference population.	Mean absolute scores (standard deviation (SD)) on EQ-5D at baseline after VAD/VAMP and mean change scores from baseline: baseline 0.52 (0.33); T2, 0.03; T3, 0.14; T4, 0.14; T5, -0.14; T6, 0.12; T7, 0.17. Mean absolute scores (SD) on EQ-5D at baseline and 12 months follow-up for patients who proceeded to PSCT: baseline –patients who proceeded to 12 month follow-up 0.60 (0.33); 12 months follow-up-patients with baseline 0.77 (0.13), 12 months follow-up all patients 0.79 (0.18).	Utility values on EQ-5D: (i) Intensive chemotherapy: 6 months = 0.81, 12 months = 0.80, 18 months = 0.81, 24 months = 0.77. (ii) Intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue: 6 months = 0.65, 12 months = 0.62, 18 months = 0.69, 24 months = 0.75. Stated that patients in an undefined state following curative primary

						therapy would have a QoL 19.5 % lower than general population (0.8), which equates to 0.644.

Uyl-de-Groot and colleagues[92] investigated the HRQoL of patients with newly diagnosed MM who were treated in a tandem transplantation programme. All patients were scheduled for intensive treatment with VAD/VAMP chemotherapy followed by HDM and transplantation of whole blood stem cells and finally re-infusion of the previously collected peripheral stem cells. The EQ-5D questionnaire was completed, at several time points, by 51 patients with a mean age of 53 years. Table 25 shows the EQ-5D utility estimates at different time points. The utility estimates vary between 0.38 and 0.69, with the lower utility estimates during treatment periods or immediately after discharge of treatment. The longer term QoL estimates after discharge of treatment range from 0.64 to 0.69.

Table 25: EQ-5D utility estimates for multiple myeloma patients from Uyl-de-Groot and colleagues

	Baseline	**Discharged HDT**	**1 month** [a]	**Admitted PBSCT**	**Discharged PBSCT**	**6 months** [b]	**12 months** [b]
EQ-5D value	0.52	0.55	0.66	0.66	0.38	0.64	0.69

[a] 1 month after HDT discharge

[b] After peripheral blood progenitor cell transplantation (PBSCT) discharge

Slovacek and colleagues[91] analysed the effect of selected demographics, psychosocial and health aspects on HRQoL in MM survivors treated with HDT (melphalan) followed by autologous peripheral blood progenitor cell transplantation (PBPCT). Thirty two patients of mean age 60 years completed the EQ-5D questionnaire. The EQ-5D estimate was 0.689.

Mujica-Mota and colleagues[90] mapped HRQoL measurements from EORTC QLQ-C30 estimates to the EQ-5D utility measure for patients with relapsed and refractory MM from the SUMMIT 1 trial. Few details are given in this abstract. The authors stated that the utility scores appear similar across patient groups as defined by serological response to bortezomib, with an overall utility score of 0.65.

Van Agthoven and colleagues[89] estimated the cost utility of intensive chemotherapy versus intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue in newly diagnosed and untreated patients with MM. There were 129 patients in the intensive chemotherapy arm and 132 in the myeloablative arm and all were less than 65 years old. Little detail was given on the methodology or results. The authors state that patients in an

undefined state following intentionally curative primary therapy would have HRQoL 19.5% lower than those in the general population, i.e. 0.644.

Strasser-Weippi and colleagues[88] evaluated baseline HRQoL in elderly patients recently diagnosed with MM who were previously untreated. Ninety two patients (of median age 66 years) participated in the HRQoL sub-study of an RCT of continuous or intermittent prednisolone plus vincristine, melphalan, cyclophosphamide, prednisolone, interferon-∞2b (VMCP-IFN∞2b) for induction therapy. They used the EORTC QLQ-C30 questionnaire for these patients and compared them to a reference population for the general population of same age and gender (see Appendix 10 for observed scores). The study found a significant impairment of physical and psychosocial dimensions of QoL in patients with MM at baseline compared with a healthy reference population. Low psychosocial QoL at baseline was associated with poor prognosis.

Gullbrandsen and colleagues[87] compared HRQoL scores of MM patients at diagnosis and over time with the scores of a reference population. Patients from two prospective Nordic Myeloma Study Group trials for high dose melphalan (HDM) with autologous blood stem cell support and MP completed the EORTC QLQ-C30 questionnaire. There were 221 patients for HDM who were less than 60 years old and 203 patients for MP who were more than 60 years old. The reference population consisted of 3000 randomly selected adults from the Norwegian population (see Appendix 10). At diagnosis, the most distressing problems were pain and fatigue, reduced physical functioning, limitations in role functioning and reduced overall HRQoL. These differences from the reference population were statistically significant, and large or moderate according to the rating systems. After the start of treatment, small to moderate improvement in mean QoL scores were observed for most domains.

5.2.1 Summary and conclusions of the HRQoL review

The systematic review did not find any generic preference-based HRQoL studies that were directly related to the population of interest. The utility estimates from HRQoL studies in patients with MM who had intensive therapy vary between 0.38 and 0.69, with the lower utility estimates during treatment periods or immediately after discharge from treatment.[92] The longer term HRQoL estimates after discharge from treatment range from 0.64 to 0.69. This may indicate that that HRQoL is lower during the treatment period and improves after treatment has finished. Furthermore, long term HRQoL may be stable over time. It is unclear whether patients with complete response following treatment have a higher HRQoL than those with other responses.

5.3 Review of the Janssen-Cilag submission to NICE (Bortezomib)

A structured data extraction form was used to guide the review of the Janssen-Cilag submission to NICE (Appendix 11). The manufacturer submission (MS) reports the total costs, the QALYs gained and cost-effectiveness associated with the interventions under consideration in the appraisal. The model evaluates lifetime costs and benefits for bortezomib in combination with MP (VMP), for previously untreated MM patients not eligible for HDT-SCT, compared to MPT, CTDa and MP. The perspective of the analysis is clearly stated as being that of the National Health Service (NHS) and Personal Social Services (PSS), capturing direct costs and benefits only.

Modelling approach

A decision-analytic cost-utility model, developed in Microsoft Excel, was used in this submission. The model uses a cohort of newly diagnosed myeloma patients treated with MP as the baseline treatment. Treatment effects for VMP, MPT, CTDa are then modelled over time by adjusting the baseline patient experience via hazard ratios. A survival model appears to be used, which estimates OS and PFS curves for each of the comparators. The model also includes further lines of treatment (second and third-line) to estimate the total treatment costs.

The analytic framework was based on a variant of Quality-Adjusted Analysis of Time Without Symptoms or Toxicity (Q-twist[93]) using partitioned survival analysis and utilises the area under and the difference between time to event curves to estimate mean durations spent within the disease states of interest.

Survival is partitioned into 3 different states: (1) prior to response to treatment; (2) response but no progression; and (3) post-progression. Death represents the final state. The time to response or death were estimated from life tables constructed directly from the VISTA trial patient level data.[26] PFS for MP was estimated from a meta-analysis of the MP arms of included RCTs to compute MP PFS values at 6, 12, 18 and 24 months. PFS was extrapolated beyond 24 months, assuming an exponential survival distribution, using the hazard rate for all time periods beyond 24 months equal to the hazard rate calculated between months 18 and 24. OS for MP was estimated in a similar way to PFS, but using 48 months of summary survival data from the MP arms of the included RCTs.

For the comparator treatments, relative hazard ratios were taken from the random effects results of the meta-analysis that used OS and PFS summary data. OS and PFS hazard rates

were computed for each time period by multiplying the VMP-to-MP, MPT-to-MP and CTDa-to-MP hazard ratios by the appropriate hazard rate for that time period. The computed hazard rates were then used to generate the VMP, MPT and CTDa OS and PFS life tables that extend out to the end of the 30 year lifetime horizon of the model.

The hazard ratios were estimated using a piece-wise constant hazard model using derived survival data from the KM curves for each of the included RCTs. Hazard ratios were estimated at 48 months for OS for each of the RCTs, except the VISTA trial which only had 36 months follow-up. For estimation of the OS hazard for thalidomide, data from five RCTs were used, which included RCTs that had included thalidomide maintenance. Data were synthesised using Bayesian meta-analysis with fixed and/or random effects models. Results from the random effect model were used in the cost-effectiveness model. [redacted]

Following the first-line therapy and upon disease progression it was assumed that the second-line treatment would consist of bortezomib + high dose dexamethasone (HDD), CTDa or HDD. Most patients received CTDa after first-line VMP and bortezomib and HDD for all other first-line therapies. All patients received lenalidomide plus dexamethasone as third-line treatment.

AEs were included in the analysis by estimating the incidence of AEs (grade 3 and 4) across the RCTs for each of the comparators and combining this with the unit costs of treating the AEs. Unit costs were mostly based upon those used in a previous NICE report for lenalidomide (TA 171).[31] The most common AEs for MPT were non-haematologic toxicity, neutropenia, deep venous thrombosis; for MP they were neutropenia, anaemia and thrombocytopenia; and for VMP they were neutropenia, oedema, leukopenia and thrombocytopenia.

Assumptions

The manufacturers' model makes the following assumptions:

- Dose of thalidomide of 150 mg per day for MPT and 167 mg per day for CTDa
- AEs are included in the model as the cost of treating them; the incidence of AEs does not influence the treatment duration, efficacy or patient utility.

- Costs included for second and third-line treatments. Most patients who received VMP as first-line receive CTDa as second-line and most who did not receive VMP as first-line treatment do receive it as second-line.
- Thalidomide RCTs which included maintenance therapy with thalidomide were included in the meta-analysis

Appraisal of the manufacturer cost-effectiveness analysis

The Janssen-Cilag manufacturer's submission was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements[77] and the Philips and colleagues checklist (see Appendix 12).[94] The submission meets all of the requirements for methodological quality and generalisability, except that it did not provide any evidence that the economic model had been validated.

The evaluation provided a clear statement of the decision problem to be addressed, including the population, which appeared to follow the scope for the appraisal issued by NICE. The comparators included (VMP, CTDa, MP and MPT) were appropriate as these are being routinely used or considered for use within the NHS in England and Wales. The perspective for the model was the NHS and PSS. A survival modelling methodology was used which seemed appropriate given the clinical nature of MM. The lifetime horizon used in the model reflects NICE guidance. The model structure was clearly presented with a description and justification of the key assumptions and data inputs used. Measures of clinical effectiveness are from a systematic review of RCTs with an MTC. Benefits for the model are measured in QALYs using the EQ-5D for measuring utility. All benefits and costs are discounted at 3.5% as outlined in NICE guidance.[77] Data on post progression survival was extrapolated from observed data using an exponential distribution. Uncertainty was assessed through a one-way deterministic sensitivity analysis, and probabilistic sensitivity analysis (PSA). It was unclear if the model had been fully validated as no details were provided.

Estimation of QALYs

HRQoL utility values are assigned to each of the states: prior to response to treatment, response to treatment without progression, and post progression, based on a study evaluating chemotherapy followed by SCT in people with MM.[89] For the response state, a utility value of 0.81 was used, based on the utility of the general public at an age (median 54 years) corresponding to that of the patients in the study. A utility value of 0.64 was applied to the post-progression disease state. A utility value of 0.77 was applied to patients prior to the response to treatment. The submission considered this the most appropriate source of utility values because it is the only study that reports utility values according to response and

progression status and, secondly, utility values were derived using the EQ-5D rather than the less methodologically robust indirect mapping approaches used in the other studies. However, as shown in the systematic review of HRQoL, there are several other more relevant HRQoL studies. In particular, it is unlikely that patients with MM would have the same HRQoL as the general population.

Estimation of costs

Treatment unit costs and doses were based on the BNF 2009[35] and MIMS 2009.[95] The duration of treatment was based upon the mean treatment duration in the trials and was assumed to incorporate discontinuation of treatment due to progression, death and AEs. The duration of treatment with MP was 7 cycles as per the VISTA trial.[26] For bortezomib, 31.5 vials were used per patient (VISTA trial), the reason why the number of vials used is far fewer than the full treatment course of 52 vials is not given. The submission used an average dose of 150 mg per day for thalidomide obtained from the 5 MPT RCTs included in the MS meta-analysis. Within the CTDa combination, a daily dose of 167 mg was used for thalidomide. This is the weighted average as per protocol escalating dose from the MMIX RCT prior to the maintenance phase. A mean duration of treatment with thalidomide of 315 days was used, based on the duration reported in the MPT RCTs.

The resource use cost for the management of first-line MM was assumed to be the same for patients receiving VMP, MPT, CTDa and MP. There was an outpatient cost of £102 per visit and a total of nine outpatient visits. In addition, patients receiving VMP had this outpatient cost each time they were administered bortezomib.

Cost-effectiveness results

Table 26 shows the base-case results from the submission. The ICER for VMP versus MP is estimated to be £10,498. Furthermore the ICERs of VMP versus MPT and VMP versus CTDa are estimated to be £11,907 and £10,411 respectively. The submission states that the incremental analysis shows extended dominance of MTP over CTDa. However the assessment group has found an error in the calculation of third-line costs for CTDa, (correct cost £24,978, instead of £16,652). Correction of this error, resulted in an ICER of £51,552 per QALY gained for CTDa versus MP.

Table 26: Base-case results for the Janssen-Cilag submission

	Mean QALYs	Mean cost £	ICER vs MP (Cost/QALY)	ICER (Cost/QALY) vs next best option with lower cost
MP	2.86	£54,434	-	-
CTDa	3.07	£56,668	£10,905	£10,905
MPT	3.41	£59,322	£8912	£7,724
VMP	4.03	£66,676	£10,498	£11,907

One way sensitivity analyses were undertaken for a limited number of parameters, including different survival distributions for OS and PFS, alternative hazard ratios for OS, dose and duration of thalidomide, utilities, time horizon and discounting rate. The results are generally robust to changes in the sensitivity analyses. The model is most sensitive to the following parameters: underlying MP survival hazard, hazard ratios for OS, dose of thalidomide, and duration of treatment with thalidomide in the MPT arm.

A PSA was undertaken using Monte Carlo simulation with 10,000 iterations. All parameters in the model were included except medication costs. For the PSA, at the £20,000 and £30,000 willingness to pay thresholds, VMP has the highest probability of being cost effective: 64% and 75% respectively.

Two scenario analyses were conducted. Scenario A did not include the costs of subsequent therapy after first-line treatment. In this scenario, the cost-effectiveness results were less favourable for each of the treatments and the ICERs increase to £48,437, £16,956 and £21,099 per QALY gained for CTDa, MPT and VMP compared to MP respectively. Scenario B assumed the same second-line therapies as those treated with MP in the VISTA RCT. The results were similar for this scenario to the base case analyses.

5.3.1 Summary of general concerns

- Hazard ratio used for OS for thalidomide was derived from a meta-analysis that included RCTs with thalidomide maintenance
- The utility estimates were from a study with the wrong population, ie younger patients who received high dose therapy. Furthermore, patients who had responded to treatment were assumed to have the same utility as the general population.
- There was an error in the calculation of third-line costs for CTDa
- There was no evidence provided of model validation.

5.4 Review of the Celgene submission to NICE (Thalidomide)

Overview

A structured data extraction form was used to guide the review of the Celgene submission to NICE (Appendix 11). The submission states that its objective is to provide an evaluation comparing the costs and benefits of MPT with those of VMP and MP in patients with MM who are older than 65 years or who are ineligible to receive HDT. The evaluation has two stages. First, a short unsystematic review examines the literature for any relevant cost-effectiveness models in general and specifically in previously untreated MM patients who are not eligible for HDT. The review of cost-effectiveness studies indicates that a literature search was undertaken, although no details of the search strategy or methods for the review are provided. Searches identified five publications, with only one having relevance to the scope of the appraisal. The study by Deniz and colleagues[71] compared MPT with MP as first-line treatment for MM in Scotland and provided the basis for the model developed for the submission by Celgene. Second, an economic model has been developed using data on the clinical effectiveness of MPT[23,58] and VMP[26] through a Bayesian mixed treatment comparison. The perspective of the economic evaluation is stated as being that of the NHS and PSS, including direct costs and benefits only. The analysis takes a lifetime horizon (30 years), presenting costs and outcomes (i.e. years of life gained and QALYs gained) for the three treatment arms of MPT, MP and VMP and an incremental analysis of costs and outcomes for MP and VMP when compared with MPT.

Modelling approach

A Markov model was developed to compare the difference in the progression of MM and of the costs of treatment when managed with the three different treatment options of MPT, VMP or MP through a series of different health states. It was developed from a model produced by Deniz and colleagues,[71]which compared MPT and MP as first-line treatment for MM in Scotland.

The model has four different health states that are defined by the stage of disease progression or the occurrence of AEs. The four states are pre-progression without AEs, pre-progression with AEs, post progression and an absorbing state of death. All patients start in the pre-progression without AEs state and move to other states if their condition worsens or they incur an AE. As MM is a progressive condition, people can only move to a worse state or remain in the same state. The submission provides limited discussion of the rationale for the approach or of the basis for the transition probabilities used to determine progression between states and other approaches assessing the phases of treatment may reflect variations in HRQoL more closely.

The model has a cycle length of six weeks (42 days) with a maximum of 12 cycles for MPT and MP and nine cycles for VMP. The cycle length and the number of cycles correspond to those employed in clinical RCTs.[23,26,58] The time horizon used in the model equates to a lifetime horizon, although characteristics of the cohort used in the model are not clearly stated. The consequences of a shorter time horizon of five years were examined in the sensitivity analysis.

Treatment effects were calculated from a random-effects Bayesian MTC of data originating from three RCTs.[23,26,58] The MTC was undertaken despite differences in the dosage used in the RCTs comparing MP with MPT. It used measures of survival time before and after progression as the primary outcomes. TTP and PFS were used and assumed to be equivalent. The outcome from the MTC was a measure of the risk of progression, provided through the percentage of patients experiencing PFS at six month intervals up to 30 months, with extrapolation beyond this point using an exponential distribution. It was assumed that post-progression survival (PPS) would be the same irrespective of pre-progression treatment, with the different arms assumed to receive the same alternative treatment after progression (i.e. second and third-line treatments). PPS was calculated by combining the MPT, MP and MEL100 (VAD, cyclophosphamide and melphalan 100mg/m^2) arms from IFM 99-06 trial to create an average survival curve.[23] Average survival at different time points was then extrapolated with an exponential distribution. Treatment interruptions or discontinuations were encompassed in the trial efficacy data for MP and MPT, with no alteration to costs in the base case. Changes in cost were encompassed in sensitivity analyses through a reduction in dose as they are likely to reflect clinical practice. No data were available for VMP on discontinuation.

AEs were included for people on active treatment only if they were treatment related and considered to be clinically significant (i.e. grade 3 or above or occurred in 2% or more of patients in either arm). Those associated with disease progression were not incorporated into the model. The treatment related AEs were included in the model through an estimate of the risk of AEs per cycle based on trial data.[23,26] The effects of AEs on HRQoL were also included in the model. A literature search revealed no HRQoL data specific to MM, and so HRQoL decrements were obtained for different patient populations. Costs of AEs were also included.

Assumptions

The manufacturers' model makes the following additional assumptions:

- Post-progression survival is modelled to be the same across different treatment strategies;
- Patients assumed to discontinue first-line treatment upon disease progression;
- Deaths can only occur at or after progression and are assumed to be due to disease related deterioration.
- AEs are included in the model as a utility decrement at the time of the event and the cost of treating them. They are assumed to not affect the disease progression rate or OS, or treatment duration, efficacy or dose.
- Assumes venous thromboembolism (VTE) anti-thrombotic prophylaxis for five months for patients receiving MPT with no resultant risk in incidence of VTEs and anti-viral prophylaxis for VMP.

Appraisal of the manufacturer cost-effectiveness analysis

The Celgene manufacturer's submission was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements[77] and the Philips and colleagues checklist (see Appendix 12).[94] Although the economic evaluation lacked detail on some criteria, it adhered to the scope of the appraisal and followed the many aspects of the NICE reference case.

The evaluation provided a clear statement of the decision problem to be addressed, which appeared to follow the scope for the appraisal issued by NICE. Despite stating that the model focused on first-line therapy for people with MM who are ineligible for HDT and/or are aged over 65 years, insufficient details were provided of the population cohort used in the model itself. The comparisons of MP, MPT and VMP were appropriate as these are being routinely used or considered for use within the NHS in England and Wales. The setting for the evaluation was England and Wales and the perspective for the model of the NHS and PSS. A Markov modelling methodology was used which was developed from a previous evaluation.[71] The methodology seemed appropriate given the progressive nature of MM through distinct stages. The lifetime horizon (30 years) used in the model reflects NICE guidance.

Although the model structure was presented, limited details are given linking the model structure to the baseline risk of the condition. The submission outlines and justifies the assumptions used in the model and the different benefit, resource and cost inputs and their sources. Measures of clinical effectiveness are from a systematic review of RCTs with an MTC. Benefits for the model are measured in QALYs using the EQ-5D for measuring utility. All benefits and costs are discounted at 3.5% as outlined in NICE guidance.[77] Data on post

progression survival were extrapolated from observed data using an exponential distribution. Whilst uncertainty has been assessed through a one-way deterministic sensitivity analysis, no probabilistic analysis or model validation processes were undertaken. As a consequence, the analysis provides only a partial assessment of the uncertainty in the model with the possibility of correlation between parameters and difficulty in summarising the implications of uncertainty.

Estimation of QALYs

No systematic review was undertaken to identify HRQoL values associated with the benefits of the treatment, but a literature search was conducted to identify utility decrements for AEs. The HOVON 24 study,[89] an RCT of intensive chemotherapy followed by myeloblative therapy with autologous stem cell rescue compared to intensive chemotherapy, provided HRQoL data using the EQ-5D to assess the benefits of treatment for people with MM. Although not directly relevant in terms of the population and treatments included in the scope for the technology appraisal, it does provide an indication of the possible utilities for managing people with MM when specific assumptions are applied. The utility values used were 0.64 for people not responding to treatment and 0.81 for people who did respond (using general public utility for same age group). A utility value of 0.77 at 24 months was used for those who continue to respond to treatment with intensive chemotherapy and had not progressed. An assumption was made that pre-progression patients and post-progression patients matched responders and non-responders in the HOVON trial.[89] However, other more relevant HRQoL studies (see section 5.2) show that the utility values used in the manufacturer's submission are higher than would be experienced by people with MM, whether newly diagnosed (0.52), undergoing treatment (0.38 to 0.55), or after treatment at 6 months (0.64) and 12 months (0.69) (see section 5.2).

The literature search for utility decrements for AEs did not identify specific values for people with MM and so utility values from different population groups were used (e.g. breast, colon and rectal cancer). Average percent reduction in utility by each AE was calculated from these values and applied to the cohort in the model.

Estimation of costs

Resources and costs were obtained from several sources. NHS resources were from an unpublished survey of UK haematologists by Celgene Ltd. Inpatient, outpatient and day case hospitalisation costs were derived from NHS Reference costs,[96] including inpatient and day care costs for disease-related complications and treatment related AEs, outpatient consultations and disease monitoring tests and treatment care costs in primary care. Costs of

medicines were from the BNF Edition 57[35] and costs of blood transfusions from Wilson and colleagues [97] with costs inflated to 2008.[98] When on active treatment, patients receive the mean observed treatment dose from the trials. Other resource use and cost data were provided for outpatient consultations, disease monitoring and treatment of AEs/complications. No indirect costs were included in the model. The costs of AEs were calculated by combining resource use data from the survey of haematologists with unit costs to estimate total costs. These costs and trial data on the frequency of AEs [23] were then used to calculate a weighted average cycle cost. The methods for deriving resources and costs used and the sources were clearly described. The model did not include outpatient consultation costs.

Cost-effectiveness results

The submission reports the benefits (i.e. TTP, patients progressed, deaths, proportion of patients with AEs, median OS, mean survival in years of life (life years), and total QALY) and the total costs (i.e. medication, monitoring and management of AEs) separately for each treatment pathway in the model.

Comparison of the benefits used for the model showed considerable benefit for those receiving MPT or VMP over MP on median TTP, median OS, total life years and total QALYs. In contrast, more people receiving MPT (43.2%) or VMP (40.9%) suffered AEs compared to those receiving MP (13.4%). The total costs of the different treatment strategies used within the model showed considerable variation between MP (£1365) and VMP (£42,616). The cost of the medications was the main reason for these differences.

The base case analyses (Table 27) produced two comparisons, MPT versus MP and VMP versus MPT, with differing outcomes. When compared to MP, MPT had an ICER of £18,188 per life year gained and £23,381 per QALY gained. In contrast, the comparison of VMP with MPT showed that VMP produced a small benefit in additional life years and QALYs at a large additional cost (£21,483). The resultant ICERs were £200,237 per life year gained and £303,845 per QALY gained.

Table 27: Base-case results for the Celgene submission

	MPT v MP	VMP v MPT
Incremental Life Years	1.09	0.11
Incremental QALYs	0.85	0.07
Incremental Costs	£19,768	£21,483
Incremental cost per LY gained	£18,188	£200,237
Incremental cost per QALY gained	£23,381	£303,845

The submission assessed uncertainty through one-way deterministic sensitivity analyses. No PSA was conducted as the manufacturer stated that the efficacy of MPT and VMP were essentially the same and that the cost differences would be the key driver for the model. The submission included a number of one way sensitivity analyses for parameter values and model structure. The parameters with the greatest effect on the model results were for the changes in treatment efficacy with a range of £16,586 to £33,275 per QALY gained for MPT versus MP and a range of £148,873 to £1,000,435 per QALY gained for VMP versus MPT.

The submission concludes that MPT represents a cost-effective use of NHS resources compared to MP as a first-line therapy for people with MM who are not eligible for HDT and/or are aged over 65 years. In contrast, when comparing MPT and VMP the manufacturer stated there was negligible clinical benefit from VMP at an additional cost that resulted in the ICERs exceeding £300,000 per QALY. When these findings were assessed through sensitivity analysis, the ICERs were reasonably robust.

5.4.1 Summary of general concerns

- The economic evaluation focuses on the effectiveness of first-line treatment for people with MM who were ineligible for HDT, reflecting the scope for the NICE technology appraisal. Exclusion of second-line or third-line treatment options may over-simplify the evaluation with consequences for the incremental benefits and costs that would result from different possible options available. Given that first-line treatment may, in part, determine subsequent treatment options, it would be helpful to include these in the evaluation.
- All deaths are assumed to be caused by disease related deterioration and only occur at or after progression. In practice, deaths may and do occur prior to progression and as such the evaluation may overestimate the benefits that are accrued.

- Post-progression survival was the same irrespective of pre-progression treatment which would affect the incremental benefits.
- No HRQoL studies relevant to the evaluation were identified by the manufacturer and utitlity values from comparisons of different MM populations using alternative management strategies were used.

5.4.2 Comparison of manufacturer's results

The manufacturers' economic models had similar structures but used different methodology: one used a survival model and the other a Markov model. Both models compared first-line treatment with VMP, MPT and MP. Janssen-Cilag also included CTDa as a comparator. The ICERs produced by the Janssen-Cilag and Celgene submissions vary considerably from £11,907 to £303,845 per QALY gained for VMP versus MPT. These differences stem from the number of vials used for treatment with bortezomib, the hazard ratios for thalidomide and the inclusion of second-line and third-line treatments.

5.5 SHTAC independent economic assessment

5.5.1 Overview

We developed a new model to estimate the costs, benefits and cost effectiveness of MPT, VMP and CTDa compared with MP, in newly diagnosed patients with MM ineligible for HDT-SCT. CTDa was included in order to compare all relevant comparators, however there are limitations to the effectiveness data, as the effectiveness estimate for OS was not statistically significant and the MMIX RCT included a second randomisation to thalidomide maintenance for some patients. The model was populated with clinical effectiveness data from the included RCTs in our systematic review of effectiveness (Section 4), HRQoL data from a systematic review of HRQoL studies (Section 5.2) and cost data derived from published studies (where available), and from national and local NHS unit costs.

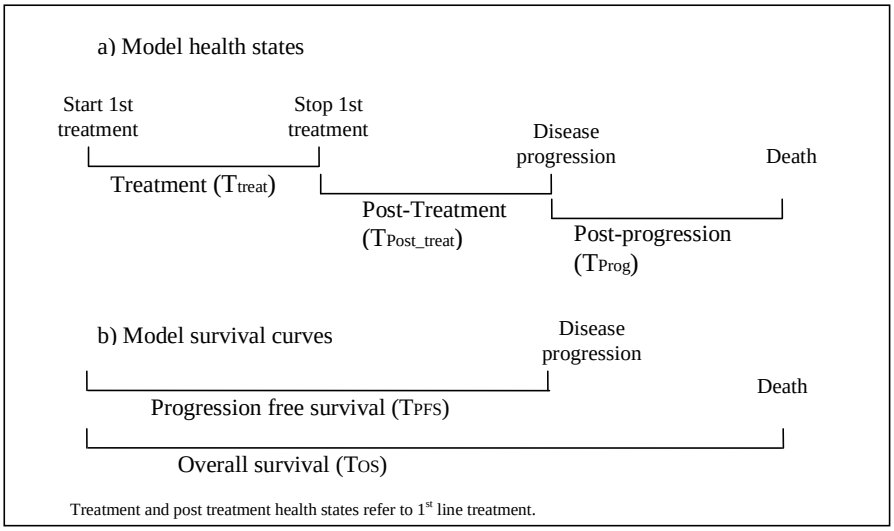
The economic evaluation was from the perspective of the NHS and PSS, since only these direct costs were included. The model estimates the lifelong costs and benefits from each of the treatments. The costs and benefits were discounted at 3.5%, as recommended by NICE.[77] The base price year for the costs was 2009. The intervention effect in terms of improvement in OS and PFS was derived from the systematic review of effectiveness reported in Section 4.1.2.1 and 4.1.2.5. The outcome of the economic evaluation is reported as cost per QALY gained.

5.5.2 Description of the SHTAC model

A survival model was used to compare the cost-effectiveness estimates of VMP, CTDa, and MPT versus MP. The model uses a survival analysis approach to estimate the mean OS and PFS for each of the interventions for a cohort of patients with newly diagnosed MM. The model consisted of cycles of six weeks in length to be consistent with the cycle lengths used for chemotherapy treatment. A lifetime horizon of 30 years was modelled to capture all clinical events using partitioned survival analysis for OS and PFS. Two survival curves were constructed for OS and PFS (Figure 7b), based on the derived probability of death and progression in each model cycle respectively. The mean time spent in each state was calculated from the survival curves for OS and PFS (Figure 7a).

Survival was classified into three health states: *Treatment* is the time patients are treated with first-line therapy, *post-treatment* is the mean time from end of first-line treatment therapy until disease progression and *post progression* is the mean time from disease progression until death.

Figure 7: Schematic of the survival model adopted for the cost effectiveness model



The mean time spent in each state is as follows:

Treatment (T_{treat}) is the mean duration of first-line treatment.

Post-Treatment (T_{Post_treat}) is the mean time from stopping first-line treatment until progression, ie T_{PFS} - T_{treat}

Post-Progression (T_{prog}) is the time from disease progression until death, ie T_{OS} - T_{PFS}, where T_{OS} is mean OS and T_{PFS} is mean PFS.

Each health state was associated with a HRQoL utility estimate which was multiplied by the length of time spent in that state. The total QALYs over the life time of a patient were calculated by aggregating the estimated QALYs from each health state.

Due to lack of data on subsequent therapies, it was unclear how the subsequent therapies affected HRQoL and survival and therefore second-line therapy is only included in the model as a cost.

The methodology used for deriving the parameters for the survival curves for the alternative treatments is as follows:

i) Construct the baseline survival curves for MP using the adjusted event probability for each time interval.

ii) Construct the survival curves for other treatments by using the event probability for each time interval; i.e. event probability for MP multiplied by hazard ratio for treatment option.

For the baseline MP treatment, OS and PFS at regular time points were derived for each of the included studies from our meta-analysis of the clinical RCTs. The data from the RCTs were combined to form baseline MP OS and PFS curves. These curves provided the probability of an event (death or disease progression), i.e. hazard rate, for MP in each time interval (see section 5.5.3.1).

The treatment effects for the other interventions compared to MP (hazard ratios) were taken from our systematic review of clinical effectiveness (Section 4.1.2). As the hazard ratio of the treatments versus MP varied over time, a constant hazard ratio was not appropriate. We estimated the hazard ratio for each six-monthly period for each of the treatments versus MP.

The hazard rate for death was derived for each of the treatments by multiplying the baseline MP probability of death by the hazard ratios for each time interval. The hazard rate for disease progression was derived in a similar manner. This method provided a closer fit to the trial data, than approximations such as fitting distributions. Parameters used in the model and the data sources used to derive them are described in more detail in Section 5.5.3. The methodology used for deriving the survival curves is described in more detail in Appendix 13.

The costs in the model comprise drug treatment, consultation, and monitoring costs and costs for treating AEs. Patients remained on drug treatment unless their disease progressed or they

died. All patients who had not died received second-line therapy and this was assumed to start at the mean time of disease progression for the cohort. Third-line therapy was not included as it was assumed that most patients would receive lenalidomide, irrespective of the initial treatment. Costs used in the model are described in more detail in section 5.5.3.5.

A list of the model assumptions is given below. Assumptions are applied to all treatment options unless explicitly stated otherwise. All assumptions were tested in sensitivity analyses.

The model includes the following assumptions:

- For bortezomib, each patient receives one vial per administration
- Costs included for second -line treatments. Most patients who received VMP as first-line receive CTDa as second-line and most who did not receive bortezomib as first-line treatment receive it as second-line.
- Costs and outcomes of third-line and subsequent treatments are assumed to be the same between arms
- Patients discontinue first-line treatment upon disease progression
- HRQoL is better for those with complete response than those with less than complete response and is assumed to improve when patients stop treatment
- AEs are not modelled explicitly in the model for patient outcomes, ie OS and PFS, but are included as additional cost for treating the AEs in the model.

In each cycle the total costs and QALYs are calculated by multiplying the individual costs and HRQoL by the number of people in the cohort still alive for each of the treatments. The total lifetime costs and QALYs are calculated by aggregating the costs and QALYs for all cycles. The total discounted QALY gain, and cost of treatments are calculated. Thus the cost effectiveness of each of the treatments is calculated,

$$Cost\ effectiveness = \frac{Cost\ \ for\ treatment - Cost\ \ for\ MP\ treatment}{QALYs\ \ for\ treatment\ \ - QALYs\ \ for\ MP\ treatment}$$

5.5.2.1 Evaluation of uncertainty

The evaluation of the cost-effectiveness of treatment for MM is based on uncertain information about variables such as the clinical effect, HRQoL and resource use. This uncertainty was evaluated using deterministic and probabilistic sensitivity analyses. One-way deterministic sensitivity analyses were conducted to evaluate the influence of individual

parameters on the model results and test the robustness of the cost-effectiveness results to variations in the structural assumptions and parameter inputs (section 5.5.5.1).

Multi-parameter uncertainty in the model was addressed using PSA (section 5.5.5.3).[99] In the PSA, probability distributions are assigned to the point estimates used in the base case analysis. The model is run for 1000 iterations, with a different set of parameter values for each iteration, by sampling parameter values at random from their probability distributions. The uncertainty surrounding the cost-effectiveness of the treatment is represented on a cost-effectiveness acceptability curve (CEAC) according to the probability that the intervention will be cost effective at a particular willingness to pay threshold. Appendix 14 reports the parameters included in the PSA, the form of distribution used for sampling each parameter, and the upper and lower limits assumed for each variable.

5.5.2.2 Model validation

The SHTAC model was validated by checking the model structure, calculations and data inputs for technical correctness. The structure was reviewed by clinical experts for appropriateness for the disease and its treatment. The SHTAC model was checked for internal consistency against the MS economic models by running the SHTAC model with the inputs used in MS models to ensure similar results. The robustness of the model to changes in input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude. Finally, the model results were compared with those from the manufacturers' submissions.

5.5.3 SHTAC Data sources

5.5.3.1 Baseline MP curves

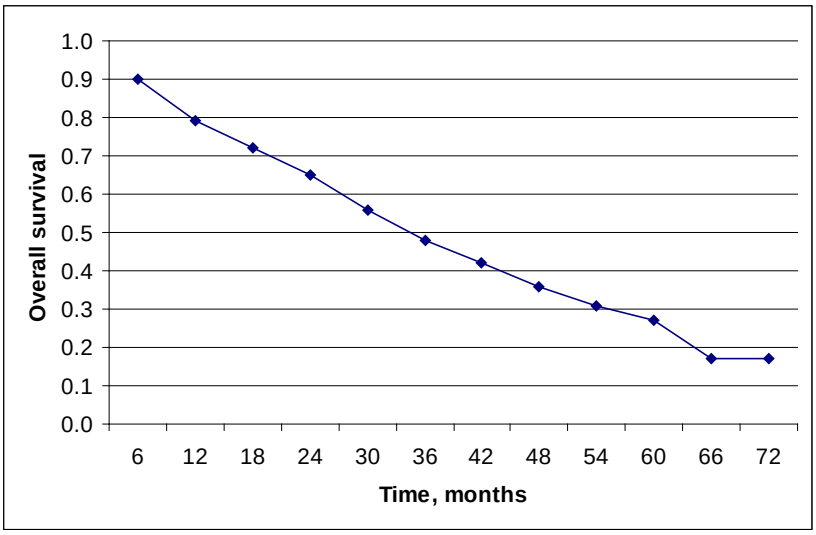
The baseline MP OS curve was generated using the MP OS curves from the RCTs included in our systematic review of clinical effectiveness (Section 4.1.2.1). Survival probabilities (at six month intervals) were extracted from a scanned copy of the KM plots for each MP group using the digitizing software Enguage[100] (Appendix 13). A weighted average of the survival probabilities for each time point was calculated to provide a summary MP OS curve (Table 28) using the number of participants in the trials as weights.

Table 28: OS probabilities extracted from Kaplan-Meier plots for MP study arms using digitizing software

Trial MP arm	Number in MP arm	Time, months											
		6	12	18	24	30	36	42	48	54	60	66	72
Facon[23]	196	0.88	0.78	0.72	0.63	0.55	0.48	0.39	0.31	0.26	0.23	0.19	0.17
Hulin[58]	116	0.90	0.83	0.71	0.62	0.47	0.39	0.38	0.30	0.28			
Palumbo[24]	164	0.96	0.84	0.75	0.71	0.65	0.59	0.53	0.49	0.49	0.36		
Vista Trial[101]	338	[redacted]											
MMIX[52]	426	[redacted]											
MP Weighted Average [a]		0.90	0.79	0.72	0.65	0.56	0.48	0.42	0.36	0.31	0.27	0.17	0.17

[a] Weighted by size of trial arm. The average could not be weighted by numbers at risk at each time point because Palumbo[25] and Vista trial CSR[101] did not report this for six-month time point intervals, and MMIX[52] did not report numbers at risk at all.

Figure 8: Summary curve for MP OS obtained from weighted average of individual MP curves



A baseline MP PFS curve was generated using the PFS curves from the trial data included in our systematic review of clinical effectiveness (Section 4.1.2.5) in a similar way to the baseline OS curves, see Appendix 13 and Table 29. A weighted average of the PFS

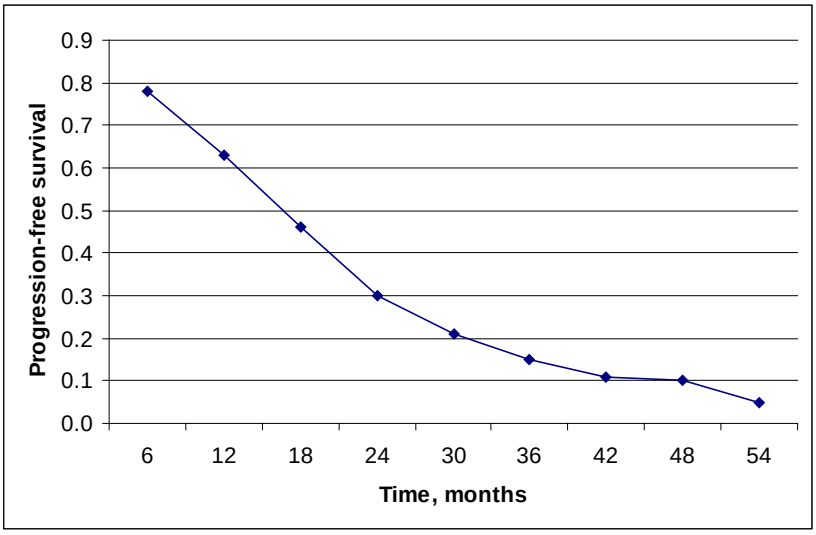
probabilities for each six month time point was calculated to provide a summary MP PFS curve (Figure 9) using of participants in the trials as weights.

Table 29: Progression-free Survival probabilities extracted from Kaplan-Meier plots using digitizing software

Study MP arm	Number in MP arm	Time, months								
		6	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**
Facon[23]	196	0.77	0.63	0.49	0.34	0.22	0.14	0.08	0.06	0.05
Hulin[58]	116	0.8	0.66	0.51	0.33	0.17	0.12	0.06	0.05	0.05
Palumbo[24]	164	0.88	0.60	0.41	0.28	0.22	0.19	0.18	0.18	
Vista Trial[26]	338	0.77	0.63	0.43	0.28					
MP Weighted Average [a]		0.78	0.63	0.46	0.30	0.21	0.15	0.11	0.10	0.05

[a] Weighted by size of trial arm. MMIX data could not be included because a PFS curve was not available.

Figure 9: Summary curve for PFS obtained from weighted average of individual PFS data in MP arms of trials



The probability of an event at each time interval for the MP treatment arm (Hazard OS and Hazard PFS) is calculated from the baseline MP OS and MP PFS curves. These probabilities

are shown in Table 30. The hazard rate for an event for MP per cycle is estimated for each time point t_i,:

$$h(t_i) = 1 - \left(\frac{s(t_i)}{s(t_{i-1})} \right)^{\frac{1}{(t_i - t_{i-1})}}$$

where s(t) is the survival function over time t.

For OS, few individuals were followed up for more than 36 months, and so a constant hazard rate was assumed after 36 months using the hazard rate in the first 36 months. For PFS, few individuals were followed up for more than 24 months, and so a constant hazard rate was assumed after 24 months using the hazard rate in the first 24 months. The methodology used to derive the survival curves is described in more detail in Appendix 13.

Table 30: Hazard rate for MP for OS and PFS (event rate per cycle)

Months	Cycles	Hazard rate OS	Hazard rate PFS
6	4.4	0.024	0.056
12	8.7	0.030	0.048
18	13.0	0.021	0.070
24	17.4	0.023	0.094
30	21.7	0.034	0.067
36	26.1	0.035	0.067
36+	26+	0.028	0.067

5.5.3.2 Overall survival and progression free survival hazard ratios for treatments versus MP

The relative effectiveness of the treatments versus MP for OS and PFS were represented as hazard ratios. The hazard ratios were obtained from the KM plots in the trial publications (Section 4.1.2.1 and 4.1.2.5). As the hazard ratio of the treatments versus MP varied over time, a constant hazard ratio was not appropriate. We derived the hazard ratio for each six-monthly period for each of the treatments versus MP.

The hazard ratio (HR) for each treatment $_j$ versus MP at each time point t_i is,

$$HR_i = \frac{h_j(t_i)}{h_{mp}(t_i)}$$

The hazard ratios for the MPT trials summary were combined using simple weighted averages of the proportion of surviving patients in each trial arm at each time point, weighted by numbers of patients in the trial. The hazard ratios were assumed to be constant after 36 months for OS and 24 months for PFS as there were few patients with more than this length of follow up in the trials Hazard ratios of OS and PFS are shown in Table 31 and Table 32.

The event rate at each time interval for MPT, VMP and CTDa was estimated by multiplying the risk of death or progression by the hazard ratio for each cycle. The effects of using alternative hazard ratios were evaluated in sensitivity analyses. It should be noted that the MMIX RCT included a second randomisation to maintenance therapy with thalidomide for some patients after first-line therapy and there were no data available for OS and PFS for patients who did not have maintenance therapy.

Table 31: Hazard ratios for OS from trial publications and by derivation from publication KM plots

Months	Facon[23] MPT	Hulin[58] MPT	SHTAC MPT trials summary	SanMiguel[26] VMP	MMIX[53] CTDa
0-6	0.52	0.95	0.67	[redacted]	[redacted]
6-12	0.57	0.50	0.55	[redacted]	[redacted]
12-18	0.49	0.91	0.71	[redacted]	[redacted]
18-24	0.56	0.64	0.59	[redacted]	[redacted]
24-30	0.64	0.33	0.46	[redacted]	[redacted]
30-36	0.74	0.79	0.76	[redacted]	[redacted]
36+	0.59	0.64	0.62	[redacted]	[redacted]

Table 32: Hazard ratios for PFS from trial publications and by derivation from publication KM plots

Months	Facon[23] MPT	Hulin[58] MPT	SHTAC MPT trials summary	SanMiguel[26] VMP	MMIX[53] CTDa
0-6	0.36	0.61	0.45	0.47	[redacted]
6-12	0.61	0.76	0.67	0.62	[redacted]
12-18	0.49	0.70	0.57	0.74	[redacted]
18-24	0.70	0.51	0.62	0.48	[redacted]
24+	0.55	0.62	0.58	0.58	[redacted]

5.5.3.3 Complete response

Complete response outcome data for each treatment option is described in Section 4.1.2.3. For each treatment option, the relative risk of complete response compared to MP was derived using Review Manager 5. The complete response rate for MP was estimated using the trial data by simple weighted average of the MP arm using the number of trial participants as the weight. Complete response for the other treatment options was derived by multiplying the MP complete response rate by the relative risk. Table 33 shows the complete response data used in the model for MP, VMP, MPT and CTDa.

Table 33: Complete Response for different treatments

	Complete response, %
MP	2.6
MPT	14.2
VMP	21.7
CTDa	14.4

5.5.3.4 Health-related HRQoL

Although our systematic review of HRQoL studies (Section 5.2) did not find any generic preference-based HRQoL studies of people with untreated MM who were not eligible for HDT with SCT, it did identify two studies that assessed HRQoL in this group using the EORTC QLQ C-30. A targeted search was therefore conducted for studies that mapped data from the EORTC QLQ C-30 onto the EQ-5D to enable the estimation of health state values based on EORTC QLQ C-30 data. The EORTC QLQ C-30 is the most commonly used instrument to measure the HRQoL of cancer patients. Two studies were identified.[102,103]

McKenzie and van der Pol[103] used an Ordinary Least Squares (OLS) regression analysis with data from an RCT of palliative therapies for 199 patients with inoperable oesophageal cancer, with an average age of 74.8 years. The regression results for the mapping are shown in Table 34.

Table 34: Regression results for mapping between EORTC QLQ-C30 and EQ-5D from McKenzie and van der Pol[103]

	Coefficient
Global QoL	0.0016
Physical functioning	0.0004
Role functioning	0.0022
Emotional functioning	0.0028
Cognitive functioning	0.0009
Social functioning	0.0002
Fatigue	-0.0021
Pain	-0.0005
Nausea	-0.0024
Dyspnoea	0.0004
Insomnia	0.00004
Appetite loss	0.0003
Constipation	0.0001
Diarrhoea	-0.0003
Financial difficulties	-0.0006
Constant	0.2376

Kontodimopoulos and colleagues[102] used an OLS regression with data from 48 gastric cancer patients, split into equal subgroups by age, sex and chemotherapy scheme. Three scales were significant predictors ($p<0.05$ or better) of EQ-5D indices: physical functioning, emotional functioning and global health status. The regression results for the mapping are shown in Table 35.

Table 35: Regression results for mapping between EORTC QLQ-C30 and EQ-5D from Kontodimopoulos and colleagues[102]

	Coefficient
Physical functioning	0.00508
Emotional functioning	0.00313
Global health status	0.00546
Constant	-0.18143

Our systematic review of HRQoL studies found two studies in the population of interest but these used the EORTC QLQ-C30.[87,88] For both studies, we mapped the EORTC QLQ-C30 HRQoL scores to the EQ-5D using each of the mapping algorithms described above (Table 36 and Table 37).

Table 36: EQ-5D utility values derived by mapping from EORTC QLQ-C30 HRQoL scores from Strasser-Weipi and Ludwig[88]

Mapping algorithm	Multiple Myeloma	Reference population
McKenzie and van der Pol	0.59	0.82
Kontodimopoulos	0.58	0.88

Table 37: EQ-5D utility values derived by mapping from EORTC QLQ-C30 HRQoL scores from Gulbrandsen[87]

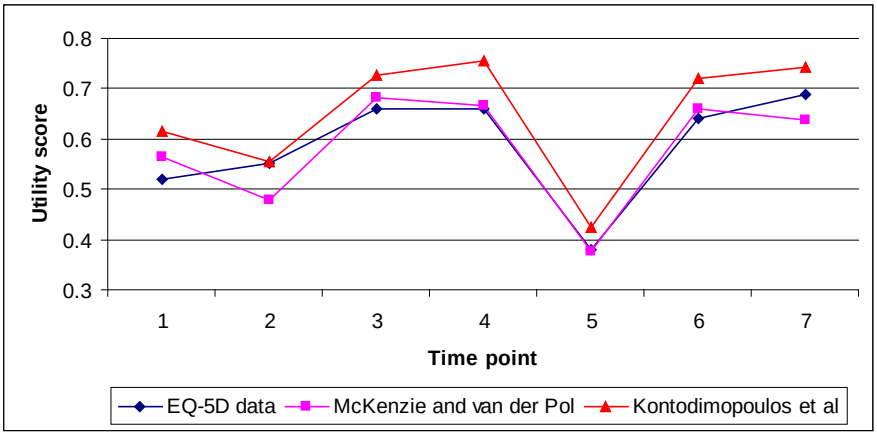
Mapping algorithm	Reference population	Time, months					
		0 m	1 m	6 m	12 m	24 m	36 m
McKenzie and van der Pol	0.81	0.55	0.58	0.68	0.68	0.68	0.69
Kontodimopoulos	0.86	0.52	0.58	0.69	0.69	0.69	0.71

Gulbrandsen and colleagues[87] provide HRQoL at different time points. Based on this study, it appears that HRQoL is lower during the treatment period and improves after treatment has finished and this is consistent with HRQoL results from Uyl-de-Groot and colleagues.[92] Long term HRQoL appears to be stable over time. In addition the utility estimates from the HRQoL studies in populations treated with HDT are similar to those from Gulbrandsen and colleagues.[87]

The accuracy of the mapping studies was assessed for the study by Uyl-de-Groot and colleagues[92] which reported EORTC QLQ-C30 and EQ-5D results. Figure 10 shows the comparison between the EQ-5D utility estimates using the two mapping methods compared

with the EQ-5D data from Uyl-de-Groot and colleagues. For these data, the mapping algorithm by McKenzie and van der Pol provides the better fit and for most time points is a good fit to the data.

Figure 10: Comparison of results from mapping studies from EORTC QLQ-C30 to EQ-5D with EQ-5D data from Uyl-de-Groot and colleagues[92]



We suggest that the most appropriate source of HRQoL data for the treatment period and post treatment values is from Gulbrandsen and colleagues[87] from the mapping by McKenzie and van der Pol. These utility estimates are shown in Table 37. The utility estimates for the treatment period are for the one month time-point, i.e. 0.58, and for the post treatment is an average of the 6 month to 36 month time-points, i.e. 0.68.

Complete response

HRQoL data from the MMIX RCT[56] were analysed to determine whether patients with complete response had a better HRQoL after response than those with other levels of response. EORTC QLQ-C30 data were available for 0, 3, 6 and 12 months after initial treatment commenced. We mapped the EORTC QLQ-C30 data to EQ-5D health utilities using the algorithm from McKenzie and van der Pol.[103] For the first three periods, the EQ-5D were similar for both CTDa and MP groups and similar to those from Gulbrandsen and colleagues.[87] [redacted]. We analysed whether this difference was due to more patients with complete response in the CTDa group. At 12 months, the utility for those with complete response was higher than those with other response [redacted].

In the model we estimate the utility for the post treatment health state as a weighted average of those who had a complete response [redacted] and those with lesser response [redacted].

5.5.3.5 Estimation of costs

Drug costs

Drug unit costs and doses were based on the BNF 2009.[35] Duration of treatment was based on recommendations from the SPC,[29,33] expert clinical opinion and the published trials. A summary of the dose and duration of treatment for each of the comparators is given in Table 38.

The duration of treatment varied between seven cycles for CTDa to nine cycles for VMP. We assumed that MP would be given for the same number of cycles as thalidomide and bortezomib when it was given in combination with them. The SPC of thalidomide states that a maximum number of 12 cycles of 6 weeks each should be used, as used in the trial by Facon and colleagues.[23] However one of our clinical experts advised that a shorter duration of 8 cycles was more representative of clinical practice.

The dose of thalidomide was assumed to be 150 mg based upon the dosages used in the IFM RCT (100mg),[58] and the MMIX RCT (200mg)[48] The dose recommended by the SPC is 200 mg per day, but one of our clinical experts advised that in practice, few patients are able to tolerate such a high dose. Bortezomib is administered as a 3-5 second bolus intravenous injection. The cost of the 3.5 mg vial is £762.68. The cost of bortezomib administration was £153.40.[96]

Table 38: Summary data for treatment duration, dose and unit cost

	Melphalan	Prednisolone	Bortezomib	Thalidomide	Cyclophosphamide	Dexamethasone	Source
Drug dose	9 mg/m^2	60 mg/m^2	1.3 mg/m^2	150 mg/day	250 mg/m^2/week	20mg/day for 4 days every 28	BNF,[35] SPC,[29,33] VISTA,[26] MMIX[48] and clinical expert opinion
No. cycles	8[a]	8[a]	9	8	7	7	
Cycle length	6 weeks	6 weeks	6 weeks	6 weeks	6 weeks	6 weeks	
Duration	10-12 months	10-12 months	54 weeks	10-12 months	6-8 months	6-8 months	
Days of cycle	Days 1-4	Days 1-4	Cycles 1-4: 1,4,8,11,22,25,29,32 Cycles 5-9: 1,8,22,29	Daily	4 doses/cycle	30 doses/course	
Unit costs	Melphalan £11.46 for 25-tablet pack (2mg); Total cost £126.24	Prednisolone £20 for 50-tablet pack (25mg); Total cost £25.71	Bortezomib £762.68 per 3.5 mg vial; Total cost £39,643.76	£298.48 per 28-tablet (50 mg) pack; Total cost £10,745.80	£12.44 per 100-tablet pack (50 mg); Total cost £44.41	£13.92 per 100-tablet pack (2 mg); Total cost £58.46	BNF[35]

[a] Number of cycles for MP in combination with bortezomib or thalidomide as for those treatments.

The total cost for bortezomib depends on the wastage from the vial. In the NICE appraisal of bortezomib for relapsed MM,[30] the appraisal committee considered the issue of vial sharing. They expressed a number of concerns including issues related to maintenance of best aseptic practice and the practical constraints of patient numbers and geographical locations of myeloma centres. The Committee was not convinced that vial sharing could be considered either safe or routinely achievable in practice across the NHS.

One of our clinical experts advised that they attempted to administer bortezomib in groups of three persons to minimise wastage. However, this may not be possible in smaller units. In the base case analysis we assumed that only one vial would be used per patient and then varied this assumption in a scenario analysis.

Patients on thalidomide also received thromboprophylaxis for 5 months in the form of low molecular weight heparin (dalteparin 5000 units once daily SC)[28] at a total cost of £428.88. In addition to chemotherapy, patients also require treatment with other medication, such as bisphosphonates, but the cost for these was assumed to be similar across all interventions, and have therefore not been included in the model costs.

Second-line treatment

Following disease progression after first-line therapy, patients receive second-line treatment. Based on clinical advice, NICE guidance,[30] trial data and assumptions used in the Janssen-Cilag submission, it was assumed that most individuals would receive bortezomib as second-line therapy unless they had already received it as first-line therapy. High dose dexamethasone (HDD) and CTDa were also used as these are common second-line treatments in the UK.[30] Most patients who had VMP as first-line treatment had CTDa as second-line. The dose for HDD was 40mg per day and the cost of treatment was £189.31. The assumed distribution of second-line treatments following first-line treatment is shown in Table 39.

Table 39: Monitoring tests completed at each outpatient appointment for multiple myeloma

	First-line treatment			
Second-line treatment	MP	MPT	VMP	CTDa
Bortezomib + HDD	70	70	15	70
CTDa	15	15	70	15
HDD	15	15	15	15

Consultations

Based on clinical advice, we assumed patients receive on average one consultation every month during their treatment period and one consultation every three months thereafter. The outpatient consultation cost was £121.11 (Reference cost code 370: Medical oncology follow-up consultation). [96]

Monitoring tests

The monitoring tests used for the management of MM, based on those used for the MMIX RCT,[48]are shown in Table 40 with their unit costs.

Table 40: Monitoring tests completed at each outpatient appointment for multiple myeloma

Test	Unit cost, £	Costs source
Full blood count	£3.02	Southampton University Hospital Trust, 2009[104]
Biochemistry (calcium, creatinine, albumin and uric acid)	£5.15	
Protein electrophoresis	£13.85	
Immunoglobin (IgA, IgG, IgM)	£41.55	
Urinary light chain excretion	£13.85	

Adverse events

For each comparator, the incidence of AEs was estimated using evidence from the RCTs included in our systematic review of clinical effectiveness (Section 4.1.2.7). AEs included in the model were treatment-related serious (grade 3 and grade 4) AEs and the incidence was taken from the VISTA trial[26] for VMP, from the IFM 99-06 trial for MPT[23] and from MMIX trial for CTDa. The IFM 99-06 trial was used for MPT as this trial had more comprehensive reporting than the other MPT trials. For MP a weighted average was calculated using data from the MP arm from each of these trials.

Although AE data is consistently reported across studies as percentage patients, the types of AEs reported differed between the studies. This summary extracts key AEs (haematological, gastrointestinal, infections, neuropathy and thrombosis) for use within the model (and is not a comprehensive analysis of all AEs). Gastrointestinal AE numbers for MMIX were calculated from constipation grade 3 and grade 4 as reported and other gastrointestinal AEs (grade not specified but proportion calculated for grade 3 and grade 4). Total infection for the VISTA study was calculated by totalling figures for pneumonia and herpes zoster (which assumes

that there were no others). Infections were not specified for other studies. The definition of haematological AEs may not be exactly consistent across studies but gives an indication of possible rates for thrombocytopenia/cytopenia. AE data were not available for the MMIX RCT for the incidence of neutropenia and anemia and for these AEs we have assumed the same incidence for CTDa as for MPT. Where events grade 3 and 4 were not reported separately, we assumed there were twice as many grade 3 as grade 4 events as this was the ratio for the total numbers of grade 3 and 4 AEs.

The unit costs of treating AEs were estimated based on those used in a NICE technology appraisal for lenalidomide (TA 171),[31] and the Celgene MS (Section 5.4, Appendix 12). The NICE technology appraisal for lenalidomide[31] collected information on the proportion of patients who would receive treatment, the location where treatment would be administered, and treatments administered for each specific disease-related complication. The unit cost of inpatient and day-case treatment for the AE, was calculated from CHKS (Casper Healthcare Knowledge Systems) data, which contains individual patient-level data from most UK hospital trusts, and NHS reference cost data. This report did not include all relevant AEs costs. The Celgene MS used a similar methodology to calculate unit costs and these were used for AEs of infection, dizziness or fatigue. There was no distinction made in that report between the costs of grade 3 and 4 AEs and so for these AEs we have assumed equal costs for grade 3 and 4. We used the cost of diarrhoea for the cost of gastrointestinal AEs as this cost was between the costs of nausea and constipation. The unit costs for treating the AEs are shown in Table 42.

The total costs of treating AEs were estimated by multiplying each AE incidence by the appropriate unit cost for that AE.

Table 41: Incidence of AEs at grade 3 and 4 reported for different treatments

Adverse event, %	VISTA		Facon 99/06		MMIX		MP weighted average
	VMP	MP	MPT	MP	CTDa	MP	
Haematological							
Thrombo/cytopenia	37	30	14	10	[redacted]	[redacted]	19
Neutropenia	40	38	48	26	[redacted]	[redacted]	34
Anaemia	19	28	14	14	[redacted]	[redacted]	23
Gastrointestinal	20	5	11	3	[redacted]	[redacted]	3
Nervous system							
Peripheral neuropathy	14	0	6	0	[redacted]	[redacted]	>1
Dizziness/fatigue	9	1	8	0	[redacted]	[redacted]	1
Infections	10	7	13	9	[redacted]	[redacted]	7
Thrombosis	1	1	12	4	[redacted]	[redacted]	2

Table 42: Unit costs for treating AEs at grade 3 and 4

Adverse event	Unit cost, £		Source
	Grade 3	Grade 4	
Thrombocytopenia	£164.37	£683.62	TA171 [31]
Neutropenia	£386.85	£998.33	TA171 [31]
Anemia	£384.75	£551.63	TA171 [31]
Gastrointestinal	£830.84	£1,302.90	TA171 [31]
Peripheral neuropathy	£174.75	£317.37	TA171 [31]
Dizziness / fatigue	£172.24	£172.24	Celgene MS
Infection	£1,018.01	£1,018.01	Celgene MS
DVT	£347.17	£1,014.29	TA171 [31]

5.5.4 Results of SHTAC independent economic evaluation

This section reports the cost-effectiveness results for a typical person with MM who received treatment with bortezomib in combination with MP or thalidomide in combination with MP compared with those receiving MP. Results for costs and QALYs are presented for each treatment, with costs and benefits discounted at 3.5%.[77] The survival curves for OS from the model are shown in Figure 11. The results show increased survival for MPT, VMP and CTDa versus MP. The cost-effectiveness is presented as incremental cost per QALY compared to existing treatment with MP. The summary results of the non discounted treatment effects are

shown in Table 43. In the base-case analysis, OS varied from 4.20 years for MP to 6.66 years for MPT. Survival for MPT is slightly longer than for VMP. [redacted]

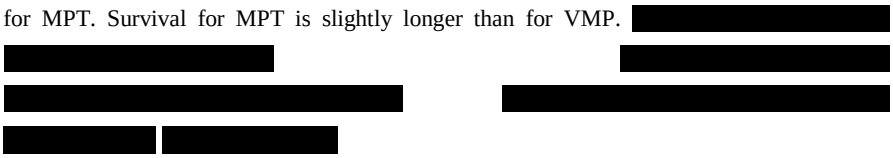


Figure 11: Overall survival curves for MP, MPT, VMP and CTDa (*Academic in confidence*)

Table 43: Summary of the duration in each health state for treatment with MP, MPT, VMP and CTDa

	Duration, years			
	MP	**MPT**	**VMP**	**CTDa**
Treatment	0.92	0.92	1.04	0.81
Post treatment	0.88	2.13	2.00	1.37
Post progression	2.39	3.61	3.60	2.52
Overall survival	4.20	6.66	6.64	[redacted]

The baseline discounted cost-effectiveness results are shown in Table 44. Each of the treatments is more expensive than MP, with the additional cost ranging from £8,600 (CTDa) to more than £35,000 (VMP) over a patient lifetime. The incremental cost-effectiveness versus MP for MPT, VMP and CTDa is £9,174, £29,837 and £33,216 per QALY gained respectively.

Table 44: Baseline cost-effectiveness results versus MP

	MP	**MPT**	**VMP**	**CTDa**
Total cost, £	£21,555	£32,762	£57,304	£30,147
Total QALY	2.42	3.64	3.62	2.68
Incremental cost vs MP, £	-	£11,207	£35,749	£8,592
Incremental QALY vs MP	-	1.22	1.20	0.26
ICER vs MP	-	£9,174	£29,837	£33,216

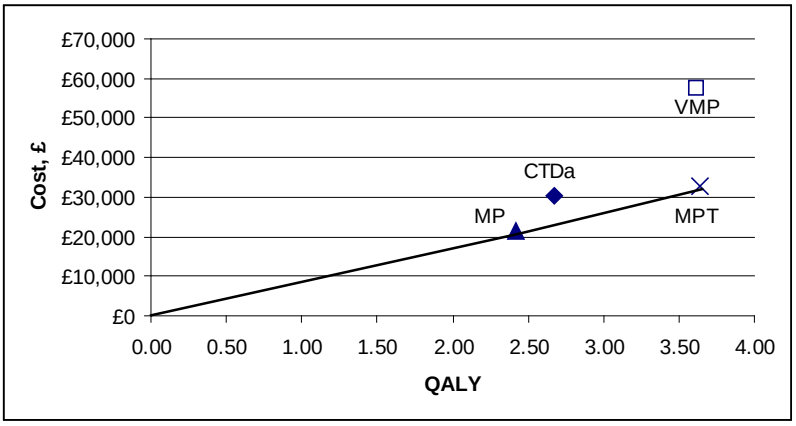
In Table 45 each comparator is presented in successive rows ordered by the number of QALYs generated. Each option is then compared to the next best option with lower cost. In summary the incremental analysis suggests extended dominance of MPT over CTDa, and

MPT dominates VMP as it is more effective and cheaper (Figure 12). The comparison of VMP versus MPT suggests that VMP and CTDa are unlikely to be cost-effective treatment options at the conventional willingness to pay threshold of £20,000 to £30,000 per QALY gained. However there is much uncertainty around the results for CTDa because the OS effectiveness estimates were not statistically significant and the results from the MMIX RCT included those of participants who had received thalidomide maintenance therapy.

Table 45: Incremental baseline cost-effectiveness results

	QALY	Cost, £	ICER (£ / QALY)
MP	2.42	£21,555	-
CTDa	2.68	£30,147	£33,216
VMP	3.62	£57,304	£28,907
MPT	3.64	£32,762	Dominates VMP

Figure 12: Cost-effectiveness plane for treatments MP, CTDa, VMP and MPT



5.5.5 Sensitivity analysis

5.5.5.1 Deterministic Sensitivity Analysis

One-way deterministic sensitivity analyses were performed, in which model parameters were systematically and independently varied, using a realistic minimum and maximum value. The sensitivity analysis investigated the effect of uncertainty around the model assumptions, structure, and parameter values on the cost-effectiveness results, in order to highlight the most influential parameters. The effects of uncertainty in multiple parameters were addressed using PSA, which is reported later in this section (Section 5.5.5.3). Where possible, the parameters were varied according to the ranges of the confidence intervals of these parameters, based on

the published estimates. Where these data were not available an alternative suitable range was chosen. The same ranges were used in the deterministic analyses and PSA and these are described in Appendix 14.

Table 46 to Table 48 shows the results of the deterministic sensitivity analyses for each of the treatments versus MP for the most influential parameters. Other parameters, such as AE cost, complete response rate and utility values, were varied in the sensitivity analyses but were found to only have a negligible effect on the results. The cost-effectiveness results are fairly robust to changes in parameters in the deterministic sensitivity analysis. For each of the treatments, the model results are most sensitive to the hazard ratio for OS, cost and dosage of the treatment and the overall baseline survival curve used for MP. The deterministic sensitivity results for MPT versus MP are shown in Table 46 and varied between £6,470 and £22,855 per QALY gained.

Table 46: Deterministic sensitivity analyses for MPT versus MP

Parameter	Baseline	Upper value	Lower value	Upper value ICER, (£/QALY)	Lower value ICER, (£/QALY)	Range
Hazard ratio for OS	0.64	0.82	0.5	£22,855	£6,470	£16,385
Dosage thalidomide, mg/day	150	200	100	£11,804	£6,543	£5,261
MP OS baseline curve [a]	0.028	0.039	0.02	£11,279	£7,811	£3,468
Unit cost thalidomide	£298.48	£358.18	£238.78	£10,752	£7,595	£3,156
Second-line treatment Bortezomib MP[b]	70	80	60	£7,811	£10,536	£2,725
Second-line treatment Bortezomib MPT [b]	70	80	60	£10,479	£7,869	£2,610
Number of cycles, MPT	8	9	7	£10,338	£7,998	£2,339

[a] Probability of death per cycle

[b] First-line treatment with MP or MPT

The deterministic sensitivity results for VMP versus MP are shown in Table 47 and varied between £20,451 - £87,716 per QALY gained. VMP is dominated by MPT for all parameters, except the MPT treatment effectiveness for OS (hazard ratio). This is also the case, if the

model assumes that vials for bortezomib can be shared, rather than assuming one vial per patient. Using the lower confidence interval for OS, the cost-effectiveness estimate of VMP versus MPT is £33,979 per QALY gained.

Table 47: Deterministic sensitivity analyses for VMP versus MP

Parameter	Baseline	Upper value	Lower value	Upper value ICER, (£/QALY)	Lower value ICER, (£/QALY)	Range
Hazard ratio for OS	[redacted]	[redacted]	[redacted]	£87,716	£20,451	£67,265
MP OS baseline curve [a]	0.028	0.039	0.02	£37,812	£24,791	£13,021
Unit cost bortezomib	£762.38	£914.86	£609.90	£33,796	£25,879	£7,917
Discount rate benefits	3.5%	5%	2%	£33,814	£26,095	£7,718
Utility progression	0.68	0.75	0.61	£27,804	£32,192	£4,388
Number of cycles VMP	9	10	8	£31,830	£27,753	£4,077
Cost of bortezomib administration	£153.40	£199.41	£107.38	£31,648	£28,026	£3,623

[a] Probability of death per cycle

The deterministic sensitivity results for CTDa versus MP are shown in Table 48 and varied between -£29,388 and £16,989 per QALY gained. [redacted]

Table 48: Deterministic sensitivity analyses for CTDa versus MP

Parameter	Baseline	Upper value	Lower value	Upper value ICER, (£/QALY)	Lower value ICER, (£/QALY)	Range
Hazard ratio for OS	[redacted]	[redacted]	[redacted]	-£29,388	£16,989	£46,377
MP OS baseline curve [a]	0.028	0.039	0.02	£49,520	£24,758	£24,763
Thalidomide dose, mg/day	150	200	100	£43,686	£22,746	£20,940
Second-line Bortezomib [b] **MP**	70	80	60	£26,781	£39,651	£12,870

Second-line Bortezomib [b] CTDa	70	80	60	£39,570	£26,862	£12,708
Unit cost thalidomide	£298.48	£358.18	£238.78	£39,498	£26,934	£12,564
Number of cycles CTDa	7	8	6	£39,771	£27,070	£12,702

[a] Probability of death per cycle

[b] First-line treatment with MP or CTDa

5.5.5.2 Scenario analysis

In addition to the sensitivity analyses four alternative scenarios were undertaken to investigate the uncertainty around structural assumptions (Table 49).

Scenario A – no subsequent therapies

The basecase scenario included the cost of second-line therapy. This scenario investigates the cost effectiveness of first-line therapy only without including the subsequent treatment costs. In this case, MPT and CTDa are slightly less cost effective versus MP and VMP is considerably less cost effective. The cost effectiveness estimate for VMP versus MP increases to £37,727 per QALY gained.

Table 49: Scenario analyses A to D

	ICER (Cost per QALY gained, £)		
	MPT	**VMP**	**CTDa**
Basecase analysis	£9,174	£29,837	£33,216
Scenario A	£9,738	£37,727	£34,013
Scenario B	£9,369	£22,549	£33,492
Scenario C	£24,390	£29,837	£33,216
Scenario D	£20,698	£71,264	£80,840

Scenario B – vial sharing

The basecase scenario assumes that it is not possible for patients to share vials of bortezomib. This scenario investigates the cost effectiveness where patients do share vials of bortezomib. With vial sharing and no wastage, bortezomib becomes more cost effective versus MP, with ICER of £22,549 per QALY gained.

Scenario C – inclusion of thalidomide maintenance trials

The basecase scenario uses the efficacy for MPT using only RCTs that did not include thalidomide maintenance. This scenario investigates the cost effectiveness using the estimate

for MPT efficacy from a meta-analysis that includes trials with thalidomide maintenance. Janssen-Cilag conducted a MTC for MPT efficacy with trials that included thalidomide maintenance and derived a hazard ratio [redacted] for MPT versus MP. Using this hazard ratio, makes MPT less cost effective with an ICER of £24,390 per QALY gained versus MP. In addition, MPT no longer dominates VMP, with an ICER of £32,739 for VMP versus MPT.

Scenario D –treatment effectiveness beyond the end of trial

The basecase scenario extrapolates beyond the end of the trial by assuming a constant hazard ratio for the treatment effectiveness compared to MP. Although this is a standard methodological assumption, it is unclear how the treatment effectiveness changes beyond the end of the trial. This scenario investigates an alternative assumption whereby there is no treatment benefit for VMP, MPT and CTDa over MP, ie the event rates for these treatments are the same as for MP after the end of the trial. Using this assumption has a large effect on the model results and all treatments are less cost effective compared to MP. The ICERs for each of the treatment options more than double to £20,698 (MPT), £71,264 (VMP) and £80,840 (CTDa) per QALY gained versus MP.

5.5.5.3 Probabilistic Sensitivity Analysis

In the PSA, the main parameters were sampled probabilistically from an appropriate distribution using similar ranges as used in the deterministic sensitivity analyses. The parameters sampled were: discount rate, number of treatment cycles, utility values, complete response rate, cost of AEs, parameters for the survival curves and the proportions of patients receiving bortezomib as second-line therapy. The distribution assigned to each variable included in the PSA and the parameters of the distributions are reported in Appendix 14.

One thousand simulations were run. The PSA results are presented in Table 50 and shows similar results to the deterministic analyses (Table 46 to Table 48). The scatterplots for cost and health outcomes for the treatment options for the PSA are shown in Figure 14. The cost acceptability curve is shown in Figure 13 and indicates at the £20,000 and £30,000 willingness to pay thresholds, MPT has the highest probability of being cost-effective of 0.95 and 0.95 respectively.

Table 50: Baseline PSA cost-effectiveness results versus MP

	MP	MPT	VMP	CTDa
Total cost, £	£21,620	£33,050	£57,545	£30,371
Total QALY	2.44	3.68	3.66	2.70
Incremental Cost vs MP	-	£11,495	£35,991	£8,816
Incremental QALY vs MP	-	1.26	1.24	0.28
ICER vs MP	-	£9,124	£29,102	£31,612

Figure 13: Cost-effectiveness acceptability curve from the PSA

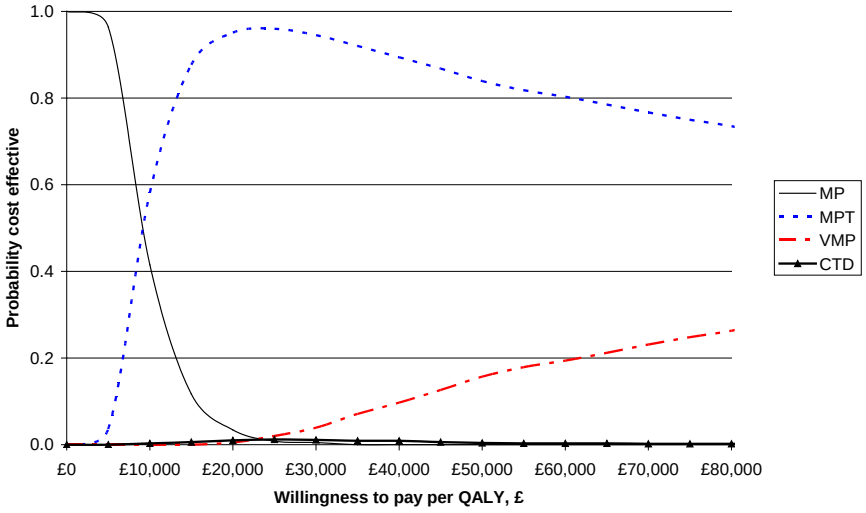
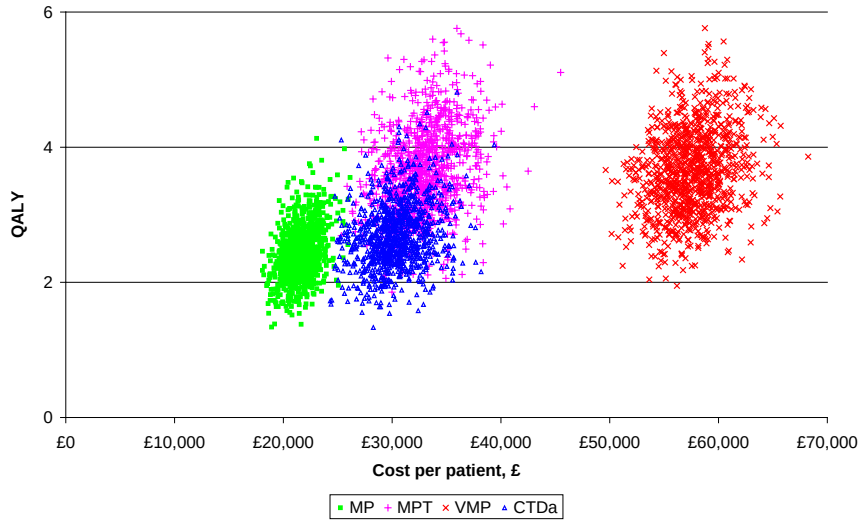


Figure 14: Scatterplots of the costs and health benefits from PSA for MP, MPT, VMP and CTDa



5.5.6 Summary of cost-effectiveness

- A systematic search of the literature found five abstracts of economic evaluations for treatment for patients with previously undiagnosed MM, ineligible for HDT-SCT. None of the studies contained sufficient information for critical appraisal. Three of the abstracts compared MPT to MP in patients in Scotland, Wales, and Australia. Each abstract concluded that MPT was a cost effective alternative to MP. Two abstracts compared VMP, MPT and MP in Canadian and US patients. Both studies concluded that the VMP regimen was cost effective compared to MP and MPT. The latter study stated that VMP dominated MPT (ie more effective at a lower cost). All studies were industry funded.
- A systematic review of studies of QoL for patients with MM identified six studies. Only two of these studies were for the population of interest and both studies did not include generic preference-based utility measures. The other four QoL studies provided utility estimates for patients with MM who had intensive therapy.
- Two manufacturers submitted evidence to be considered for the appraisal of bortezomib and thalidomide treatment. Janssen-Cilag, the manufacturer of bortezomib, constructed a survival model that estimated OS and PFS based on treatment effects from a MTC of the RCTs. They included second and third-line treatment. The base-case results from the submission found all treatments (VMP, MPT and CTDa) to be cost-effective. The ICER for VMP versus MP is estimated to

be £10,498. Furthermore the ICERs of VMP versus MPT and VMP versus CTDa are estimated to be £11,907 and £10,411 respectively.

- Celgene, the manufacturer of thalidomide, constructed a Markov model with health states for pre-progression (with or without AEs), post progression and death. They assumed that survival after disease progression was the same irrespective of first-line treatment. Treatment effects for disease progression were calculated from a random-effects MTC. The base-case results from the submission estimated an ICER of £23,381 per QALY gained for MPT versus MP and £303,845 per QALY for VMP versus MPT.
- The authors of this report developed an independent survival model. The survival model consisted of two survival curves which estimated the mean time to death and disease progression. These survival durations were used to derive the time spent in three health states: treatment, post treatment and progression. Utility values were applied to these health states to estimate total QALYs for each treatment option. Costs were included for medications and outpatient costs and AEs. The model base case results showed increased increased survival for each of the treatments compared to MP at an increased cost. The OS was marginally longer for MPT than for VMP at a considerably lower cost. The cost effectiveness estimates for MPT, VMP and CTDa versus MP were £9,174, £29,837 and £33,216 per QALY gained respectively. However MPT dominated VMP as it was cheaper and more effective.
- The effect of a range of parameter values in the economic model were evaluated in sensitivity analyses. The model results were found to be robust to changes in the parameter values. The model results are most sensitive to changes in the parameter values of the hazard ratios for OS.
- The PSA estimated the probability of each of the treatments to be cost effective at the £20,000 and £30,000 willingness to pay thresholds. MPT has the highest probability of being cost-effective with probabilities of 0.95 and 0.95 respectively.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Bortezomib is already used as a monotherapy within the NHS for patients with relapsed MM and therefore oncology departments will have experience of administering this treatment. However, increased use of bortezomib will result in an increase in staff time to cover its administration. Some clinicians will also have experience of treating patients with thalidomide because of the UK based MMIX RCT of CTDa versus MP. It is not clear whether there will be additional resource implications with increased use of thalidomide

because of the requirement that it is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

7 DISCUSSION

7.1 Statement of principle findings

Clinical effectiveness

- Five RCTs were included in the systematic review of clinical effectiveness. One examined the effectiveness of VMP, three examined the effectiveness of MPT, and one examined the effectiveness of CTDa. The comparator in all RCTs was MP. Two RCTs had a maintenance phase with thalidomide which followed the initial treatment phase. The maintenance phase did not meet the inclusion criteria. Reporting on the results of these RCTs was therefore limited to outcomes that had been reported at a time point prior to the start of maintenance therapy with thalidomide.
- Judgements about aspects of study quality could not be made for some studies because of a lack of detailed reporting in the published papers. Consequently there is uncertainty about some aspects of study quality. In particular it was not possible to determine whether the amount and pattern of censoring in the RCTs was comparable between study groups.
- OS was increased in the intervention group in comparison to the groups receiving MP in both of the MPT versus MP RCTs that provided data for this outcome. Meta-analysis of the OS data from two RCTs of MPT versus MP confirmed the superiority of MPT and was in agreement with a published meta-analysis of three MPT versus MP trials.[105] OS was also increased in the single VMP versus MP RCT. Because OS data for the single RCT of VMP is not as mature as that for the two RCTs of MPT it was not possible to determine whether OS was greater with MPT or VMP.
- More participants in the intervention arms of the included RCTs achieved a complete response to treatment than in the MP comparator arms. The difference was reported to be statistically significant in four of the included studies with a fifth study not reporting a *p*-value. It should be noted however that the proportion of participants achieving a complete response to treatment was not assessed according to ITT principles in one RCT which only reported data for approximately three quarters of the enrolled participants, and the proportions of data missing from each trial arm appeared to be unequal but no explanation for this was provided. The remaining four RCTs reported results for approximately 95% or more of the participants and the proportion of data missing from each arm seemed comparable. A meta-analysis of

the complete response outcome data from three MPT versus MP RCTs confirmed that MPT was superior in comparison to MP in terms of the proportion of patients achieving complete response.

- PFS was reported to be statistically significantly longer in the intervention group in comparison to the groups receiving MP in both of the MPT versus MP RCTs that provided data on this outcome, and the single VMP versus MP RCT. Only the RCT of VMP versus MP reported on time to disease progression, which was the primary outcome of this trial. There was a statistically significant difference in median time to disease progression in favour of the VMP group.
- AEs occurred with all treatments. Some AEs were statistically significantly increased in trial intervention arms. The combination of bortezomib and MP was associated with a statistically significant increase in grade three AEs in comparison to the MP group. [redacted]

Cost-effectiveness

- A systematic search of the literature found five abstracts of economic evaluations for treatment for patients with previously undiagnosed MM, ineligible for HDT-SCT. None of the studies contained sufficient information for critical appraisal.
- A systematic search for published studies of QoL for patients with MM identified six studies. Only two of these studies were for the population of interest and both studies did not include generic preference-based utility measures. The other four QoL studies provided utility estimates for patients with MM who had intensive therapy.
- Two manufacturers submitted evidence to be considered for this review for bortezomib and thalidomide treatment. Janssen-Cilag, the manufacturer of bortezomib, constructed a survival model that estimated OS and PFS based on treatment effects from a MTC of the trials. The base-case results from the submission found all interventions to be cost-effective with ICERs of less than £11,000 per QALY gained versus MP for MPT, VMP and CTDa.
- Celgene, the manufacturer of thalidomide, constructed a Markov model with health states for pre-progression (with or without AEs), post progression and death. The base-case results from the submission estimated MPT to be cost effective compared

to MP, whilst the ICER for VMP versus MP was more than £40,000 per QALY gained.

- The authors of this report developed an independent survival model. From this independent model, the incremental cost-effectiveness versus MP for MPT, VMP and CTDa is estimated as £9,174, £29,837 and £33,216 per QALY gained respectively. However MPT dominated VMP as it was cheaper and more effective. The model results are most sensitive to changes in the parameter values of the hazard ratios for OS. The PSA showed that MPT has the higher probability to be cost-effective at the £20,000 and £30,000 willingness to pay thresholds.

Discussion of cost effectiveness results

The results for the manufacturers' and SHTAC's economic analyses are shown in Table 51. The results of the analyses vary considerably. The costs vary substantially between the analyses, for example the cost of MP varies between £1,365 for the Celgene submission to £54,434 for the Janssen-Cilag submission. The costs from the Celgene analysis were lower as they had not included any subsequent treatment costs, whereas the SHTAC analysis included costs for second-line treatment and the Janssen-Cilag included costs for second- and third-line treatment.

Table 51: SHTAC baseline cost-effectiveness results versus MP

	Analysis	MP	MPT	VMP	CTDa
Total cost, £	SHTAC	£21,555	£32,762	£57,304	£30,147
	Janssen-Cilag	£54,434	£59,322	£66,676	£56,668
	Celgene	£1,365	£21,133	£42,616	-
Total QALY	SHTAC	2.42	3.64	3.62	2.68
	Janssen-Cilag	2.86	3.41	4.03	3.07
	Celgene	2.43	3.28	3.35	-
Incremental cost vs MP, £	SHTAC	-	£11,207	£35,749	£8,592
	Janssen-Cilag	-	£4,888	£12,242	£2,234
	Celgene	-	£19,768	£41,251	-
Incremental QALY vs MP	SHTAC	-	1.22	1.20	0.26
	Janssen-Cilag	-	0.55	1.17	0.21
	Celgene	-	0.85	0.92	-
ICER vs MP, £	SHTAC	-	£9,174	£29,837	£33,216

	Janssen-Cilag	-	£8,912	£10,498	£10,905
	Celgene	-	£23,381	£44,838	-

The incremental costs for MPT versus MP vary between £4,888 (Janssen-Cilag) and £19,768 (Celgene). The Celgene submission uses higher dosages of thalidomide (238 mg/day) for longer periods (11 cycles) than the other two analyses. The incremental costs for VMP versus MP vary between £12,242 (Janssen-Cilag) and £41,251 (Celgene). These differences are largely due to the assumptions around the number of vials of bortezomib used, with Janssen-Cilag assuming a mean of 31.5 vials used per person, whereas the mean number of vials used is over 40 in the SHTAC and Celgene economic evaluations. The incremental costs for CTDa versus MP vary between £2,234 (Janssen-Cilag) and £8,592 (SHTAC) and these differences are due to an error in the cost calculation for third-line therapy for CTDa in the Janssen-Cilag analysis.

The total QALY estimates between the studies are reasonably similar with estimates for all treatment arms varying between 2.42 and 4.03 QALY. The incremental QALY estimates for MPT versus MP vary widely and these differences are due to the estimates chosen for the hazard ratio for OS compared to MP. The incremental QALY estimates for MPT versus MP range from 0.55 (Janssen-Cilag) to 1.22 (SHTAC).

The different assumptions and methodology described above results in a range of estimates for the cost effectiveness of the treatment options. The ICER for MPT versus MP varies between £9,174 (SHTAC) and £23,381 (Celgene) per QALY gained. The ICER for VMP versus MP varies between £10,498 (Janssen-Cilag) and £44,838 (Celgene) per QALY gained. The ICER for CTDa versus MP varies between £10,905 (Janssen-Cilag) and £33,216 (SHTAC) per QALY gained.

7.2 Strengths and limitations of the assessment

The review has the following strengths

- The systematic review and economic evaluation have both been carried out independent of any vested interest, and the results are presented in a consistent and transparent manner.
- The project was undertaken following the established methodology and principles for conducting a systematic review. The methods used were set out in a research protocol (Appendix 1), which drew on the NICE scope to define the research question, inclusion and quality assessment criteria, data extraction process and the

other methods to be employed during the evidence synthesis. The research protocol was circulated to clinical experts and agreed with NICE before the project started.

- An advisory group reviewed and commented on drafts of the protocol and the final report.
- A de novo economic model has been developed following recognised guidelines. The main results have been summarised and presented. The model structure and data inputs are clearly presented in this report. This should facilitate replication and testing of our model assumptions.
- Clinical evidence to populate the model has been extracted from reasonable quality RCTs included in the systematic review. The effect of treatment on OS and progression free survival was assessed using appropriate measures to model cost and outcome differences over the model time horizons.

In contrast, the review also has certain limitations

- Only two RCTs contributed data on OS following treatment with thalidomide and MP. The doses of thalidomide used differed between the two RCTs, as did the ages of the included participants, and the 72 week treatment period is not reflective of typical UK practice. It is therefore difficult to assess what the impact of MPT on OS would be when prescribed according to UK clinical practice to a typical MM patient in England and Wales.
- Only one RCT contributed data on OS following treatment with bortezomib and MP and the published peer-reviewed follow-up data are immature. At the data-analysis cut-off date in the published paper not all patients had complete their assigned treatment.
- No evidence on OS or PFS following treatment with CTDa met the inclusion criteria for the systematic review of clinical effectiveness because the only included RCT that assessed CTDa had a second randomisation to maintenance therapy with thalidomide for some participants after the completion of first-line treatment.
- No head-to-head trials were identified which compared bortezomib in combination with an alkylating agent and a corticosteroid, with thalidomide in combination with an alkylating agent and a corticosteroid.
- Assessment of the impact of treatment on quality of life was very limited. Data on HRQoL could only be included from one RCT, the study of VMP versus MP. Although one of the RCTs that assessed MPT versus MP reported on HRQoL these outcomes could not be included in the systematic review of clinical effectiveness

because this RCT has included the use of thalidomide maintenance therapy in the later part of the RCT.

- There were limited data available for meta-analysis. Furthermore most studies did not report all the data items that were necessary to enable meta-analysis to be conducted. These missing data items were therefore estimated using published methods. A mixed treatment comparison was not carried out because of doubts about the validity of doing so due to potential differences in participant characteristics, delivery of MP treatment in the comparators arms, and differences in length of follow-up. Furthermore, CTDa could not have been included in such an analysis because the single RCT that assessed CTDa included randomisation to maintenance therapy for some participants.
- For pragmatic purposes in the economic model, analyses were included for CTDa although the OS and PFS data included some patients who had received thalidomide maintenance from the MMIX RCT as no other data available for CTDa.
- Where possible, the data included in the model are in the public domain. However some data for OS and PFS were extracted from an MS where these were not reported in sufficient detail in published sources and these are reported as AIC and CIC, as appropriate.
- There were few HRQoL studies for the population of interest and these were only disease-specific HRQoL studies, using the EORTC Q30 QoL measure. It was necessary to derive EQ-5D utility estimates using a mapping algorithm.

7.3 Uncertainties

- It is not clear whether participants in the European trials reflect the population of patients that would received these treatments in the UK. The participants in these trials in general had a better performance status than the participants in the UK MMIX clinical trial who are likely to more accurately reflect the typical UK MM patient who is ineligible for HDT with SCT.
- It is not clear for OS and PFS outcomes how much data has been censored and for what reason. Therefore it was not possible to determine whether the amount and pattern of censored data was comparable between the trial groups. Whether censoring had any effect on the reported outcomes is unknown.
- Alterations in the doses of study drug were permitted in all studies and the target doses of thalidomide varied between the included RCTs. Although some trials provided some details on the duration and intensity of treatment it is not clear whether these dose alterations had a significant effect on the outcomes.

- Duration of MPT treatment in the two IFM RCTs[23,58] was longer than would be generally considered necessary or desirable in the UK. It is not certain what impact a shorter treatment period would have had on trial outcomes.
- Very limited data from subgroup analyses were available for the comparisons of VMP versus MP, and CTDa versus MP, and no subgroup data were available from the RCTs of MPT versus MP. The outcomes from the available subgroup analyses should be interpreted with caution
- Concern was expressed by a clinical advisor that the incidence of AEs may be underestimated by the clinical trials. In particular the incidence of peripheral neuropathy occurring with thalidomide was believed to be lower in the trials than that observed in UK clinical practice. Peripheral neuropathy, if it develops, can worsen quickly, and can be irreversible. This limits the duration of treatment with thalidomide or with bortezomib for some patients and there can be a need for long term treatment of neuropathic pain with gabapentin. Peripheral neuropathy can also preclude later treatment with bortezomib. Similarly the incidence of somnolence/dizziness/fatigue that occurs with thalidomide treatment may have been underestimated.
- The second-line and other subsequent treatments received by participants in the included RCTs were variable. They did not reflect current UK practice in which most patients in the UK will receive bortezomib as their second-line therapy. This is due to NICE guidance which recommends bortezomib only as a second-line therapy. The impact of second-line and later therapies on trial outcomes is unknown.
- There is some uncertainty around the appropriate dosage for thalidomide. The daily dosages in the RCTs varied between 100 and 200 mg per patient. The summary of product characteristics for thalidomide in the electronic Medicines Compendium states a daily dose of 200 mg. However our clinical expert advised that in practice, most patients will not be able to tolerate such a high dose and a lower dose of 100 mg is more common. In the economic analysis, we took the conservative assumption that the dose would be 150 mg. Lower dosages will result in more favourable cost effectiveness estimates.
- It is unclear the effect of second-line and subsequent treatment has on patient survival and HRQoL. In the RCTs, there was a large number of different treatment for second-line treatment. In the absence of appropriate data, we included second-line treatment as a cost and did not model its effect on health outcomes.

- There was considerable heterogeneity in the reporting of AEs in the RCTs. For this reason, the cost of treating AEs were included in the model but any short term utility decrements due to the AEs were not included.

The cost effectiveness results for CTDa should be treated with caution as the effectiveness estimates from the MMIX RCT include patients who received thalidomide maintenance therapy. [redacted]

8 CONCLUSIONS

8.1 Implications for service provision

Service provision is unlikely to change greatly, although there will be additional intravenous administration to cover if bortezomib use is extended.

8.2 Suggested research priorities

Head to head trials of combination chemotherapy regimens containing bortezomib versus regimens containing thalidomide are desirable. For the results of such a trial to be easily generalisable to UK clinical practice drug doses and treatment periods should reflect those in widespread use in the UK. All trials of first-line therapy for MM in patients who are ineligible for HDT and SCT should include assessments of patient HRQoL in response to treatment.

The patients in the RCTs included in the clinical effectiveness review received a variety of second-line and subsequent treatments. This does not reflect current UK practice which is that most patients receive bortezomib as their second-line therapy. If research is conducted to assess the impact of second-line treatments on patient outcomes it would also be desirable to assess whether the sequence of treatment, for example first-line therapy with a thalidomide containing regimen followed by second-line treatment with a bortezomib containing regimen or vice-versa, has any impact on patient outcomes.

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10 APPENDICES

Appendix 1: Report methods for synthesis of evidence of clinical and cost-effectiveness as described in the research protocol

A systematic review of the evidence for clinical-effectiveness and cost-effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'.[40]

Search strategy

A search strategy will be developed and tested by an experienced information specialist. The strategy will be designed to identify studies reporting clinical-effectiveness, cost-effectiveness, health-related quality of life, resource use and costs, epidemiology and natural history.

A draft search strategy for Medline will be adapted for other databases. Literature will be identified from several sources including electronic databases, bibliographies of articles, and grey literature sources. Reference lists contained within manufacturers' submissions to NICE will be searched for any additional studies which meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished references. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager software.

All databases will be searched from 1999 (earliest use of thalidomide for MM[37] and earliest description of bortezomib as a potential cancer therapy[38]) to the current date. Searches will be restricted to English language and updated around December 2009.

Inclusion and exclusion criteria

Interventions	Bortezomib in combination with an alkylating agent and a corticosteroid for first-line treatment of MM Thalidomide in combination with an alkylating agent and a corticosteroid for first-line treatment of MM (Studies of treatment with either bortezomib or thalidomide as a single agent will not be included.)
Participants	People with previously untreated MM who are not candidates for high-dose chemotherapy with stem cell transplantation. (Studies of MM patients who have received previous treatment(s) will not be included.)
Comparator	Interventions described above will be compared with each other and the following comparators:

	Melphalan or cyclophosphamide in combination with prednisolone or dexamethasone (Other chemotherapy regimens or stem cell transplantation will not be included)
Outcomes	Studies will be included if they report on one or more of the following outcomes: overall survival progression-free survival time-to-progression response rates health-related quality of life cost-effectiveness (such as incremental cost per QALY gained) Adverse effects of treatment will be reported if available within the trials that meet the inclusion criteria.
Design	The following types of study will be eligible for inclusion: Randomised controlled trials for clinical effectiveness. If no RCTs are found, or if the data from available RCTs is incomplete (e.g. absence of data on outcomes of interest) evidence from good-quality observational studies may be considered. Economic evaluations (such as cost-effectiveness studies, cost utility studies, cost benefit studies) (Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken; Systematic reviews and clinical guidelines will be used as a source of references; Case series, case studies, narrative reviews, editorials and opinions will be excluded; Non-English language studies will be excluded)

Inclusion and data extraction process

Studies will be selected for inclusion through a two-stage process. Literature search results (titles and abstracts) will be screened independently by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion/exclusion criteria and checked independently by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data will be extracted by one reviewer using a standardised data extraction form and will be checked for accuracy by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment strategy

The quality of included clinical effectiveness studies will be assessed using NHS CRD (University of York) criteria.[40] Methodological quality of economic evaluations will be undertaken based on recognised criteria for appraising economic evaluations.[79,106] Quality criteria will be applied by one reviewer and checked by a second reviewer with any disagreements resolved by consensus and involvement of a third reviewer where necessary.

Methods of analysis/synthesis

Clinical and cost-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies. Where appropriate the results from individual clinical effectiveness studies will be synthesised through meta-analysis, with causes of heterogeneity of results examined. The systematic review may explore the possibility of conducting an indirect comparison of thalidomide and bortezomib used in combination with an alkylating agent and a corticosteroid versus a common comparator. The specific methods for meta-analysis and for the detection and investigation of heterogeneity will depend upon the particular outcome measure under consideration.

Report methods for economic analysis

The cost-effectiveness of bortezomib or thalidomide used in combination with an alkylating agent and a corticosteroid for first-line treatment of MM will be assessed through a review of previous cost-effectiveness studies and, if appropriate, through the development of a decision analytic model. The purpose of the review is to identify recent relevant evaluations, in order to analyse the methodological approaches undertaken, and to discern whether and how existing models can be adapted for use in the current project.

Model structure

Where necessary, a *de novo* decision analytic model will be developed to assess the cost-effectiveness of bortezomib and thalidomide. The exact structure of the model will be designed to reflect important clinical events over the course of the disease and will be validated through discussion with expert advisors. Modelling will be conducted according to accepted methodology for economic evaluations.[77,94] The perspective will be the NHS and Personal Social Services (PSS). Costs and benefits will be discounted using standard rates (3.5%).[77] The model will be developed using standard software such as Microsoft Excel and Tree-Age Pro.

The model will contain a hypothetical cohort of individuals and will estimate changes in disease progression, morbidity and mortality for the MM treatments under consideration. The

time horizon for the model will be 15 years, which for the majority of patients in the hypothetical cohort is likely to be equivalent to a lifetime horizon.

Whilst *de novo* modelling is planned, the possibility of adapting an existing published model along the lines of the proposed model will be explored, through contact with experts in the field.

Clinical effectiveness data

The parameters of the model will be informed primarily by the systematic review of effectiveness studies. Additional targeted searches will be undertaken to identify specific data to populate the model. These will include searches for data on the epidemiology and natural history of MM; the health related quality of life impacts of disease stages and the adverse effects of treatment; the cost of treatment and health care costs. Where these data cannot be identified through searches, estimates will be based on information supplied by our expert advisory group and others.

Baseline disease progression will be predicted using trial data where available or good quality observational studies (such as the Mayo clinic study which has followed cohorts of patients with MM over a 13 year period[107]). Treatment effect will be modelled over time by adjusting the baseline prediction of treatment pathway and disease progression, based upon reported hazard ratios in the systematic review for time-to-progression to more severe states, and overall survival.

Costs and resource estimation

The resources necessary for providing the treatments will be estimated from the systematic review of effectiveness, and from discussion with expert advisers. Unit costs for these resources will be developed based on data in published sources such as the Unit Costs of Health and Social Care, PSSRU.[98] Data on the cost of assessing and treating MM will be sought from Southampton University Hospitals Trust (SUHT), which routinely supplies SHTAC with cost data and clinical expertise. Information on resource use and costs will also be derived from sponsor submissions to NICE, as appropriate.

Outcomes

The model will provide a cost-effectiveness analysis, reporting the costs of treatments under consideration in the appraisal and their long term consequences in terms of life years saved and QALYs gained and additional costs. Results will be expressed in terms of incremental cost-effectiveness ratios (e.g. incremental costs per QALY gained).

Uncertainty in model parameters and structure will be investigated through one way deterministic and probabilistic sensitivity analyses where appropriate and feasible. The key variables to be explored will include: treatment effect estimates (e.g. overall survival, and disease progression); baseline disease progression estimates; treatment costs; health related quality of life. Cost-effectiveness acceptability curves (CEACs) will be generated in any probabilistic sensitivity analysis, to illustrate the probability of the treatment being cost-effective over a range of willingness to pay values.

Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 15 October 2009. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in red in the assessment report (followed by an indication of the relevant company name in brackets unless it is obvious from the context). Any 'academic in confidence' data will be highlighted in yellow.

Appendix 2: Example Medline search strategies for clinical effectiveness and cost-effectiveness

Clinical Effectiveness

1 (bortezomib or velcade).mp.
2 thalidomid*.mp.
3 thalidomide/
4 or/1-3
5 exp multiple myeloma/
6 exp Plasmacytoma/
7 exp Paraproteinemias/
8 (myeloma* or (multiple adj myeloma*) or plasmacytom* or plasmocytom* or MGUS or (monoclonal adj gammopath*)).mp.
9 or/5-8
10 4 and 9
11 randomized controlled trial/
12 randomized controlled trial.pt.
13 controlled clinical trial/
14 controlled clinical trial.pt.
15 clinical trial.pt.
16 exp Clinical Trial/
17 random*.tw.
18 exp Research Design/
19 (systematic$ adj2 review$).mp.
20 (systematic$ adj2 overview$).mp.
21 (meta analy* or metaanaly*).ti,ab,pt.
22 exp meta analysis/
23 ((hand or manual or computer or electronic or database) adj2 search*).ti,ab.
24 (open adj label*).tw.
25 double-blind method/
26 single-blind method/
27 ((singl* or doubl* or tripl* or trebl*) adj5 (blind* or mask*)).tw.
28 exp cohort studies/
29 cohort*.ti,ab.
30 or/11-29
31 10 and 30
32 limit 31 to (english language and humans and yr="1999 -Current")
33 (editorial or comment or letter).pt.
34 32 not 33
35 from 34 keep 1-381

Cost-effectiveness

1 exp economics/
2 exp economics hospital/
3 exp economics pharmaceutical/
4 exp economics nursing/
5 exp economics medical/
6 exp "Costs and Cost Analysis"/
7 Cost Benefit Analysis/
8 value of life/
9 exp models economic/
10 exp fees/ and charges/
11 exp budgets/
12 (value adj2 (money or monetary)).tw.

13 (economic adj2 burden).tw.
14 (expenditure* not energy).tw.
15 budget*.tw.
16 (economic* or price* or pricing or financ* or fee* or pharmacoeconomic* or pharma economic* or pharmaco-economic*).tw.
17 (decision adj1 (tree* or analys* or model*)).tw.
18 Resource Allocation/
19 (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.
20 ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
21 (cost adj2 (util* or effective* or efficac* or benefit* or cosequence* or analys* or minimi* or saving* or breakdown* or lowering or estimate* or variable* or allocation* or control* or illness* or affordable* or instrument* or technolog* or fee* or charge* or charges)).tw.
22 Markov Chains/
23 Monte Carlo Method/
24 exp Decision Support Techniques/
25 (resource adj2 (use* or utili* or allocat*)).tw.
26 or/1-25
27 (bortezomib or velcade).mp.
28 thalidomid*.mp.
29 thalidomide/
30 or/27-29
31 exp multiple myeloma/
32 exp Plasmacytoma/
33 exp Paraproteinemias/
34 (myeloma* or (multiple adj myeloma*) or plasmacytom* or plasmocytom* or MGUS or (monoclonal adj gammopath*)).mp.
35 or/31-34
36 26 and 30 and 35
37 multiple myeloma/ec
38 *multiple myeloma/
39 26 and 38
40 "multiple myeloma".ti.
41 26 and 40
42 36 or 37 or 39 or 41
43 limit 42 to (english language and humans and yr="1999 -Current")
44 (editorial or comment or letter).pt.
45 43 not 44

Appendix 3: Response criteria

	EBMT, IBMTR and ABMTR criteria [a]	**IFM criteria** [b]
Complete response (CR) requires all of the following:	Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.	Absence of the original monoclonal protein in serum and urine by immunofixation. No confirmation needed.
	Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.	Less than 5% of plasma cells in a bone-marrow aspirate. No confirmation needed.
	No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).	
	Disappearance of soft tissue plasmacytomas	Disappearance of soft-tissue plasmacytomas
Very Good Partial Response (VGPR)		More than a 90% decrease in monoclonal protein in serum and urine. No confirmation needed
Partial response (PR) requires all of the following:	More than 50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.	More than a 50% reduction in the concentration of serum monoclonal protein. No confirmation needed.
	Reduction in 24 h urinary light chain excretion either by >90% or to <200 mg, maintained for a minimum of 6 weeks.	More than a 75% reduction in 24-h urinary light chain excretion. No confirmation needed.
	For patients with non-secretory myeloma only, >50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.	
	More than 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).	Reduction in the size of soft-tissue plasmacytomas
	No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).	
Minimal response (MR)	25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.	

	50–89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.	
	For patients with non-secretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.	
	25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).	
	No increase in the size or number of lytic bone lesions lesions (development of a compression fracture does not exclude response).	
EBTM: No change IFM: Stable disease	Not meeting the criteria of either MR or progressive disease.	Not meeting the criteria of either CR, PR, or progressive disease
Plateau	Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.	
Relapse from CR, requires at least one of the following:	Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.	
	Greater than 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.	
	Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).	
	Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.	
Progressive disease (for patients not in CR): requires at least one of the following:	A greater than 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.	A greater than 25% increase in the concentration of serum monoclonal protein, which must also be an absolute increase of more than 5 g/L and confirmed by at least one repeated assessment;
	A greater than 25% increase in the 24 h urinary light chain excretion excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation.	A greater than 50% increase in the 24-h urinary light chain excretion, confirmed by at least one repeated assessment

	A greater than 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.	
	Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.	A confirmed increase in the size of existing bone lesions or soft-tissue plasmacytomas
	Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).	Development of new bone lesions or soft-tissue plasmacytomas
	Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.	Development of hypercalcaemia, not attributable to any cause other than multiple myeloma

[a] EBMT, IBMTR and ABMTR criteria are provided for definition of response, relapse and progression in patients with multiple myeloma treated by high dose therapy and stem cell transplantation. However it appears that the same criteria have been applied to the patients ineligible for these therapies. Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed. Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR. MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

[b] The achievement of any response needed an improvement in bone pain and performance status, correction of hypercalcaemia, and no increase in size or number of lytic bone lesions. The best response at 12 months was defined as the highest amount of disease improvement achieved by a patient at any follow-up visit while on treatment, from randomisation to month 15, except if progressive disease had occurred during that period without response assessment at 12 months (between 9 and 15 months)

Appendix 4: Table of excluded studies

Excluded Reference	Reason for exclusion
Anon. 2007 Melphalan prednisone thalidomide versus melphalan prednisone in patients aged >= 75 years with untreated multiple myeloma: Preliminary results of the randomized, double-blind, placebo-controlled IFM 01-01 trial.. Clinical Lymphoma & Myeloma 7, 455-456.	Not a clinical trial report
Anon. 2008 Thalidomide added to standard therapy prolongs overall survival in newly diagnosed multiple myeloma patients over age 75. ONCOLOGY 22, 87	Not a clinical trial report
Morgan, G.J.; Jackson, G.H.; Davies, F.E.; Drayson, M.T.; Owen, R.G.; Gregory, W.M.; Cohen, D.C.; Szubert, A.J.; Bell, S.E.; Ross, F.; Child J.A. 2008. Maintenance Thalidomide May Improve Progression Free but Not Overall Survival; Results from the Myeloma IX Maintenance Randomisation. Blood 112. Abstract 656	Thalidomide maintenance
Morgan, G.J.; Davies, F.E.; Owen, R.G.; Rawstron, A.C.; Bell, S.; Cocks, K.; Gregory, W.M.; Jackson, G.H.; Drayson, M.T.; Jenner, M.W.; Child J.A. 2007. Thalidomide combinations improve response rates; Results from the MRC IX study Blood 110. Abstract 3593	Thalidomide maintenance
Davies, F.E.; Child J.A.; Hawkins, K.; Bell, S.; Brown, J.; Drayson, M.T.; Jackson, G.H.; Morgan, G.J. 2004. Newly diagnosed myeloma pateints are at risk of venous thrombotic events - High risk patients need to be identified and recieve thromboprophylaxis: The MRC experience. Blood 104. Abstract 2395	Outcomes
Kapoor, P.; Rajkumar, S.V.; Dispenzieri, A.; Lacy, M.Q.; Dingli, D.; Kyle, R.; Gertz, M.A.; Greipp, P.R.; Kumar, S.; Mandrekar, S.J. 2009. Melphalan and Prednisone (MP) Versus Melphalan, Prednisone and Thalidomide (MPT) as Initial Therapy for Previously Untreated Elderly and/or Transplant Ineligible Patients with Multiple Myeloma: A Meta-Analysis of Randomized Controlled Trials . 51st ASH Annual Meeting and Exposition. New Orleans, LA December 5-8 2009, Abstract number 615.	Meta-analysis (insufficient details in abstract)

Appendix 5: Clinical effectiveness included studies data extraction forms

Data extracted by……JB……Extraction checked by…JP……...

Reference and Design	Intervention	Participants	Outcome measures
Author: San Miguel et al[26] VISTA Trial Abstracts for follow-up data[59,60] Year: 2008 Country: 22 countries in Europe, North and South America, Asia Study design: Multicentre RCT Setting: Secondary care Number of centres: 151 centres Recruitment dates: December 2004 to September 2006 Funding: Supported by Johnson & Johnson Pharmaceutical Research & Development and Millennium Pharmaceuticals	Intervention: Nine 6-week cycles of melphalan (9mg/m^2) plus prednisone (60mg/ m^2) on days 1 to 4, plus bortezomib (1.3 mg/m^2 by iv bolus) on days 1,4,8,11,22,25,29, and 32 during cycles 1 to 4 and on days 1,8,22 and 29 during cycles 5 to 9. Control: Nine 6-week cycles of melphalan (9mg/m^2) plus prednisone (60mg/ m^2) on days 1 to 4. Treatment discontinued on withdrawal of patient's consent, disease progression or the occurrence of unacceptable toxic effects. Dose of melphalan or bortezomib reduced if any prespecified haematologic toxic effect or Grade 3 or 4 nonhaematologic toxic effect; bortezomib-	Number of Participants: 682 VMP: 344 MP: 338 Sample attrition/dropout: Not clearly or explicitly described – numbers provided for adverse event data but reasons for all withdrawals not given. Timing of withdrawals not reported. Sample crossovers: None Inclusion criteria for study entry: Newly diagnosed untreated symptomatic measurable myeloma patients not candidates for HD therapy plus SCT because of age (≥65 y) or co-existing conditions. Measurable disease defined as presence of quantifiable M protein in serum or urine or measurable soft-tissue or organ plasmacytomas. Exclusion criteria for study entry: None stated. Characteristics of participants: Age (years): median(range) VMP 71(57-90), MP 71 (48-91) Age <65y VMP 14 (4%), MP 9 (3%) Age ≥75y VMP 107 (31%), MP 101 (30%). Gender (m:f): VMP 175:169 (51%:49%), MP 166:172 (49%:51%) Ethnicity: White VMP 304 (88%), MP 295 (87%) Asian VMP 33 (10%), MP 36 (11%) Black VMP 5 (1%), MP 7 (2%) Other VMP 2 (1%), MP 0 Region: Europe VMP 79%, MP 78% North America VMP 9%, MP 9%	Primary outcomes: Time to disease progression Secondary outcomes: Rate of complete response, duration of response, time to subsequent myeloma therapy, overall survival. Progression-free survival (reported in supplemental appendix) Method of assessing outcomes: Response to treatment and disease progression assessed using EBMT criteria and previously validated computer algorithm, on basis of M protein in serum and urine. Definitions from appendix – PFS is time between randomisation and either disease progression or relapse from CR or death. Blood and 24-hour urine samples collected every 3 weeks during 54 week treatment phase and then every 8 weeks until disease progression.

	associated neuropathic pain and perhipheral sensory neuropathy managed with use of established dose-modification guidelines (referenced). Other interventions used: Patients with myeloma-associated bone disease received bisphosphonates unless such therapy was contraindicated (referenced).	Other VMP 11%, MP 13% Karnofsky performance status ≤70: VMP 122 (35%), MP 111 (33%) Myeloma type: IgG VMP 64%, MP 62% IgA VMP 24%, MP 26% IgD VMP 1%, MP 1% IgM VMP 1%, MP1% Light chain VMP 8%, MP 8% Biclonal VMP 2%, MP 2% Lytic bone lesions, no/total no.(%): VMP 224/343 (65%), MP 222/336 (66%) Median plasma cells on bone marrow biopsy: VMP 40%, MP 41% ISS: Stage I VMP 19%, MP 19% Stage II VMP 47%, MP 47% Stage III VMP 35%, MP 34% Serum β_2-microglobulin level (mg/l): Median (range) – VMP 4.2 (1.7-21.6), MP 4.3 (0.6-60.9) <2.5 VMP 12%, MP 12% 2.5-5.5 VMP 55%, MP 55% >5.5 VMP 33%, MP 33% Albumin level (g/dl) : Median(range) VMP 3.3 (1.3-4.7), MP 3.3 (1.4-5.0) <3.5 VMP 58%, MP 62% ≥3.5 VMP 42%, MP 38% Haemoglobin (g/l): Median(range) VMP 104 (64-159), MP 106 (73-165) Platelet count/mm^3 median (range): VMP 221,500 (68,000-515,000), MP 221,500 (33,000-587,000) Creatinine clearance (%): <30 ml/min VMP 6%, MP 5% 30-60 ml/min VMP 48%, MP 50% >60 ml/min VMP 46%, MP 46% History of cardiac condition: VMP 121 (35%), MP 105 (31%)	Other efficacy assessment included bone marrow examination and skeletal survey as required by EBMT or on basis of clinical/biochemical measurements. Relapse from complete response defined as reappearance of M protein on immunofixation. Seven prespecified and one post-hoc subgroups defined (not data extracted) Adverse events: Graded by National Cancer Institute's Common Terminology Criteria for Adverse events (ver 3.0). No further details given. Safety evaluated throughout study and until 30 days after administration of a study drug. Length of follow-up: Not specifically stated. Patients followed for survival and subsequent myeloma therapy at least every 12 weeks after disease progression. Median follow-up at data cut-off point not reported.
Results			
Primary Outcomes	**VMP (n=344)**	**MP (n=338)**	**p-value**

TTP median (from trial investigators)	24 months	16.6 months	p<0.001 HR=0.48
TTP median (from computer algorithm analysis)	20.7 months	15.0 months	p<0.001 HR=0.54
Comments: HR in favour of VMP was 0.48 (independent of age, sex, race, baseline β_2-microglobulin level, baseline albumin level, region, ISS or creatinine clearance). HR using algorithmic analysis was 0.54. HR for each subgroup of patients (7 pre-specified and 1 post-hoc) was lower for VMP than MP indicating lower risk of progression in the VMP group as assessed by investigators. However, the study may not have been powered to show this for subgroups.			
Secondary outcomes	**VMP (n=337)**	**MP (n=331)**	**p-value**
Response rates using EBMT criteria			
Rate of PR or better	238 (71%)	115 (35%)	p<0.001
Rate of CR	102 (30%)	12 (4%)	p<0.001
Rate of PR	136 (40%)	103 (31%)	Not reported
Minimal response	32 (9%)	72 (22%)	Not reported
Stable disease	60 (18%)	113 (40%)	Not reported
Progressive disease	3 (1%)	7 (2%)	Not reported
Response rates using IURC (post hoc analysis)			
Rate of PR or better	251 (74%)	128 (39%)	p<0.001
Rate of CR	111 (33%)	13 (4%)	p<0.001
Rate of VGPR	28 (8%)	13 (4%)	Not reported
Rate of PR	112 (33%)	102 (31%)	Not reported
Stable disease	79 (23%)	192 (58%)	Not reported
Progressive disease	3 (1%)	7 (2%)	Not reported
Time to event [a]			
Median time to first response (partial response or better)	1.4 months	4.2 months	p<0.001
Median time to CR	4.2 months	5.3 months	p<0.001
Median duration of CR or PR	19.9 months	13.1 months	Not reported
Median duration of CR	24 months	12.8 months	Not reported
Median time to subsequent myeloma therapy	Not reached (based on 344 patients)	20.8 months (based on 338 patients)	p<0.001 HR=0.52
Started second-line treatment within 2 years	35%	57%	Not reported
Survival [b]			
	VMP (n=344)	**MP (n=338)**	
Treatment free interval	Not reached	9.4 months	Not reported
Deaths after median follow-up of 16.3 months	45 (13%)	76 (22%)	p=0.008 HR=0.61
Median overall survival	Not reached	Not reached	
Median progression-free survival	21.7 months	15.2 months	p<0.001 HR 0.56
At data cut-off point			

Patients still receiving assigned protocol	47 (14%)	33 (10%)	
Results from abstract [60]			
Median OS after median follow-up of 36.7 months	Not estimable	43.1 months	*Not reported*
3-year OS rate	68.5%	54.0%	*Not reported*
Risk of death after median follow-up of 36.7 months	Risk reduced by 35% in VMP group compared to MP group		*p=0.0008 HR 0.653*
Received subsequent therapy	178 (52%)	233 (69%)	*Not reported*
Median time to subsequent therapy	28.1 months	19.2 months	*HR 0.527, p<0.0001*
Median treatment-free interval	17.6 months	8.4 months	*HR 0.543, p<0.0001*
Median survival from start of subsequent therapy	30.2 months	21.9 months	*HR 0.815 p=0.21*
Results from abstract [59]			
Survival after median follow-up of 25.9 months	*Not reported*	*Not reported*	*p=0.0032 HR=0.64*
3 year survival rates	*72%*	*59%*	*Not reported*
Time to next therapy	*28.1 months*	*19.2 months*	*p<0.000001 HR=0.53*
Treatment free interval	*16.6 months*	*8.4 months*	*p<0.00001 HR=0.54*
Required subsequent therapy	*38%*	*57%*	*Not reported*
Comments: [a] time to event data determined by computer algorithm using EBMT criteria. [b] Data based on 344 patients in VMP group and 338 patients in MP group. HR after median follow-up of 16.3 months was 0.61 in favour of VMP (p=0.008). *From abstract[59]:* *HR for survival after median follow-up of 25.9 months was 0.64 in favour of VMP (p=0.0032)* *HR for Time to next therapy was 0.53 in favour of VMP (p<0.000001).* *HR for Treatment free interval was 0.54 in favour of VMP (p<0.00001).*			
Results from abstract[60]	**VMP (n=344, number analysed not reported)**	**MP (n=338, number analysed not reported)**	**p-value**
Sustained response in QLQ-C30 domains - cognitive functioning - nausea/vomiting	 27% not reported	 28% not reported	 not reported p=0.0095
- appetite loss	not reported	not reported	p=0.0170
- diarrhoea	not reported	not reported	p=0.0082
- Global health	49%	40%	not statistically significant
- Pain	40%	32%	not statistically significant
- Insomnia	32%	24%	not statistically significant

Comments: the aim of the study was to describe the rate of patients who experienced a sustained HRQoL improvement after best response and the overall HRQoL impact of best response. A sustained HRQoL improvement was defined as a change in score of at least 5 points for at least 2 consecutive cycles after best response (CR, PR or MR). The rate of sustained improvement and the time to sustained improvement were calculated in the population of patients who were followed for at least 2 cycles after best response (n=363). All EORTC domain scores were similar at baseline across the study arms. Worse health was reported in all domains with VMP arm at best tumour response onset. However, after best response onset, patients in the VMP arm had a higher sustained HRQoL improvement rate than those in the MP arm in 14 of the 15 EORTC QLQ-C30 scores. The differences for Nausea and Diarrhea remained significant in the Cox models when adjusted for baseline score, score at best response, and type of response (CR, PR or MR).							
Adverse Events	**VMP (n=340)**			**MP (n=337)**			**p-value**
Median number of treatment cycles	8 (46 weeks)			7 (39 weeks)			Not reported
Death rates during treatment	5%			4%			ns
Treatment-related deaths	1%			2%			ns
Rate of serious adverse events	46%			36%			Not reported
Discontinued treatment due to adverse events	50 (15%)			47 (14%)			Not reported
Discontinued treatment due to treatment-related events	37 (11%)			35 (10%)			Not reported
Additional discontinuations (bortezomib)	63 (19%)			-			
Adverse events, No (%) [a]	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	
Any event	338 (99%)	181 (53%)	96 (28%)	326 (97%)	148 (44%)	92 (27%)	p=0.02 for Grade 3; nr for grade 4
Haematologic events [b]:							Not reported
- Thrombocytopenia	178 (52%)	68 (20%)	58 (17%)	159 (47%)	55 (16%)	47 (14%)	
- Neutropenia	165 (49%)	102 (30%)	34 (10%)	155 (46%)	79 (23%)	49 (15%)	
- Anaemia	147 (43)	53 (16%)	9 (3%)	187 (55%)	66 (20%)	26 (8%)	
- Leucopenia	113 (33%)	67 (20%)	10 (3%)	100 (30%)	55 (16%)	13 (4%)	
- Lymphopenia	83 (24%)	49 (14%)	18 (5%)	58 (17%)	30 (9%)	7 (2%)	
Gastrointestnial events:All	19%			5%			Not reported
- Nausea	164 (48%)	14 (4%)	0	94 (28%)	1 (<1%)	0	
- Diarrhoea	157 (46%)	23 (7%)	2 (1%)	58 (17%)	2 (1%)	0	
- Constipation	125 (37%)	2 (1%)	0	54 (16%)	0	0	
- Vomiting	112 (33%)	14 (4%)	0	55 (16%)	2 (1%)	0	
Infections:	56	16	6	36	13	4	Not reported
- Pneumonia	(16%)	(5%)	(2%)	(11%)	(4%)	(1%)	

- Herpes zoster	45 (13%)	11 (3%)	0	14 (4%)	6 (2%)	0	
Nervous system disorders: - Peripheral sensory neuropathy - Neuralgia - Dizziness	151 (44%) 121 (36%) 56 (16%)	43 (13%) 28 (8%) 7 (2%)	1 (<1%) 2 (1%) 0	16 (5%) 5 (1%) 37 (11%)	0 1 (<1%) 1 (<1%)	0 0 0	Not reported
Other conditions: - Pyrexia - Fatigue - Anorexia - Asthenia - Cough - Insomnia - Peripheral oedema - Rash - Back pain -Dyspnea -Hypocalaemia - Arthalgia - Deep-vein thrombosis	99 (29%) 98 (29%) 77 (23%) 73 (21%) 71 (21%) 69 (20%) 68 (20%) 66 (19%) 58 (17%) 50 (15%) 44 (13%) 36 (11%) 4 (1%)	8 (2%) 23 (7%) 9 (3%) 20 (6%) 0 1 (<1%) 2 (1%) 2 (1%) 9 (3%) 11 (3%) 19 (6%) 4 (1%) 3 (1%)	2(1%) 2 (1%) 1 (<1%) 1 (<1%) 0 0 0 0 1 (<1%) 2 (1%) 3 (1%) 0 0	64 (19%) 86 (26%) 34 (10%) 60 (18%) 45 (13%) 43 (13%) 34 (10%) 24 (7%) 62 (18%) 44 (13%) 25 (7%) 50 (15%) 6 (2%)	6 (2%) 7 (2%) 4 (1%) 9 (3%) 2 (1%) 0 0 1 (<1%) 11 (3%) 5 (1%) 8 (2%) 2 (1%) 2 (1%)	2 (1%) 0 0 0 0 0 0 0 1 (<1%) 3 (1%) 2 (1%) 1 (<1%) 0	Not reported

Comments: Median dose intensities for MP same in both groups.
[a] Listed adverse events were reported in at least 15% patients, Grade 3/4 events in at least 5% patients. Other events of clinical relevance (e.g. DVT) also listed. Patients could have more than one adverse event. Included are all patients who received at least one dose of study drug.
[b] rates of red cell transfusion were 26% in the VMP group, 35% in the MP group; rates of erythropoiesis-stimulating agents for treatment-related anaemia were 30% and 39% respectively.
At time of cut off 74% of peripheral neuropathy events had either resolved (56%) or decreased at least one toxicity grade (18%) within a median of 2 months.

Discontinuations	**VMP (n=340)**	**MP (n=337)**	**p-value**
Total discontinued treatment	139 (41%)	166 (49%)	nr
Discontinued due to progressive disease	24 (7%)	72 (21%)	nr
Discontinued due to treatment related events	37 (11%)	35 (10%)	nr

Discontinued due to patient choice	32 (9%)	18 (5%)	nr
Discontinued due to death	14 (4%)	17 (5%)	nr
Discontinued due to maintenance of CR	9 (3%)	1 (<1%)	nr
Other reasons for discontinuation	10 (3%)	11 (3%)	nr
Comments: Percentages calculated by reviewer			

Methodological comments

Allocation to treatment groups: Randomisation (1:1) was stratified according to baseline levels of β_2-microglobulin (<2.5, 2.5 to 5.5, or >5.5 mg/l), serum albumin (<3.5 or ≥3.5 g/dl) and region (North America, Europe or other region).

Blinding: Not stated but study described as open-label.

Comparability of treatment groups: baseline demographic and disease characteristics stated to be well balanced between groups (no p values given).

Method of data analysis: TTP, time to subsequent myeloma therapy and overall survival analyses from randomisation to event of interest. Differences between groups compared using stratified log-rank tests with ITT analysis (all randomised patients). Distributions estimated using Kaplan-Meier method. For time-to-progression analyses, data from patients in whom there was no disease progression were censored at the last assessment or at the start of subsequent therapy. Hazard ratios estimated using stratified Cox proportional hazards model for ITT and subgroups defined according to baseline characteristics (7 pre-specified analyses according to age, sex, race, baseline β_2-microglobulin level, baseline albumin level, region, disease stage and post-hoc creatinine clearance). Response rates were analysed in patients who could be evaluated for a response (not ITT) and compared between groups using stratified Cochran-Mantel-Haenszel chi-square test. Treatment differences tested at a two-sided alpha level of 0.05. Safety population was all randomised patients who received at least one doe of study drug.

Sample size/power calculation: sample size of 340 patients per group was determined to provide a power of 80% to detect a 33% improvement in time to progression in patients receiving VMP as compared with MP. Three interim analyses planned using O'Brien-Fleming method. On basis of third analysis (data cut-off June 15, 2007), the data and safety monitoring committee recommended that the trial be stopped since the pre-specified statistical boundary (an alpha level of 0.0108) for the primary end point of TTP has been crossed (HR in bortezomib group 0.54, p<0.001). Data from the third analysis are presented. Not clear if study powered for sub-group analyses.

Attrition/drop-out: not explicitly reported but withdrawals given in adverse event data. Not all reasons for discontinuations in VMP group reported.

General comments

Generalisability: Patients ≥65 so probably generalisable in terms of population.

Outcome measures: Defined and graded.

Inter-centre variability: Not stated.

Conflict of interests: Data collected by sponsors and analysed in collaboration with senior academic authors who vouch for the completeness and accuracy of the data and analyses. Eleven of 21 authors report conflicts of interest.

Quality Criteria[40]

Criteria for assessment of risk of bias in RCTs	Answer*	Notes & Comments
Was the method used to generate random allocations adequate?	NR	
Was the allocation adequately concealed?	NR	
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Y	No p values given

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Open label
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	UN	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y	No details given

*** answer yes/no/not reported/unclear**

Additional Outcomes/Comments/Notes

Outcomes from abstract[60] *median follow-up of 36.7 months*	**VMP (n=178)**	**MP (n=233)**	**p-value**
Received subsequent therapy containing:			
- bortezomib	43 (24%)	116 (50%)	
- thalidomide	81 (46%)	110 (47%)	
- lenalidomide	57 (32%)	30 (13%)	
Overall response rate to subsequent therapy			
- bortezomib	47%	59%	
- thalidomide	41%	53%	
- lenalidomide	59%	52%	
Comments: Patients could have received more than one agent, either in combination or separately in different subsequent lines of therapy.			

Outcomes from abstract[59]	**VMP (n=129)**		**MP (n=194)**		**p-value**
Received bortezomib	16%		43%		
Received thalidomide	49%		44%		
Received lenalidomide	19%		6%		
	VMP (n=129)		**MP (n=194)**		
Subsequent therapy and number of patients who received it*	CR (%)	PR (%)	CR (%)	PR (%)	
Bortezomib or bortezomib combination (n=105)	6%	33%	10%	45%	

Thalidomide combination (n=149)	4%	44%	3%	52%	
Lenalidomide combination (n=37)	4%	52%	0	55%	
Comments: * other agents were used as subsequent therapy such as dexamethasone; patient could receive multi-agent regimens.					

Data extracted by…JO P……Extraction checked by…….JB……...

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author: Facon et al.[23] IFM 99/06 Year: 2007 Country: France, Belgium, & Switzerland Study design: Multicentre RCT Setting: Not stated, appears to be secondary care. Number of centres: 73 Intergroupe Francophone du Myelome (IFM) centres. Number in each country not stated. Recruitment dates: May 22nd 2000 to August 8th 2005 Funding: Sponsored by the Centre Hospitalier et Universitaire de Lille; by a research grant from the French Ministry of Health; and by the Swiss Group for Clinical Cancer Research (SIAK). Laphal, and later Pharmion supplied free thalidomide.	Intervention, MPT: Oral thalidomide not exceeding 400mg daily taken throughout the 12 MP cycles. Thalidomide stopped on day 4 of the last MP cycle. Advice was to initiate thalidomide at a dose of 200mg per day, increasing to 400mg per day after 2-4 weeks in the absence of severe adverse effects. Initial dose defined as the greatest dose used in the first four weeks of treatment. + MP for 12 x 6 week cycles comprising Melphalan 0.25mg/kg and prednisone 2 mg/kg on 4 days (days 1 to 4) per cycle. Both drugs taken orally. Control, MP only: MP for 12 x 6 week cycles comprising Melphalan 0.25mg/kg and prednisone 2 mg/kg on 4 days (days 1 to 4) per cycle. Both drugs taken orally. The trial had a third arm, reduced intensity stem-cell transplant using melphalan 100 mg/m^2 which has not been data extracted. Dose reductions: Thalidomide dose modification allowed at	Number of Participants: 447 to all three groups (one group not reported on here) MPT: 125 assigned (but 1 died before treatment initiation) MP+ placebo: 196 assigned (but 3 died before treatment initiation) Sample attrition/dropout: Not clearly described – numbers withdrawn provided but reasons for withdrawals not provided for each type of event e.g. death, progression, toxicity etc. Timing of withdrawals not reported. Sample crossovers: None Inclusion criteria for study entry: Generally patients aged between 65 and 75 years of age with previously untreated multiple myeloma at stage II or III (Durie-Salmon (DS) criteria). Prior treatment with minimum-dose radiotherapy to	Primary outcome: Overall survival Secondary outcomes: response, progression-free survival, survival after progression, and toxicity Method of assessing outcomes: Visits after inclusion at 3 months, 6 months, and every 6 months thereafter until withdrawal from the trial. At every visit response was assessed. After withdrawal from trial patient treatment and status updated every 6 months. These data also requested at other specific points for patients still alive at last known status. For achievement of response there had to be improvement in bone pain and performance status, correction of hypercalcaemia, and no increase in size or number of lytic bone lesions. Response definitions: Complete response – absence of the original monoclonal protein in

	discretion of local investigators. Thalidomide temporarily stopped if patients developed deep vein thrombosis or pulmonary embolism but treatment resumed once patients had undergone therapeutic anticoagulation. No thromobprophylaxis prospectively planned Treatment stopped: Thalidomide stopped for any non-haematological grade 3 or 4 toxic effects. Other interventions used: Clondronate orally 1,040mg per day continuously to all paitents.	localised lesions for symptom relief allowed. Additionally patients younger than 65 years were included if they were ineligible for high-dose treatment. Patients with Durie-Salmon stage I multiple myeloma who met criteria of high-risk stage I disease also eligible (criteria not listed, ref provided). Exclusion criteria for study entry: Previous neoplasms (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or higher, if unrelated to multiple myeloma; substantial renal insufficiency with creatinine serum concentration of 50mg/L or more; cardiac or hepatic dysfunction; peripheral neuropathy; HIV infection, or hepatitis B or C infections. Characteristics of participants (as assigned, includes those who died before treatment): Age ≥ 70 years: MPT 50/125 (40%); MP 84/196 (43%) Gender (m:f): MPT 63:62 (50%:50%); MP 109/87 (56%:44%) Ethnicity: not reported Immunoglobulin A isotype: MPT 25/125 (20%); MP 43/196 (22%) DS stage II or III: MPT	serum and urine by immunofixation, fewer than 5% plasma cells in a bone-marrow aspirate, and the disappearance of soft tissue plasmocytomas. Very good partial response - -more than 90% decrease in monoclonal protein in serum and urine. Partial response – reduction in the size of soft-tissue plasmocytomas, more than a 50% reduction in the concentration of serum monoclonal protein, and more than a 75% reduction in 24-hour urinary light chain excretion. Progressive disease definition: at least one of: greater than 25% increase in serum monoclonal protein concentration which must also be an absolute increase of more than 5 g/L, confirmed by at least one repeated assessment; a greater than 50% increase in the 24-hour urinary light chain excretion, confirmed by at least one repeated assessment; a confirmed increase in the size of existing bone lesions or soft-tissue plasmocytomas; development of new bone lesions or soft-tissue plasmocytomas; or the development of hypercalcaemia, not attributable to any cause other than multiple myeloma.

		112/125 (90%); MP 177/196 (91%) DS substage B: MPT 12/125 (10%); MP 15/196 (8%) International staging system (ISS) stage 1: MPT 38/112 (34%); MP 61/182 (34%) ISS stage 2: MPT 42/112 (38%); MP 67/182 (37%) ISS stage 3: MPT 32/112 (29%); MP 54/182 (30%) WHO performance index 3-4: MPT 10/125 (8%); MP 13/196 (7%) Bone lesions: MPT 90/125 (76%); MP 154/196 (79%) β_2 microglobulin ≥ 3.5 mg/L: MPT 69/112 (62%); MP 110/182 (60%) Albumin < 35 g/L: MPT 24/125 (19%); MP 45/194 (23%) Creatinine ≥ 20 mg/L: MPT 11/124 (9%); MP 13/196 (7%) Calcium ≥ 105 mg/L: MPT 17/125 (14%); MP 40/196 (20%) C-reactive protein ≥ 6 mg/L: MPT 50/114 (44%); MP 85/173 (49%) Lactate dehydrogenase ≥ 300 U/L: MPT 65/107 (61%); MP 116/175 (66%) Chromosome 13 deletion: MPT 49/101 (49%); MP 72/147 (52%) Translocation (11;14): MPT 11/58 (19%); MP 11/95 (12%) Translocation (4;14): MPT 10/57 (18%); MP 7/95 (7%)	Stable disease definition: patient not meeting criteria of complete response, partial response, or progressive disease. The best response at 12 months was defined as the highest amount of disease improvement achieved by a patient at any follow up visit while on treatment, from randomisation to month 15, except if progressive disease had occurred during that period without response assessment at 12 months (between 9 and 15 months). Adverse events: method of monitoring or assessing not reported. Reported for the safety population (all those randomised but excluding those who died before receiving treatment). Length of follow-up: Not clearly stated but a 2 year follow-up appears to have been planned. Outcomes reported for two date points with median follow ups of 36.8 months (Inter-quartile range (IQR) 20.8-51.2) in October 2005, and 51.5 months (IQR 34.4-63.2) in January 2007.
Results			
Primary Outcomes	**MPT**	**MP**	**p-value**

Overall Survival, Median (SE, IQR) number of deaths/number of patients after median follow up of 51.5 months (IQR 34.4 – 63.2)	51.6 months (4.5, 26.6 – not reached) 62/125 (50%) [a]	33.2 months (3.2, 13.8-54.8) 128/196 (65%) [a]	p=0.0006
Toxic death	n=0	n=4 (2%), all due to infection	
Early death – in first 3 months of treatment	3/124 (2%)	13/193 (7%)	
Comments: Hazard ratio for median overall survival in favour of MPT = 0.59 (95% CI 0.46-0.81). When adjusting for prognostic factors (e.g. WHO performance index; β_2 microglobulin, albumin etc) the results showed that MPT remained the superior treatment (HR 0.49, 95% CI 0.33-0.73, p=0.0002). At the initial analysis (median follow up 36.8 months) no difference in overall survival was recorded as a function of initial thalidomide dose (≤200 mg per day vs >200 mg per day, p=0.93). [a] Percentages calculated by reviewer			
Secondary outcomes	**MPT**	**MP**	**p-value**
Progression-free Survival, Median (SE, number of events/number of patients) after median follow up of 51.5 months	27.5 months (2.1, 92/125)	17.8 months (1.4, 171/196)	p=0.0001
Survival time after progression, Median (SE, number of events/number of patients) after median follow up of 51.5 months	13.4 months (2.3, 52/83)	11.4 months (1.9, 111/154)	
At least partial response at 12 months	57/75 (76%)	57/165 (35%)	p<0.0001
At least very good partial response at 12 months	35/75 (47%)	11/165 (7%)	p<0.0001
Complete response at 12 months	10/75 (13%)	4/165 (2%)	p=0.0008
Not withdrawn (still on 1st line treatment; 1st line ceased as planned & no further treatment, alive without progression, not withdrawn for other reason)	31/124 (25%)	42/193 (22%)	
Withdrawn and not receiving 2nd line treatment	38/124 (31%)	25/193 (13%)	
- up to death	11/38 (29%)	24/25 (96%)	
- still alive	27/38 (72%)	1/25 (4%)	

Withdrawn and having received 2nd line treatment	55/124 (44%)	126/193 (65%)	
Comments: Hazard ratio for median progression-free survival in favour of MPT = 0.51 (95% CI 0.39-0.66) after median follow up of 51.5 months. At the initial analysis (median follow up 36.8 months) no difference in progression-free survival was recorded as a function of initial, maximum or average thalidomide doses (p=0.22, p=0.75, p=0.92 respectively). Details of 2nd line treatments given presented in table following the QA table.			
Adverse Events & Safety	**MPT**	**MP**	**p-value**
Discontinuation of thalidomide because of toxic effects	56/124 (45%)		
- peripheral neuropathy	n=23		
- thrombosis	n=7		
- somnolence, dizziness, or fatigue	n=8		
- cutaneous toxic effects	n=4		
- psychiatric complications	n=1		
Withdrawn because of other reasons	n=13		
- haematological toxic effects	n=5		
- infection	n=7		
- stroke	n=1		
Grade 3 and 4 Adverse Events, numbers of patients (%)	**MPT (n=124)**	**MP (n=193)**	**p-value**
Haematological			
- anaemia	17 (14%)	27 (14%)	p= 0.94
- neutropenia	60 (48%)	51 (26%)	p<0.0001
- thrombocytopaenia	17 (14%)	19 (10%)	p= 0.29
- severe haemorrhage	0	3 (1.5%)	too few events to be clinically meaningful
Thrombosis or embolism	15 (12%)	8 (4%)	p= 0.008
Peripheral neuropathy	7 (6%)	0	p= 0.001
Somnolence/fatigue dizziness	10 (8%)	0	p<0.0001
Infection	16 (13%)	18 (9%)	p= 0.32
- fever of unknown origin	1 (1%)	2 (1%)	
- pneumonia	9 (7%)	5 (2.5%)	
- septicaemia	4 (3%)	6 (3%)	
- meningitis	2 (2%)	0	
- other	1 (1%)	6 (3%)	
- herpes zoster	3 (2.5%)	6 (3%)	
Cardiac	2 (2%)	1 (0.5%)	too few events to be clinically meaningful
- arrhythmia	2 (2%)	0	

- myocardial infarction/angina	0	0	
- cardiac failure	0	1 (0.5%)	
- hypertension	0	0	
Gastrointestinal			
- nausea	1 (1%)	2 (1%)	too few events to be clinically meaningful
- constipation	13 (10%)	0	p<0.0001
- mucositis	0	1 (0.5%)	too few events to be clinically meaningful
- bleeding	0	2 (1%)	too few events to be clinically meaningful
Any grade ≥3 non-haematological toxic effect	52 (42%)	30 (16%)	p<0.0001
Comments: Note that Facon et al analysed safety at the October 2005 date point after 36.8 months of follow up, a shorter follow-up than for the outcomes of overall survival, progression-free survival, and survival after progression analyses. In the MPT group 15 patients experienced 17 episodes of thrombosis or pulmonary embolism. Thalidomide was resumed in eight of the 15 patients with thrombosis after full anticoagulation, and without recurrent in seven patients (one patient had three episodes). In the MPT group 69 (55%) of patients experienced peripheral neuropathy. Of these the majority, 62 patients, had grade 1 or 2 peripheral neuropathy and 7 patients had grade 3 peripheral neuropathy (these are the 7 noted above), and none had grade 4.			
Median duration of treatment (IQR)	11 months (5-15)		
Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE			

Methodological comments

Allocation to treatment groups: States randomly assigned in a 3:2:2 ratio (MP:MPT:Mel100; Mel100 arm not included here). No further details.

Blinding: No details provided.

Comparability of treatment groups: Not described and no evidence presented to indicate whether similarity of groups had been statistically tested (although methods describe how this would be done). Visual inspection of the data suggests groups similar for most baseline characteristics reported on.

Method of data analysis: Parameters generally described by number and percentage of patients. Distributions of parameters assessed at inclusion compared between treatment groups using χ^2 tests for categoric variables and Kruskal-Wallis rank test for continuous variables (although no evidence from such tests presented as noted above). Best response rates at 12 months compared using theχ^2 test or Fisher's exact test when necessary. Curves for overall survival, progression-free survival, and survival after progression calculated from randomisation and from progression (for survival after progression) using the Kaplan-Meier method. Time to event data expressed as median (SE and IQR). Comparison between treatment groups and hazard ratios for death, progression or death without progression, or death after progression were estimated through the unstratified proportional hazards model, with 95% CI. Adverse events rates compared through χ^2 test or Fisher's exact test when necessary. Comparisons of overall survival between groups were adjusted on prognostic factors using a stepwise multivariate proportional hazards model, by forward selection with likelihood ratio test. All analyses done on an ITT population (not defined but numbers presented in tables indicate true ITT). Adverse events were analysed on the safety population (all those who received treatment, i.e. not including those who died before start of treatment). Confirmatory analysis on the primary endpoint was done on the per-protocol population at the first follow up but data not reported. Authors of this study do not report if it was necessary to censor any data and if so how this was done.

Sample size/power calculation: Sample size was estimated to be 500 patients (for the three arms of the trial) to guarantee, in a two-sided test, a power of 80% to detect an increase in the median survival time of 18 months (with an accrual time of 3 years and additional follow-up of 2 years). Power calculation

assumed a median survival time of 30 months in the control group and used the Bonferroni correction for a global type I error rate of 5%. Slightly fewer than 500 patients were recruited (447 overall), because recruitment was stopped earlier than planned (although this is not explicitly stated) in August 2005 when a clear survival advantage for MPT was found. The authors do not comment on any possible implications of the recruitment shortfall.
Attrition/drop-out: Withdrawals reported (see outcomes above).

General comments: The ITT analysis included patients not treated per-protocol: MP - 6 protocol violations at inclusion; 3 protocol violations during follow up; MPT – 0 protocol violations at inclusion; 2 protocol violations during follow up.
Generalisability: This trial focuses on patients 65-75 years and the results may therefore only be applicable to patients in this age bracket.
Outcome measures: Methods for grading of adverse events not described.
Inter-centre variability: No comments made regarding possible inter-centre variability.
Conflict of interests: States that the study sponsor had no role in study design, data collection, data analysis, data interpretation or writing of the report. Three authors had received scientific adviser board and lecture fees from Pharmion, Celgene and Janssen-Cilag. The remaining authors had no conflict of interest to declare.

Quality Criteria[40]

Criteria for assessment of risk of bias in RCTs	Answer*	Notes & Comments
Was the method used to generate random allocations adequate?	NR	
Was the allocation adequately concealed?	NR	
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Unclear	Baseline characteristics provided but no p-values and no statement indicating whether groups were similar.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	NR	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	No comments made by authors of paper on this.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear	ITT analysis was conducted but no indication of whether missing data had to be accounted for and if so, how this was done.

*** answer yes/no/not reported/unclear**

Additional Outcomes/Comments/Notes

Outcomes	**MPT**	**MP**	**p-value**
Initial daily dose of T 200mg or less	n=64/124 (52%)		
Initial daily dose of T 200mg or more	n=60/124 (48%)		

Initial daily dose of T 100mg	n=9		
Initial daily dose of T 300mg	n=5		
No change of dose throughout first-line treatment	n=66/124 (36 at ≤ 200 mg/day; 30 at >200 mg/day)		
Dose increased during first-line treatment	n=11/124		
Dose reduced during first-line treatment	n=47/124		
Second line treatment administered	55/124 (44%)	126/193 (65%)	
Second line treatment thalidomide alone or in combination	10/55 (18%)	55/126 (44%)	
Second line treatment VAD	15/55 (27%)	42/126 (33%)	
Second line treatment dexamethasone	7/55 (13%)	12/126 (10%)	
Second line treatment alkylating agent-based regimens	14/55 (25%)	13/126 (10%)	
Bortezomib	7/55 (13%)	3/126 (2%)	
Other	2/55 (4%)	1/126 (1%)	
Comments: Less than half of the patients at first progression on MP received rescue with thalidomide alone or in combination. Only 12 patients given MP or MPT underwent a transplant. These outcomes reported for the shorter median follow up of 36.8 months.			

Data extracted by…JO P……Extraction checked by……JB……...

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author: Hulin et al.[58] IFM 01/01 Trial Year: 2009 Country: France & Belgium Study design: Multicentre RCT Setting: Not stated, appears to be secondary care. Number of centres:	Intervention, MP+T: Oral thalidomide 100mg daily dose at bedtime for 72 weeks + MP for 12 x 6 week cycles comprising Melphalan 0.2mg/kg on days 1 to 4; prednisone 2 mg/kg on days 1 to 4. Control, MP+placebo: Oral placebo at bedtime for 72 weeks + MP for 12 x 6 week	Number of Participants: 232 (229 received treatment) MP+T: 115 (113 received treatment) MP+ placebo: 117 (116 received treatment) Sample attrition/dropout: 3 discontinued before treatment (failed inclusion criteria); 208 withdrawn (MP+T n=100; MP + placebo n=108) from study for other	Primary outcomes: Overall survival Secondary outcomes: safety, response rates, progression-free survival. Method of assessing outcomes: Visits every 6 weeks until treatment completion or study withdrawal. Response assessed at 3,6,12 and 18 months.

44 Intergroupe Francophone du Myelome (IFM) centres (39 in France; 5 in Belgium) Recruitment dates: April 10th 2002 to December 22nd 2006 Funding: Sponsored by the Centre Hospitalier Universitaire de Nancy; by a research grant from the French Ministry of Health; by Laphal; by Pharmion; and by Celgene, which supplied free experimental treatment (thalidomide or placebo) for the study.	cycles comprising Melphalan 0.2mg/kg on days 1 to 4; prednisone 2 mg/kg on days 1 to 4. Dose reductions: Dose reduction to 50mg per day of thalidomide or placebo allowed at investigator discretion in event of patient intolerance to 100 mg/day dose, especially in case of mild or moderate peripheral neuropathy (grade 1 or 2). No other dose reductions allowed. Treatment stopped: Thalidomide stopped for symptomatic peripheral neuropathy (grade 3 or 4) confirmed by electromyogram. Experimental treatment stopped and unblinded in the event of any nonhaematologic grade 3 or 4 adverse events or disease progression before 72 weeks. Other interventions used: Clondronate orally 1,040mg per day continuously to all paitents. No thromobprophylaxis prospectively planned Transfusions of red blood cells and platelets, and the	reasons (details in results). Timing of withdrawals not reported. Sample crossovers: None Inclusion criteria for study entry: At least 75 years of age with newly diagnosed multiple myeloma at stage II or III (Durie-Salmon (DS) criteria). Patients with Durie-Salmon stage I multiple myeloma who met criteria of high-risk stage I disease also eligible (criteria not listed, ref provided). Patients with nonsecretory or oligosecretory multiple myeloma allowed. Exclusion criteria for study entry: Previous neoplasms (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or higher, if unrelated to multiple myeloma; substantial renal insufficiency with creatinine serum concentration of 50mg/L or more; clinically significant cardiac or hepatic dysfunction; clinically significant	After end of treatment or withdrawal from trial patient status assessed every 6 months. All clinical responses required documentation of improvement from baseline in bone pain and performance status, correction of hypercalcaemia, and no increase in size or number of lytic bone lesions. Response definitions: Complete response – absence of the original monoclonal protein in serum and urine by immunofixation, fewer than 5% plasma cells in a bone-marrow aspirate, and the disappearance of soft tissue plasmocytomas. Very good partial response - -more than 90% decrease in monoclonal protein in serum and urine. Partial response – reduction in the size of soft-tissue plasmocytomas, a more then 50% reduction in the concentration of serum monoclonal protein, and a more than 75% reduction in 24-hour urinary light chain excretion.

	administration of neutrophil growth factors or erythropoiesis-stimulating agents permitted as required. Plasmapheresis at initial treatment and radiotherapy to localised lesions to relieve symptoms during the treatment phase permitted.	peripheral neuropathy; history of venous thrombosis during the previous 6 months; HIV infection, or hepatitis B or C infections. Characteristics of participants (only for participants who received treatment): Age ≥ 80 years: MP+T 43/113 (38%); MP + placebo 40/116 (34%) Gender (m:f): MP+T 43:70 (38%:62%); MP + placebo 61/55 (53%:47%) Ethnicity: not reported Immunoglobulin A subtype: MP+T 31/113 (28%); MP + placebo 34/116 (30%) DS stage II or III: MP+T 100/113 (89%); MP + placebo 107/116 (93%) DS substage B: MP+T 8/113 (7%); MP + placebo 14/116 (12%) International staging system (ISS) stage 1: MP+T 25/98 (25%); MP + placebo 26/104 (25%) ISS stage 2: MP+T 39/98 (40%); MP + placebo 47/104 (45%) ISS stage 3: MP+T 34/98 (35%); MP + placebo 31/104 (30%)	Progressive disease definition: at least one of: a higher than 25% increase in serum monoclonal protein concentration constituting an absolute increase of more than 5 g/L, confirmed by at least one repeated assessment; a higher than 50% increase in the 24-hour urinary light chain excretion, confirmed by at least one repeated assessment; a confirmed increase in the size of existing bone lesions or soft-tissue plasmocytomas; development of new bone lesions or soft-tissue plasmocytomas; or the development of hypercalcaemia, not attributable to any cause other than multiple myeloma. Stable disease definition: patient not meeting criteria of complete response, partial response, or progressive disease. The best response at 12 months was defined as the best improvement achieved by a patient at any time on treatment, from random assignment to month 15. Adverse events:

		WHO performance index 3-4: MP+T 9/113 (8%); MP + placebo 7/116 (6%) Bone lesions: MP+T 87/113 (78%); MP + placebo 93/116 (82%) β_2 microglobulin ≥ 3.5g/dL: MP+T 70/101 (69%); MP + placebo 73/107 (68%) Albumin < 3.5 g/dL: MP+T 27/110 (25%); MP + placebo 34/113 (30%) Clearance creatinine ≤ 30mL/min: MP+T 11/105 (11%); MP + placebo 16/105 (15%) Significant comorbidity: MP+T 70/113 (62%); MP + placebo 69/116 (60%) Electromyogram abnormal: MP+T 17/54 (31%); MP + placebo 22/58 (38%)	Safety issues related to thalidomide closely monitored at every visit. Explanation of grading of adverse events not reported. Length of follow-up: Not explicitly stated. Median follow up 47.5 months at time of data analysis in October 2008.
Results			
Primary Outcomes	**MP+T**	**MP+Placebo**	**p-value**
Overall Survival, Median (95% CI)	44.0 months (33.4 to 58.7)	29.1 months (26.4 to 34.9)	p=0.028
Overall deaths	58/113 (51%)	76/116 (65.5%)	p=0.03
Death – myeloma progression considered major cause	n=36	n=54	
Toxic death (intestinal perforation)	n=1	n=1	
Early death – after 1 month of treatment	n=3	n=3	
Early death – after 3 months of treatment	n=5	n=6	
Comments: Hazard ratio for median overall survival in favour of MP+T = 0.68.			

Secondary outcomes	**MP+T**	**MP + placebo**	**p-value**
Progression-free Survival, Median (95% CI)	24.1 months (19.4 to 29.0)	18.5 months (14.6 to 21.3)	p=0.001
At least partial response	66/107 (62%)	35/112 (31%)	p<0.001
At least very good partial response	23/107 (21%)	8/112 (7%)	p<0.001
Complete response	7/107 (7%)	1/112 (1%)	p<0.001
Disease progression occurrence	72/113 (64%)	84/116 (72%)	
Comments: Hazard ratio for median progression-free survival in favour of MP+T = 0.62.			
Adverse Events & Safety	**MP+T**	**MP + placebo**	**p-value**
Peripheral neuropathy grade 1	20/113 (18%)	19/116 (16%)	p=0.003 reported. Although aligned in table with grade 1, appears more likely that this relates to all peripheral neuropathy.
Peripheral neuropathy grade 2	21/113 (19%)	4/116 (3%)	
Peripheral neuropathy grade 3	2/113 (2%)	2/116 (2%)	
Neutropenia grade 3 or 4	26/113 (23%)	10/116 (9%)	p=0.003
Thrombosis or embolism grade 3 or 4	7/113 (6%)	4/116 (3%)	p=0.33
Somnolence grade 2 to 4	7/113 (6%)	3/116 (3%)	p=0.19
Depression grade 2 to 4	8/113 (7%)	3/116 (3%)	p=0.11
Constipation grade 2 to 4	19/113 (17%)	12/116 (10%)	p=0.16
Nausea/vomiting grade 2 to 4	3/113 (3%)	5/116 (4%)	p=0.5
Oedema grade 2 to 4	15/113 (13%)	8/116 (7%)	0.11
Comments: There is contradictory information in text and table 3 of this paper. For peripheral neuropathy grades 1 and 2 text states 21 (19%) grade 1 and 20 (18%) grade 2 in MP+T group but table has these the other way around (as shown here). For the MP+placebo group table states 17% with peripheral neuropathy whereas text states 16%. Text appears correct as 19/116 is 16.4%. For neutropenia (grade 3 or 4) text states 25 (22%) for MP+T group but table has 26 (23%). There were no peripheral neuropathy events reported at grade 4.			
Withdrawals	**MP+T (n=113)**	**MP + placebo (n=116)**	**p-value**
Withdrawals due to adverse events/toxicity	n=48 (42.5%) [a]	n=15 (12.9%) [a]	
- peripheral neuropathy	n=12	n=3	
- neurological events (nonperipheral)	n=10	n=1	
- thrombosis/embolism	n=7	n=1	
- haematological events	n=7	n=6	
- digestive events	n=4	n=2	
- cardiac events	n=3	n=1	
- rash	n=2	n=0	
- other	n=3	n=1	

Dose reduction required because of adverse events	n=20 (17.7%) [a]	n=3 (2.6%) [a]	
Median duration of treatment	13.5 months	18 months	
Comments: There is contradictory information in text and Fig1. Text states 9 MP+T group participants withdrew due to neurological events (nonperipheral) whereas Fig1 shows 10 participants. Data provided on timing of withdrawal due to toxicity but appears to be for study overall, not by group: within 3 months 9 patients; within 6 months 23 patients; within 12 months 38 patients. Also unclear which patients are included as patient numbers given alongside timing of withdrawals sum to 70, but only 63 patients (48 MP+T and 15 MP + placebo) withdrew due to toxicity. [a] Percentages calculated by reviewer			
Withdrawals overall	n = 100 (88.5%) [a]	n = 108 (93.1%) [a]	
due to disease progression	n=37	n=69	
due to death	n=6	n=16	
due to consent withdrawal	n=9	n=8	
due to toxicity (details above)	n=48	n=15	
Comments: [a] Percentages calculated by reviewer			

Methodological comments

Allocation to treatment groups: Described as random in a 1:1 ratio with assignments provided centrally. No further details.

Blinding: Not explicitly described but assume this is a blinded study due to use of a placebo and statement that if when experimental treatment stopped due to grade 3-4 adverse events or disease progression, unblinding occurred. Issue of patients taking thalidomide needing to comply with a risk-management programme (which would mean patients not blind to study drug) is not discussed. All patients may have been subject to the same protocol.

Comparability of treatment groups: Groups described as well balanced except for sex as there were more female participants in the MP+T group (p=0.03).

Method of data analysis: Parameters described by number and percentage of patients. Distributions of parameters assessed at inclusion compared between treatment groups using χ^2 tests for categoric variables and Kruskal-Wallis rank test for continuous variables. Best response rates at 12 months compared using the χ^2 test. Overall survival calculated from random assignment to death from any cause. Data on patients alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. Progression-free survival calculated from random assignment to progression or death. Patients who had not experienced progression were censored on the last date they were known to be alive and progression-free. Survival estimated with Kaplan-Meier product limit method and curves were compared with the stratified log-rank test on an ITT basis. Hazard ratios estimated by stratified Cox proportional hazards model for the ITT population. Adverse events compared between groups using the χ^2 test. ITT not defined.

Sample size/power calculation: Sample size was estimated to be 280 patients to guarantee, in a two-sided test, a power of 80% to detect an increase in the median survival time of 6 months. Power calculation assumed a median survival time of 22 months in the control group and a global type I error rate of 5%. Fewer than 280 patients were recruited, presumably because recruitment was stopped earlier than planned (although this is not explicitly stated) in December 2006 when a clear survival advantage for MPT was found in the IFM 99-06 trial and because the French Autorisation Temporaire d'Utilisation had made MPT available for newly diagnosed myeloma patients ineligible for high-dose therapy. The authors do not comment on any possible implications of the recruitment shortfall.

Attrition/drop-out: Reasons for withdrawals reported (see outcomes above). After loss from

the trial of those with disease progression, due to deaths, and withdrawals due to toxicity very few participants remained (MPT n=8; MP + placebo n=13).

General comments: substantial renal insufficiency with creatinine serum concentration of 50mg/L or more was an exclusion criterion. At baseline 13% of patient had severe renal failure (creatinine clearance < 30mL/min).
Generalisability: This trial focuses on patients 75 years and older, the results may therefore only be applicable to patients in this age range. Authors state doses of melphalan and thalidomide were lower than had been used in similar trials with patients 65-75 years of age.
Outcome measures: Methods for grading of adverse events not described.
Inter-centre variability: No comments made regarding possible inter-centre variability.
Conflict of interests: Two authors had consultant or advisory roles with Pharmion, Celgene and Janssen-Cilag for which they had been compensated. Three authors had received honoraria from Pharmion, Celgene and Janssen-Cilag.

Quality Criteria[40]

Criteria for assessment of risk of bias in RCTs	Answer*	Notes & Comments
Was the method used to generate random allocations adequate?	NR	
Was the allocation adequately concealed?	Yes	Participants assigned centrally
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Only difference was in proportion of women
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Unclear	Not explicitly stated but use of placebo suggests blinding in place. Plus text states that treatment was unblinded on participant withdrawal. However those on thalidomide may have had to comply with a risk management programme but this is not discussed. Most outcomes were objective therefore risk of bias low.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	Overall withdrawals similar – but greater withdrawals due to toxicity of thalidomide in MP+T group. Authors describe toxicity as acceptable.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear	Analysis described as ITT although ITT was not defined.

*** answer yes/no/not reported/unclear**

Additional Outcomes/Comments/Notes

Outcomes	**MPT**	**MP + placebo**	**p-value**
Rescue treatment administered	131 (84%) of 156 patients presenting with disease progression. Rate similar in the two groups (as in row below).		

Prescription of any type of novel agent as rescue treatment after progression	61/72 (85%)	70/84 (83%)	
Thalidomide	16/72 (22%)	53/84 (63%)	
Bortezomib	22/72 (31%)	28/84 (33%)	
Lenalidomide	11/72 (15%)	9/84 (11%)	
Thalidomide &/or lenalidomide	25/72 (35%)	59/70 (83%)	
Thalidomide &/or lenalidomide &/or Bortezomib	38/72 (53%)	68/81 (83%)	
Survival time after progression, Median (95% CI)	11.5 months	9.9 months	p=0.89
Comments: Inevitably most patients (84% as noted above) in the study who had disease progression went on to have further treatment. The possible effects of the different rescue treatment on the outcomes of overall survival and survival after progression are not commented on by the authors of this paper. Survival after progression was described as 'similar in the two groups' by the authors who state that this strongly suggests the first-line treatment is of major importance in this population of elderly patients. The impact of the initial treatment on treatment decisions at progression are not commented on.			

Data extracted by…JO P……Extraction checked by……JB……...

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author: Palumbo et al[24] Year: 2006 Linked to later publication: Palumbo et al[25] 2008 Country: Italy Study design: Multicentre RCT Setting: Not stated, appears to be secondary care. Number of centres: 54 Recruitment dates: January 2002 to May 2005	Intervention, MPT: thalidomide 100mg daily dose administered continually during the six MPT cycles. + MP six cycles, each cycle repeated every 4 weeks: oral melphalan 4mg/m^2 on days 1 to 7; oral prednisone 40 mg/m^2 on days 1 to 7. **NOTE**: After 6 x 4 week cycles of MPT, thalidomide was continued at 100mg per day as maintenance therapy. This does not meet the	Number of Participants: 331 overall (MPT: 167; MP: 164). However only 255 had been followed up for 6 months or more at time of the initial analysis included here (no thalidomide maintenance). MPT: 129 MP: 126 Sample attrition/dropout: Of the 331 overall, 76 follow up less than 6 months (MPT n=38; MP n=38). Of the 255 followed up for 6 months 63 had not completed six cycles (MPT n=32; MP n=31)	Primary outcomes: Response rates and progression-free survival Secondary outcomes: overall survival, time to first evidence of response, prognostic factors, frequency of any grade 3 or higher adverse events. Method of assessing outcomes: Visits every 4 weeks during chemotherapy regimens to monitor response to treatment by measurement of protein in serum and urine. Assessments every 2 months thereafter. Response rate assessed at 6 months and confirmed after a further 6 weeks. Bone-marrow

Funding: Supported by Associazione Italiana Ricerca Canro, Milan; Associazione Italiana Leucemie, Rome; Compagnia di S. Paolo, Turin; Fondazione Neoplasie sange Onlus, Turin; Ministero universita ricerca Scientifica e Tecnologica, Rome; Consiglio Nazionale delle Ricerche, Rome. Pharmion supplied free thalidomide for the study.	inclusion criteria of the review therefore only outcomes to 24 weeks are data extracted here. Control, MP: six cycles, each cycle repeated every 4 weeks: oral melphalan 4mg/m^2 on days 1 to 7; oral prednisone 40 mg/m^2 on days 1 to 7. **NOTE:** In the control group there was no planned maintenance therapy Dose reductions: Dose reduced by 50% on the occurrence of any non-haematological grade 2 toxic effect. Treatment stopped: Thalidomide stopped for any non-haematological grade 3 toxic effects. Other interventions used: No anticoagulation prophylaxis was given initially but the protocol was amended December 2003 and enoxaparin at 40mg per day was delivered subcutaneously during the first four cycles of therapy.	(details in results). Timing of withdrawals not reported. Sample crossovers: In the MP (control) group patients with progressive disease or relapse were permitted to crossover to receive thalidomide as salvage treatment. Inclusion criteria for study entry: Older than 65 years of age, or younger but unable to undergo transplantation, with previously untreated stage II or III (Durie-Salmon (DS) criteria) multiple myeloma and measurable disease (not defined). Exclusion criteria for study entry: Another cancer; psychiatric disease; any grade 2 peripheral neuropathy. Abnormal cardiac function, chronic respiratory disease, and abnormal liver or renal functions were not criteria for exclusion. Characteristics of participants (for those included in initial analysis): Median age, years: MPT 72; MP 72 Age < 65 years: 4/129 (3%); MP	plasmacytosis and skeletal disease were included in response evaluation. Response definitions used criteria of the European Group for Blood and Marrow Transplantation / International Bone Marrow Transplant Registry: Complete response – disappearance of myeloma protein in serum and urine and negative immunofixation. Partial response – at least 50% reduction of myeloma protein in serum and a 90% decrease in urine. Near complete response (subcategory of partial response) – disappearance of myeloma protein in serum and urine and positive immunofixation. Minimal response – serum myeloma protein reduction of 25-49% and in urine of 50-89%. No response: reduction in myeloma protein of 24% or less. Progressive disease definition: an increase of 25% or greater in myeloma protein Adverse events: Assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria (version 2). Causes of death were recorded as attributable to myeloma, study drugs, other causes or a combination of

		3/126 (2%) Age 65-70 years: 49/129 (38%); MP 51/126 (41%) Age 71-75 years: 44/129 (34%); MP 37/126 (29%) Age 76-80 years: 26/129 (20%); MP 28/126 (22%) Age > 80 years: MPT 6/129 (5%); MP 7/126 (6%) Gender (m:f): not reported Ethnicity: not reported M protein IgG class: MPT 83/129 (64%); MP 73/126 (58%) M protein IgA class: MPT 31/129 (24%); MP 37/126 (29%) Bence Jones Protein: MPT 15/129 (12%); MP 16/126 (13%) DS stage IIA: MPT 50/129 (39%); MP 49/126 (39%) DS stage IIB: MPT 4/129 (3%); MP 3/126 (2%) DS stage IIIA: MPT 64/129 (50%); MP 62/126 (49%) DS stage IIIB: MPT 11/129 (8%); MP 12/126 (10%) WHO performance index ≥3: MPT 9/129 (7%); MP 6/126 (4%) Bone marrow plasmacytosis %, median (range): MPT 45 (5-95); MP 46 (5-95) Serum β_2 microglobulin mg/L, median (range): MPT 116 patients, 3.7 (0.36-40); MP 110	these. Thromboembolism was assessed by clinically objective evidence of thrombosis and use of ultrasound echography. Length of follow-up: Data analyzed after median follow-up of 38.4 months (range, 0.23-69.45 months; SD, 16.5 months) in the MPT group and 37.7 months (range, 0-72.34 months; SD, 17.1 months) in the MP group. Due to use of thalidomide as maintenance therapy only 6 month data eligible for inclusion in review.

		patients 3.7 (0.2-37.5) β_2 microglobulin ≤ 3.5 mg/L: MPT 53/129 (41%); MP 53/126 (42%) β_2 microglobulin > 3.5 mg/L: MPT 63/129 (49%); MP 57/126 (45%) β_2 microglobulin data missing: MPT 13/129 (10%); MP 16/126 (13%) Plasma C-reactive protein mg/L median (range): MPT 105 patients, 2.53 (0.005-157); MP 100 patients 2.0 (0.001-128) Haemoglobin g/L median (range): MPT 125 patients, 106 (73-147); MP 122 patients 102 (67-155) Serum creatinine mg/L median (range): MPT 129 patients, 8 (5.6-102); MP 125 patients 8 (6-68) Calcium mmol/L median (range): MPT 115 patients, 2.25 (1.22-3.17); MP 118 patients 2.27 (1.09-2.72)	
Results			
Primary Outcomes	**MPT**	**MP**	**Absolute difference MPT-MP (95% CI)**
Complete or partial response at 6 months	98/129 (76.0%)	60/126 (47.6%)	28.3% (16.5 to 39.1)
- Complete response	20/129 (15.5%)	3/126 (2.4%)	13.1% (6.3 to 20.5)
- Partial response	78/129 (60.4%)	57/126 (45.2%)	15.2% (3.0 to 26.9)
- Near complete response	16/129 (12.4%)	6/126 (4.8%)	
- 90% to 99% myeloma protein reduction	11/129 (8.5%)	6/126 (4.8%)	
- 50% - 89% myeloma protein reduction	51/129 (39.5%)	45/126 (35.7%)	

Minimal response	7/129 (5.4%)	21/126 (16.7%)	-11.2% (-19.2 to -3.6)
No response	7/129 (5.4%)	19/126 (15.1%)	-9.7% (-17.4 to -2.2)
Progressive disease	10/129 (7.8%)	21/126 (16.7%)	-8.9% (-17.2 to -0.8)
Not available	7/129 (5.4%)	5/126 (4.0%)	
Comments:			
Secondary outcomes	**MPT**	**MP**	**p-value**
Time to partial response, median (range)	1.4 months (22-200 days)	3.1 months (25-210 days)	
Comments:			
Adverse Events & Safety	**MPT**	**MP**	**p-value**
Grade 3-4 Infections - pneumonia - upper respiratory tract - herpes zoster - fever of unknown origin	12/129 (10%) within the first 4 months of treatment: 6 (5%) patients 2 (2%) patients 1 (1%) patient 3 (2%) patients	2/126 (2%) Timing of occurrence unknown: 2 (2%) patients 0 patients 0 patients 0 patients	p = 0.01
Comments: Full adverse event reporting not data extracted because period that this covered and timing of the occurrence of the events was not reported (therefore unable to distinguish between events occurring during the first 6 months of treatment and those occurring later during thalidomide maintenance).			
Withdrawals	**MPT**	**MP**	**p-value**
Unable to complete six cycles. Due to: - adverse events - progressive diseases - withdrew consent - lost to follow-up - protocol violations	32/129 (25%) 17/32 (13.2%) [a] 9/32 3/32 3/32 0/32	31/126 (25%) 4/31 (3.2%) [a] 16/31 2/31 7/31 2/31	
Thalidomide discontinuation required	43 (33.3%)[a] patients after a median of 2.1 months		
Thalidomide dose reduction to 50mg required	37 (28.7%)[a] patients after a median of 4 months		
Comments: [a] Percentages calculated by reviewer.			

Methodological comments

Allocation to treatment groups: A simple randomisation sequence was generated by a centralised computer. Registration to the trial was via the internet to centralised database. An automated assignment procedure concealed from the investigators randomly allocated patients to treatments.

Blinding: Study described as unblinded

Comparability of treatment groups: For patients included in the six month follow-up states baseline demographics and other characteristic of the two groups were balanced but results of any statistical tests to confirm this not presented. Comparability of patient groups in final analysis not reported.

Method of data analysis: For the analysis of the six month follow-up data times of observation were censored on June 15 2005. Analysis was done on an intention to treat basis (this is not defined). The absolute difference (with 95% CI) of the proportion of patients in each response category between the two groups was calculated with CI Analysis, version 2.1.1. Methods for analysis of data not reported here also described. The incidence of any adverse event was compared by the χ^2 test or Fisher's exact test when cell counts were lower than five. The analyses were performed with SAS (version 8.2).

Sample size/power calculation: Sample size was estimated to be 380 patients (190 per arm) to detect a 10% increase in complete response in the MPT arm (from 5% to 15%), with an α error of 0.05 and a β error of 0.10. Fewer than 380 patients were recruited because at the second interim analysis (timing of this not stated) there were statistically significant improvements for the MPT group in response rate and prolongation of event-free survival compared with the MP group. In addition enrolment was falling. The steering committee therefore decided to stop the trial in May 2005 when 331 patients had been randomised (87% of planned sample size). The authors do not comment on any possible implications of the recruitment shortfall.

Attrition/drop-out: Reasons for withdrawals, but not timing of withdrawal, reported (see outcomes above).

General comments:

Generalisability: This trial focuses on patients 65 years and older, the results may therefore only be applicable to patients in this age range.

Outcome measures: Due to the use of thalidomide as a maintenance therapy only the first 6 months of data are eligible for inclusion. It is not clear whether the observed results would have been maintained longer term. Only some of the adverse events were reported with an indication of when they occurred. It was not possible to extract all adverse event data and thus adverse events are likely to be underrepresented in the data extraction.

Inter-centre variability: No comments made regarding possible inter-centre variability.

Conflict of interests: Two authors had received scientific adviser board and lecture fees from Pharmion and Celgene. However their association with Celgene involved lenalidomide only, and not thalidomide. The other authors declared they had no conflict of interest.

Quality Criteria[40]

Criteria for assessment of risk of bias in RCTs	Answer*	Notes & Comments
Was the method used to generate random allocations adequate?	Yes	Generated by computer
Was the allocation adequately concealed?	Yes	Participants assigned centrally
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Although no statistical evidence of similarity presented authors state groups were comparable and this appears to be the case.
Were the care providers, participants and outcome assessors blind to treatment	No	States study is unblinded

allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	Overall withdrawals similar – but greater withdrawals due to toxicity of thalidomide in MPT group and greater withdrawal due to progression in MP group.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear	Analysis described as ITT although ITT was not defined.

*** answer yes/no/not reported/unclear**

Additional Outcomes/Comments/Notes
Nothing to add.

Data extracted by…JO P……Extraction checked by……JB……...

Reference and Design	Intervention	Participants	Outcome measures
Author: MMIX Trial (from investigators)[48,49,51-53], Davies[42], MRC myeloma Info guide[27], Owen 2009[47]) Year: 2009 Country: UK Study design: Multicentre RCT Setting: Hospitals [redacted] Recruitment dates: June 2003 to November 2007 Funding: Core grant from the Medical Research Council. Unrestricted	Intervention, CTDa (cyclophosphamide, thalidomide, attenuated dexamethasone): Cyclophosphamide: Once a week, 500 mg orally (on days 1,8, 15 and 22) Dexamethasone: days 1-4 and 15-18 of each cycle, 20 mg daily (orally) Thalidomide: daily, 50mg daily for 4 weeks, increasing every 4 weeks by 50mg increments to 200mg daily. Cycle length 4 weeks, to maximal response, but with a min-max number of cycles of 6-9. Control, MP: daily once a day by mouth for days 1-4 of a 4-week cycle. Number of cycles 6-9. Melphalan 7mg/m^2 Prednisolone dose 40mg **NOTE**: After completion of induction chemotherapy, eligible	[redacted] Timing of withdrawals not reported. Sample crossovers: None Inclusion criteria for study entry: At least 18 years of age with newly diagnosed symptomatic multiple myeloma or non-secretory MM (criteria provided). Provided written informed consent. Prepared to use contraception. Negative	Primary outcomes: Overall survival Progression-free survival Response Secondary outcomes: Quality of life Skeletal-related events Height loss Toxicity (thromboembolic events; renal toxicity; haematologic toxicity; graft versus host disease) Proportion receiving bortezomib-dexamethasone as 'early rescue' on induction chemotherapy, or at relapse. Method of assessing outcomes: Response was

Comment [j1]: Ok if in protocol

educational grants provided by Pharmion, Novartis, Bayer-Schering, Chugai and Ortho Biotech. Leukaemia Research Fund supported some of the biological studies.	patients entered a second randomisation to thalidomide maintenance or no maintenance. The initial randomisation to chemotherapy was not maintained, although initial chemotherapy was a stratification factor. As maintenance therapy does not meet the inclusion criteria of the review only outcomes from the induction chemotherapy are data extracted here. Dose modification: MP: treatment delay indicated by neutrophil and platelet counts. Melphalan reduced to 5mg/m^2 if serum creatinine >200µmol/l. CTDa: treatment related cytopenias led to omission of cyclophosphamide for one course, then dose reduction e.g. to 400mg or 300mg. Cyclophosphamide omitted if serum creatinine is >300µmol/l despite vigorous hydration. Thalidomide stopped if a thromoboembolic event occurred. Under good anticoagulant control thalidomide could be started again at 50mg, with escalation to 100mg. Thalidomide stopped for a cycle then reintroduced at 50mg if grade 3-4 toxicity occurred. In rare instance of intolerance to low dose dexamethasone dose reduction or omission of one of the 4 day pulses per cycle was permitted. Treatment stopped: CTDa: Pregnancy or	pregnancy test. Exclusion criteria for study entry: Asymptomatic MM. Solitary plasmacytoma of bone. Extramedullary plasmacytoma (without evidence of myeloma). Previous or concurrent active malignancies, except surgically-removed basal cell carcinoma of the skin or other in situ carcinomas. Previous treatment for myeloma except: local radiotherapy to relieve bone pain or spinal cord compression; prior bisphosphonate treatment; low-dose corticosteroids, up to 4 single doses of corticosteroids (total dose 1g methylprednisolone, 200mg dexamethasone, or 1.25g prednisolone). Past history of ischaemic heart disease or psychiatric disorders – exclusion at discretion of clinician. Acute renal failure (unresponsive to 72 hours rehydration, creatine >500µmol/l or urine output <400ml/day or requirement for dialysis). [redacted]	assessed at the end of randomised induction chemotherapy. Patients were followed up locally 4-weekly during chemotherapy, then 3-monthly thereafter. Central follow-up was 3 monthly until disease progression, then annually thereafter. Quality of life was assessed with the EORTC QLQ-C30/.QLQ-MY24 and the EQ-5D at: Pre-initial randomisation (when patient unaware of treatment allocation); at 3-, 6-, and 12-months post initial randomisation and annually thereafter until maintenance randomisation or 5 years post initial randomisation A diary card was also used daily from initial randomisation for 3 months. Indicators of skeletal related events (SREs) collected at 3-montly intervals. Response definitions: Response assessments were according to the modified EBMT/IBMTR

	suspected pregnancy (including in male patient's partner) also led to stopping of thalidomide. Other interventions used: In addition to the randomisation to CTDa or MP, participants were also randomised to either sodium clodronate 1600mg daily or Zoledronic acid 4mg by infusion every 3-4 weeks. Treatment continued indefinitely, or at least until disease progression. Thromobprophylaxis: Physicians were advised to consider full anticoagulation with warfarin or low mol wt heparin for all patients at high risk of VTE[42] Provision of thalidomide had to meet the approved process for thalidomide risk management and pregnancy prevention.	[redacted]	definitions (i.e. EMBT criteria plus the categories of very good partial response, and early death). Reference provided. Survival time calculated from randomisation to date of death from any cause. If patient still alive or lost to follow up they will be censored at date last known to be alive. PFS – from randomisation to date of disease progression or death. Disease progression defined as relapse from complete response (if patient had achieved this) or progressive disease (EBMT criteria) if not in CR. Adverse events: SAEs, Hickman line infection, renal toxicity, sensory neuropathy, motor neuropathy, constipation, somnolence, infection, rash, elevated alkaline phosphatase, hypothyroidism, postural hypotension, thromboembolic events, osteonecrosis of the jaw, haematological toxicity, and pregnancy/suspected pregnancy summarised by trial

		[redacted]	arm/treatment group. Length of follow-up [redacted] The cut off date for final analysis was 5th October 2009.
Results			
[redacted]			
Comments: Outcomes of OS, PFS, and survival after progression, time to progression not data extracted because after first-line chemotherapy participants meeting eligibility criteria were entered into a second randomisation to thalidomide maintenance therapy which does not meet the inclusion criteria for this review.			
[redacted]			
Secondary outcomes	**CTDa**	**MP**	**p-value**

Quality of Life			
Comments: [redacted]			

[redacted]

Comments: Data supplied by MMIX trialists states that AEs relate to induction chemotherapy. Denominator for AEs calculated by reviewer.

Comment [j2]: ?

[redacted]

Comments:

[redacted] No other withdrawals appear to be reported.

Methodological comments

Allocation to treatment groups: Conducted by a central trials office using an automated 24hr telephone system. Random assignment in a 1:1 ratio to CTDa or MP and bisphosphonate (sodium clodronate or zoledronic acid). Allocations concealed until interventions assigned. Randomisation used a minimisation algorithm and was stratified by: centre; haemoglobin; corrected serum calcium; serum creatinine; platelets.

Blinding: Not blinded.

Comparability of treatment groups:

[redacted]

Method of data analysis: All summaries and analyses by ITT unless otherwise stated. The per-protocol population may also be used if deemed appropriate. ITT defined as all patients randomised, with the exception of those misdiagnosed. Only patients who withdraw consent for the study, or for whom no written informed consent was received are not included in the ITT population. The QoL population includes all randomised patients agreeing to take part in the QoL study. All hypothesis tests are 2-sided and at the 5% significance level; p=values less than 0.05 considered statistically significant. Primary endpoints will be ranked according to clinical relevance i.e. survival and progression-free survival have equal ranking and response a lower ranking. OS calculated from initial randomisation to death. Patients with missing follow-up data, or not known to have died at time of analysis will be censored on the last date they were known to be alive. PFS calculated from random assignment to progression or death. Patients with missing follow-up data or who had not experienced progression were censored on the last date they were known to be alive and progression free. There was no other censoring of data. Cox's proportional hazards models used to compare chemotherapy groups while adjusting for bisphosphonate treatment group and the minimisation factors. Models will be constructed for OS and PFS. The proportional hazards assumptions will be assessed by plotting hazards over time for each treatment arm. Kaplan-Meier and adjusted curves will be constructed for each chemotherapy group. Response outcomes centrally reviewed and only responses from the central review will be reported. Subgroup analyses will be conducted (6 subgroups defined).

Sample size/power calculation: Sample size was based on testing the hypothesis that CTDa is superior to MP in terms of OS and PFS. It was anticipated that 850 patients (425 per group) would be randomised to induction chemotherapy in the non-intensive pathway. 204 patients (102 per group) would provide 80% power at a 5% significance level to detect a 15% absolute difference in 5-year survival (2-tailed test). This was based on the assumption of 15% 5-year survival in the MP group. 152 events would be required for these analyses. Sample size reached. For response, if 182 patients (91 per group) were entered the trial would be powered to detect an increase in the number of patients achieving a complete response from 20% with MP as induction chemotherapy to 40% with CTDa (with 80% power at a 5% level of significance). The anticipated number per group (425) would provide more than 80% power to detect this difference. No power calculation was made for subgroups.

Attrition/drop-out: Not reported on (apart from some data on participants withdrawing consent during induction chemotherapy).

General comments: The results of this study have not yet been fully published. The assessment team has had early access to data but this has not been peer-reviewed. It is possible that some data, particularly those on QoL may alter as analyses are finalised.

Generalisability: Likely to be generalisable as the study took place in the UK.

Outcome measures: Methods for grading of adverse events not described.

Inter-centre variability: Not discussed

Conflict of interests: States None

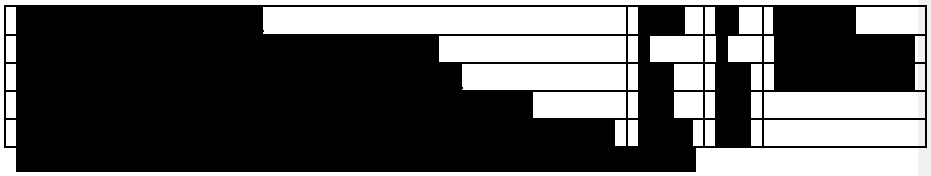
Quality Criteria[40]

Criteria for assessment of risk of bias in RCTs	Answer*	Notes & Comments
Was the method used to generate random	Yes	An automated 24hr telephone

allocations adequate?		system was used but no further information.
Was the allocation adequately concealed?	Yes	Participants assigned centrally
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Not specifically stated but appear to be from baseline characteristics provided.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not reported	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	?	Analysis was ITT, with ITT defined. Unclear how missing data was accounted for.

*** answer yes/no/not reported/unclear**

Additional Outcomes/Comments/Notes



Appendix 6: Karnofsky performance status and WHO performance status scores

Karnofsky perfomance status

100% - normal, no complaints, no signs of disease

90% - capable of normal activity, few symptoms or signs of disease

80% - normal activity with some difficulty, some symptoms or signs

70% - caring for self, not capable of normal activity or work

60% - requiring some help, can take care of most personal requirements

50% - requires help often, requires frequent medical care

40% - disabled, requires special care and help

30% - severely disabled, hospital admission indicated but no risk of death

20% - very ill, urgently requiring admission, requires supportive measures or treatment

10% - moribund, rapidly progressive fatal disease processes

0% - death

WHO performance status scores

0 - Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)

1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)

2 - Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)

3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)

4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

5 - Death

Appendix 7: SHTAC data summary of MS clinical effectiveness

SHTAC peer review of clinical effectiveness in Celgene's submission for B&T for MM

Comprehensiveness of ascertainment of published studies

Clinical effectiveness:

- The MS contains a narrative summary of trials, with the methods and results of each trial presented separately. Tabulation of details on study design and methodology, baseline characteristic of participants, efficacy outcomes, subgroups, second-line therapy, and adverse events is presented in Appendix 2 of the MS (MS page134-139).
- There is no formal systematic review of clinical effectiveness evidence in the main body of the MS. However, a systematic review was conducted to identify clinical-effectiveness evidence for the Bayesian meta-analysis that is reported in Appendix 4 of the MS which was presented as a separate document.

  - *Were databases and dates of searches specified?*
  - Appendix 4 of the MS clearly reports search dates, search strategies and databases searched.
  - *Were search strategies supplied?*
  - Yes
  - *Was enough detail provided to be reproducible?*
  - Sufficient detail was provided in Appendix 4 of the MS for the searches to be reproducible.
  - *Did they search/report on ongoing studies?*
  - No searches for ongoing studies are reported
  - *Did they search for conference proceedings?*
  - Conference proceedings were included in the searching
  - *How much of the data is CIC/AIC?*
  - The submission contains little CIC information and no AIC information. CIC information is located only on page 54 and pages 84-86 of the submission and all relates to the same clinical study report (CSR).

Cost effectiveness: The MS economic evaluation section states that a literature search was conducted to identify cost-effectiveness models, but no search strategy is presented. There does not appear to have been a search for QoL data.

Searches identified:

- *xxx clinical trials (details)*

The systematic review conducted as part of the MTC and reported in Appendix 4 included the following RCTs:

- IFM 99-06 (Facon 2007 and Facon 2004 abstract); IFM 01-01 (Hulin 2009, 3 Hulin 2007 abstracts); GIMEMA (Palumbo 2008, Palumbo 2006, and Palumbo abstracts of 2004,2005,2006, 2007, and 2008); Nordic study (Gulbransen 2008 abstract, Waage 2007 abstract, and Nordic Myeloma Study Group PowerPoint slide presentation 2009; HOVON 49 (Two Wijermans 2008 abstracts, Wijermans 2008 ASH PowerPoint presentation "Final analysis. The HOVON 49 study"); VISTA (San Miguel 2008, San Miguel 2008 abstracts, San Miguel 2007 abstract; Palumbo 2008 abstract; Harousseau 2008 abstract). The studies identified in the systematic review are the same as those reported on in the main submission document. The submission document also recognises the Myeloma IX study is ongoing but the study was not included as complete data were not available.
- *what study types (x RCTs, x cohort studies etc)*
- The included studies were RCTs
- *did any meet our inclusion criteria which we have not already included?*
- The identified studies published as full papers (IFM 99-06, IFM 01-01, GIMEMA, and VISTA) are included in the SHTAC systematic review. As the GIMEMA study included maintenance therapy with thalidomide the SHTAC review only includes outcomes reported for the period prior to the start of maintenance therapy. SHTAC also identified abstracts reporting on the Nordic myeloma group study, and the Hovon 49 study but the powerpoint presentations had not been identified. Due to the limited reporting of

methodological details and outcome data these studies were not included in the SHTAC systematic review but have been briefly mentioned as ongoing studies.

Clinical Analysis:

- *Any major differences in evidence reported?*
- The MS includes a narrative summary for individual trials, with tabulation of the studies' characteristics and results located in MS appendix 2. There was no quality assessment of the trials. Adverse events are also presented separately for each trial.
- *Are their conclusions are similar to ours?*
- Although the Celgene MSs (but not the MTC) included the OS outcome from Palumbo and colleagues[24] which SHTAC excluded due to the use of thalidomide maintenance treatment in the MPT arm, the conclusions (based on narrative summary) on the clinical effectiveness of MPT and VMP are broadly similar. MPT and MPV treatments both show better OS and PFS than MP. The conclusions from the MS MTC were the same. A summary statement on response outcomes from the included trials is not provided. The MS presents an indirect comparison (as noted below) which suggests that MPT provides better PFS outcomes than VMP at 6,12, and 18 months but the credibility intervals cross 1. The MS finds subgroup data variable and insufficient so no conclusions have been drawn.
- *Any indirect comparisons?*
- The MS included an indirect comparison to enable comparison of MPT and VMP as there are no head to head trials for this comparison. Not all the studies identified by the systematic review were included in the meta-analysis and indirect comparison. The base case excluded the GIMEMA trial (on the basis of a different regimen of thalidomide not consistent with the label, and due to cross over to thalidomide in the MP arm after disease progression), and the Nordic and Hovon 49 trials (insufficient information in abstracts for meta-analysis). These three studies were included in a sensitivity analysis (using information from slide presentations for Nordic and Hovon 49 trials).
- *Any differences in outcome measures?*
- The MS reports on the same outcome measures as the SHTAC review. Outcome data were not reported from the studies included in the systematic review presented in MS appendix 4.
- *Any extra adverse event info?*
- Adverse event information was restricted to that reported in trial publications.

Interpretation:

- *Does their interpretation of the clinical data match their analyses?*
- Limited analyses in main MS document (mainly just narrative summary) but where analyses are presented, e.g. MTC the interpretation of the clinical data broadly matches these.

Questions:

Any areas of uncertainty/discrepancy compared with the SHTAC review?

- The MS presents a narrative summary of the Palumbo and colleagues[24] study as well as the Nordic and Hovon-49 trials which have only been reported in abstract form. However, these three studies were not included in the base case MTC, and therefore the data in the base case MTC more closely matches the data included in the SHTAC review.
- SHTAC excluded most of the data from Palumbo and colleagues[24] because participants in the MPT group received thalidomide maintenance therapy. In contrast, this study was excluded from the MS MTC because the thalidomide regimen was inconsistent with the label and because participants could cross over to thalidomide at disease progression. SHTAC do not believe that on this latter point the study differs substantially from the IFM trials[23,58] where participants received treatment after disease progression that could include thalidomide, and where a greater proportion of participants in the MP groups received thalidomide at this point than in the MPT group.

SHTAC peer review of clinical effectiveness in Janssen-Cilag's submission for B&T for MM

Comprehensiveness of ascertainment of published studies

Clinical effectiveness:

- The MS contains a systematic review of clinical effectiveness evidence in the main body of the MS. Summary details on trial size, interventions, inclusion criteria, efficacy endpoints, and duration of treatment are tabulated. Trials were critically appraised. Results from the included studies were tabulated.

  - *Were databases and dates of searches specified?*
  - The MS briefly summarises the searches and clearly reports search dates, search strategies and databases searched in Appendix 1. Searches were conducted in two phases, before and after the finalisation of the scope of the appraisal.
  - *Were search strategies supplied?*
  - Yes
  - *Was enough detail provided to be reproducible?*
  - Sufficient detail was provided for the searches to be reproduced.
  - *Did they search/report on ongoing studies?*
  - No searches for ongoing studies are reported
  - *Did they search for conference proceedings?*
  - Conference proceedings were included in the searching
  - *How much of the data is CIC/AIC?*
  - The submission contains both CIC and AIC information CIC data appears on the following pages: 32-33; 33-34; 60; 61; 67; 70; Appendix 4 (from VISTA); References: All 3 clinical study reports (J&J, Velcade CSR 1, CSR 2, CSR 3). AIC data appears on pages 2; 3; 33-34; 35-36; 40-41; 43-47; 59-60; 66; Appendix 7 & 8; Appendix 11.

Cost effectiveness: A review of economic evaluations was conducted, reported in detail in appendix 9. The review sought to identify any economic evaluations and resource use studies assessing the first-line therapy of patients with multiple myeloma with regimens included in the NICE scope, as well as others e.g. VAD that did not form part of the final scope. The review included studies assessing first-line chemotherapy regimens but also included induction/mobilization regimens prior to transplantation. Appendix 9 reports on 30 studies, but the MS states that none of these cost-effectiveness studies included bortezomib-based regimens in the patient group of interest. There does not appear to have been a search for QoL data.

Searches identified:

- *xxx clinical trials (details)*

The systematic review included the following RCTs:

VMP vs MP
VISTA (Dimopoulos et al, 2008a[108];Harousseau et al, 2008[109];San Miguel et al, 2008a[59];San Miguel, 2008[110];San Miguel et al, 2008c[26];San Miguel et al, 2008b)

MPT vs MP
IFM 99-06 (Facon, 2007[23])
GIMEMA (Palumbo, 2006(not in MS ref list, presume[24] and 2008[25])
IFM 01/01 (Hulin et al, 2009[58])
HOVON-49 (Wijermans et al, 2008[65])
Gulbrandsen et al. 2008 (Gulbrandsen, 2008[62])

MP vs CTDa (Maintenance treatment:thalidomide only)
MRC myeloma IX study (Non-intensive arm) (Owen, 2009; Morgan, 2009 not in MS ref list)

- *what study types (x RCTs, x cohort studies etc)*
- The included studies were RCTs
- *did any meet our inclusion criteria which we have not already included?*
- The identified studies published as full papers (IFM 99-06, IFM 01-01, GIMEMA, and VISTA) are included in the SHTAC systematic review. As the GIMEMA study included

maintenance therapy with thalidomide the SHTAC review only includes outcomes reported for the period prior to the start of maintenance therapy. SHTAC also identified abstracts reporting on the Nordic myeloma group study (Gulbrandsen), and the Hovon 49 study. Due to the limited reporting of methodological details and outcome data these studies were not included in the SHTAC systematic review but have been briefly mentioned as ongoing studies.. Abstracts for the MRC myeloma IX study were identified, but not the two cited by the MS, the second of which is not referenced in the MS.

Clinical Analysis:

- *Any major differences in evidence reported?*
- The MS includes a narrative summary and tabulation of the studies' characteristics. The main efficacy results are very briefly summarised and tabulated. Trials were subject to critical appraisal using a modification of the CONSORT Assessment Framework. The VISTA study is additionally presented in more detail including some data that is not in the public domain. A small amount of non-RCT evidence from phase I/II trials of bortezomib is presented.
- *Are their conclusions are similar to ours?*
- Although the Janssen-Cilag MS systematic review included more studies than SHTAC, the conclusions (based on narrative summary) on the clinical effectiveness of MPT and VMP are broadly similar. The results from meta-analysis and indirect comparison are more difficult to compare with the SHTAC results because of additional data used in the MS, the different methodology (MS Winbugs MTC, SHTAC pair-wise meta-analysis). For the comparisons of MPT vs MP and MPV vs MP the direction of the overall effect is the same, although the magnitude differs. It appears that the MS MTC indicates a greater difference in effect in favour of MPV over MPT than the SHTAC pair-wise estimates suggest.
- Any indirect comparisons?
- The MS included an indirect comparison to enable comparison of MPT and VMP as there are no head to head trials for this comparison. The studies identified by the systematic review were included and in addition, unpublished updated survival data from the VISTA trial was also included in the meta-analysis and indirect comparison.
- *Any differences in outcome measures?*
- The MS reports on the same outcome measures as the SHTAC review.
- *Any extra adverse event info?*
- Adverse event information was restricted to that reported in trial publications.

Interpretation:

- *Does their interpretation of the clinical data match their analyses?*
- The interpretation of clinical data appears to match the analyses which have been undertaken.

Questions:

Any areas of uncertainty/discrepancy compared with the SHTAC review?

- The MS has included final data from the Palumbo and colleagues[24] study which SHTAC did not include, as well as the Nordic and Hovon-49 trials which have only been reported in abstract form and were therefore not included by SHTAC (with the Hovon-49 trial designated 'Unclear' because of the use of thalidomide maintenance therapy). The impact of including these studies within the MTC presented by the MS is uncertain and SHTAC cannot determine what the outcomes would have been had these data been excluded from the MTC.

Appendix 8: Table of excluded studies for systematic review of cost effectiveness

Excluded Reference	Reason for exclusion
Sampson FC, Beard SM, Scott F, Vandenberghe E. Cost-effectiveness of high-dose chemotherapy in first-line treatment of advanced multiple myeloma. *British Journal of Haematology* 2001;113:1015-9.	Participants and intervention
Deniz B, Facon T, Singer I, Micallef-Eynaud P, Joseph I, Shearer A *et al*. Economic Evaluation of Thalidomide Combined with Melphalan and Prednisone in Previously Untreated Multiple Myeloma in Scotland. *Blood* 2008;112:835.	Abstract
Cecchi M, Caccese E, Messori A, Orsi C, Tendi E. Cost-effectiveness of bortezomib in multiple myeloma. *Pharmacy World & Science* 2007;29:485-6.	Participants
Yoong K, Attard C, Jivraj F, Shustik C, Reece D. Cost effectiveness analysis of bortezomib in previously untreated multiple myeloma patients in canada. *Value in Health* 2009;12:A272.	Abstract
Joseph I, Facon T, Lewis P, Deniz HB, Caro JJ. Cost effectiveness of thalidomide combined with melphalan and prednisone in previously untreated myltiple myeloma in Wales. *Value in Health* 2009;12:A271.	Abstract
De Abreu Lourenco R, Colman S, Lee C. Thalidomide plus melphan and prednisone for australian patients newly diagnosed with multiple myeloma is cost effective when compared with melphalan and prednisone alone. *Value in Health* 2009;12:A381.	Abstract
Wang, S., Huang, H., Shi, H., Duh, M., and Chen, K. The cost effectiveness of bortezomib for the initial treatment of multiple myeloma in the United States. #1379. 51st ASH Annual Meeting and Exposition. New Orleans, LA December 5-8 2009. 2009.	Abstract

Appendix 9: Table of excluded studies for systematic review of health related quality of life

Excluded Reference	Reason for exclusion
Sherman AC, Simonton S, Latif U, Plante TG, Anaissie EJ. Changes in quality-of-life and psychosocial adjustment among multiple myeloma patients treated with high-dose melphalan and autologous stem cell transplantation. *Biology of Blood & Marrow Transplantation* 2009;15:12-20.	Outcome
Lee SJ, Richardson PG, Sonneveld P, Schuster MW, Irwin D, San Miguel JF *et al*. Bortezomib is associated with better health-related quality of life than high-dose dexamethasone in patients with relapsed multiple myeloma: results from the APEX study. *British Journal of Haematology* 2008;143:511-9.	Participants and Outcome
Sherman AC, Simonton S, Latif U, Spohn R, Tricot G. Psychosocial adjustment and quality of life among multiple myeloma patients undergoing evaluation for autologous stem cell transplantation. *Bone Marrow Transplantation* 2004;33:955-62.	Outcome
Gulbrandsen N, Wisloff F, Brinch L, Carlson K, Dahl IM, Gimsing P *et al*. Health-related quality of life in multiple myeloma patients receiving high-dose chemotherapy with autologous blood stem-cell support. *Medical Oncology* 2001;18:65-77.	Participants and Outcome
Multiple myeloma: QALY gains from optimal therapy. *Drugs and Therapy Perspectives* 2000;16:12-6.	Outcome
Ellis K, Smith AG. An evaluation of quality of life (QOL) in patients after treatment for multiple myeloma (MM). *British Journal of Haematology* 2005;129:192.	Outcome
Thomas ML. Quality of life in persons with multiple myeloma: A descriptive study. *Blood* 2001;98:4971.	Outcome
Deniz B, Morgan G, Schey S, Ishak J, Dale P, Shearer A *et al*. Economic Evaluation of Lenalidomide Combined with Dexamethasone for the Treatment of Multiple Myeloma in the UK. *Blood* 2008;112:836-7.	Outcome
Belch A, Reece DE, Bahlis NJ, White D, Teixeira B, Camacho F *et al*. Bortezomib [VELCADE (TM)], pegylated liposomal doxorubicin [DOXIL/CAELYX (R)] and dexamethasone in the treatment of previously untreated multiple myeloma patients: Impact on quality-of-life. *Blood* 2007;110:1058A-9A.	Outcome

Appendix 10: Health related quality of life studies – data extraction forms

Reference

Gulbrandsen and colleagues, 2004[87] Data extracted by: KC Extraction checked by: AC

Study Characteristics

Research question

What are the stated objectives of the study?

To compare QoL scores of multiple myeloma patients at diagnosis and over time with the scores of a reference population

Describe the type of study and study design.

Two prospective studies using a QoL questionnaire with comparison to a reference population through regression.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Patients from two prospective Nordic Myeloma Study Group trials: high dose melphalan (HDM) and melphalan and prednisone (MP)

What are the characteristics of the baseline cohort for the evaluation?

Age	< 60 yr old for HDM; > 60 yr old treated with MP
Sex	Not reported
Race (if appropriate)	Not reported
Indication / disease	Newly diagnosed multiple myeloma
Other characteristics (sample size)	221 patients for HDM and 203 patients for MP. QoL was also estimated for reference Norwegian population, consisting of 3000 randomly selected adult individuals (18-93 yr).
QoL instrument	EORTC QLQ-C30 at baseline and at 1, 6, 12, 24 and 36 months
Utility values, (Y/N)	N
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

Denmark, Sweden and Norway

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Two trials

Results

Results reported as mean difference between scores of all newly diagnosed multiple myeloma patients and age and gender adjusted reference population

	Mean score difference	95% CI for the difference	P
Functioning scales			
Global QoL	-24.3	-21.7; -26.9	<0.001
Physical functioning	-34.3	-31.8; -36.7	<0.001
Role functioning	-48.4	-45.4; -51.3	<0.001
Social functioning	-21.0	-18.1; -23.9	<0.001
Emotional functioning	-14.0	-11.7; -16.4	<0.001
Cognitive functioning	-5.8	-3.5; -8.1	<0.001
Symptom scales			
Nausea / vomiting	5.6	4.1; 7.1	<0.001
Pain	26.7	23.4; 29.9	<0.001
Fatigue	19.1	16.3; 21.9	<0.001
Single items			
Sleep disturbance	6.1	2.8; 9.3	<0.001
Appetite loss	15.4	13.1; 17.7	<0.001
Diarhoea	-1.1	-3.5; 1.2	0.349
Constipation	10.4	7.7; 13.1	<0.001
Dyspnoea	6.9	4.2; 9.6	<0.001
Financial impact	5.3	2.7; 8.0	<0.001

Change in most important functioning and symptom scales during the first 3 years for patients who received MP (values estimated from graphs)

	Reference group	0 m	1 m	6 m	12 m	24 m	36 m
Global QoL	70	46	52	60	60	60	60
Physical functioning	78	46	51	60	60	60	63
Role functioning	85	43	45	58	59	61	66
Social functioning	81	70	70	76	76	75	72
Fatigue	30	51	48	38	41	40	42
Pain	27	52	38	30	33	33	33

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes. The EORTC QoL questionnaire was used.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

At diagnosis, the most distressing problems were pain and fatigue, reduced physical functioning, limitations in role functioning and reduced overall QoL. These differences from the reference population were statistically significant, and large or moderate according to the rating systems. After the start of treatment, small to moderate improvement in mean QoL scores were observed for most domains.

What are the implications of the study for the model

This study indicates that QoL is worse initially at diagnosis but improves after end of treatment. Long term QoL appears stable but is lower than for the reference population.

Reference

Mujica-Mota and colleagues, 2004[90] Data extracted by: KC Extraction checked by: AC

Study Characteristics

Research question

What are the stated objectives of the study?

To map HRQoL measurements into generic utility measures (EQ-5D)

Describe the type of study and study design.

Utility mapping study, limited details of statistical mapping process provided..

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Patients with relapsed and refractory multiple myeloma

What are the characteristics of the baseline cohort for the evaluation?

Age	Not reported
Sex	Not reported
Race (if appropriate)	Not reported
Indication / disease	Patients with relapsed and refractory multiple myeloma
Other characteristics (sample size)	Sample size of SUMMIT1 Trial (n=202) identified but not of the sample used for mapping study.
QoL instrument	EORTC QLQ-C30 and MY24, FACT Fatigue and GOG-Ntx mapped to EQ-5D
Utility values, (Y/N)	Y
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

Although the setting is not stated, the Summit 1 trial was undertaken in the USA.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Phase 2 trial.

Results

Utility scores appear similar across patient groups as defined by serological response to VELCADE, with an overall utility score of 0.65.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Limited details of the methods or results are reported in the abstract. Questions relevant to the EQ-5D were identified from EORTC, FACT and five summary measures of severity, corresponding to the five EQ-5D dimensions were obtained. The summary measures were transformed into the corresponding EQ-5D scale for each dimension.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Method used to derive utility scores from reported HRQoL outcomes is a feasible and sensitive option for providing valid estimates of patient well being for terminal conditions.

What are the implications of the study for the model

Study provides a post treatment utility measure for relapsed or refractory multiple myeloma patients post treatment with Velcade. This is not the patient group or intervention for the evaluation.

Reference

Slovacek and colleagues, 2008[91] Data extracted by: KC Extraction checked by: AC

Study Characteristics

Research question

What are the stated objectives of the study?

To analyse an effect of selected demographics, psychosocial and health aspects on QoL in multiple myeloma survivors treated with HD chemotherapy followed by autologous peripheral blood preogenitor cell transplantation (PBPCT)

Describe the type of study and study design.

Observational study. Mailed QoL questionnaire.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Patients with multiple myeloma scheduled to be treated with HD chemotherapy (single dose of melfalan) followed by PBPCT.

What are the characteristics of the baseline cohort for the evaluation?

Age	Mean 60 yrs (53-67 yrs)
Sex	18 M, 14 F
Race (if appropriate)	Not reported
Indication / disease	Multiple myeloma treated with HD chemo followed by autologus PBPCT
Other characteristics (sample size)	Total n = 32
QoL instrument	EQ-5D and EQ-5D VAS
Utility values, (Y/N)	Y
Treatment effect, if reported	Not applicable

Country/ setting

What is the country and setting for the evaluation?

University Hospital, Hradec Kralove, Czech republic. All patients scheduled for intensive treatment of multiple myeloma.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single observational study

Results

Summarise the results

The global QoL in respondents with multiple myeloma treated with HD chemotherapy followed by autologous PBPCT was 0.689 for EQ-5D and 0.666 for EQ-5D VAS.

For individual dimensions, 59% had troubles with mobility, 19% had trouble with self care, 81% had difficulty with their normal activity, 69% had medium to serous pain, 59% had medium serious anxiety / depression.

The study also presented QoL results by age.

Age	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs
EQ-5D score	0.815	0.742	0.642	0.615
EQ-5D VAS	0.775	0.673	0.604	0.712

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes, the Czech version of the EuroQol EQ-5D questionnaire was used in the study (Slovacek, 2005 ref 2). The EQ-5D questionnaire was mailed to respondents with a covering letter. The QoL was analysed for the effect of age, sex, level of education, marital statu, number of associated disease, smoking, abuse, religion and time lapse from PBPCT.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Global QoL was at a low level for all studied patients and reduces with increasing age. Smokers and former smokers have lower QoL than non-smokers.

What are the implications of the study for the model

The study assesses a different population group and intervention than assessed in the NICE appraisal.

Reference

Strasser-Weippl and Ludwig, 2008[88]

Data extracted by: AC Extraction checked by: KC

Study Characteristics

Research question

What are the stated objectives of the study?

To evaluate the prognostic importance of baseline QOL and whether QOL at onset of therapy is a truly independent prognostic factor. To identify which dimensions of QOL are important predictors for outcome in patients with multiple myeloma.

Describe the type of study and study design.

Sub-study within a randomised controlled trial of continuous or intermittent prednisolone plus vincristine, melphalan, cyclophosphamide, prednisolone, interferon-∞2b (VMCP-IFN∞2b) for induction therapy. Maintenance therapy of IFN∞2b with or without prednisolone twice weekly.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Elderly patients recently diagnosed with multiple myeloma who were previously untreated (ECOG performance status of ≤3, adequate organ function) (n=92).

What are the characteristics of the baseline cohort for the evaluation?

Age	Median (range): 66 (43-84)
Sex	Male/Female: 51/41
Race (if appropriate)	Not reported.
Indication / disease	Multiple myeloma – Durie Salmon stage: I - 5 (5.4%); II - 26 (28.3%); III 61 (66.3%).
Other characteristics (sample size)	N=92
QoL instrument	EORTC QLQ-C30
Utility values, (Y/N)	No
Treatment effect, if reported	RCT showed similarity between 2 treatment arms with respect to response rate, progression free and overall survival. No data are presented.

Country/ setting

What is the country and setting for the evaluation?

Vienna, Austria.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

A sub-study within a randomised controlled trial.

Results

Observed, age/gender equivalent expected mean scores and deviations for myeloma patients at baseline				
	Observed	Expected	Observed - Expected	P-value
Global QoL[1]	47.28	70.63	-22.3	1.60×10^{15}
Physical[1]	58.74	80.75	-22.01	2.26×10^{10}
Role[1]	58.4	87.04	-28.64	3.82×10^{15}
Emotional[1]	66.67	83.61	-16.94	1.30×10^{7}
Cognitive[1]	78.44	82.89	-4.45	0.04
Social[1]	71.2	82.34	-11.14	0.001
Fatigue[2]	49.14	30.17	18.97	6.0×10^{9}
Pain[2]	47.64	25.92	21.72	8.5×10^{8}
Nausea/vomiting[2]	13.04	4.18	8.86	0.001
Dyspnea[2]	32.25	19.41	12.84	4.1×10^{5}
Insomnia[2]	32.61	25.79	6.82	0.035
Appetite loss[2]	28.99	7.30	21.69	1.9×10^{8}
Constipation[2]	22.71	15.30	7.41	0.024
Diarrhea[2]	8.79	9.62	-0.83	0.64
Financial difficulties[2]	12.59	10.66	1.93	0.22
Observed are means scores in myeloma patients; Expected are mean observed scores one would get in the general population if the age and gender distributions were the same as in the myeloma patients.				
[1] Higher score indicates better function. [2] higher score indicated more symptoms.				

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Regression techniques were used to evaluate QOL as a prognostic indicator in relation to outcomes such as survival.

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Study showed low levels of functional QOL scores and increased symptom scores in patients with active disease at start of first-line therapy, supporting previous reports of severe and significant impairment of QOL in multiple myeloma patients. Although independent of age and gender, they did reflect parameters of disease activity that were thought to be linked to individual psychological factors It was felt that physical measures of QOL, such as pain, fatigue, physical functioning and global quality of life were particularly important.

There is a significant impairment of physical and psychosocial dimensions of QOL in patients with multiple myeloma at baseline compared with a healthy reference population. Low psychosocial QOL at baseline is associated with poor prognosis.

What are the implications of the study for the model

The study provides baseline measure of QOL on the EORTC QLQ-C30 for patients recently diagnosed patients with multiple myeloma who have not undergone treatment. If these can be mapped to utility measures it may provide a source for the model.

Reference

Uyl-de Groot and colleagues, 2005[92]

Data extracted by: AC Extraction checked by: KC

Study Characteristics

Research question

What are the stated objectives of the study?

To investigate the subjective well-being of patients with newly diagnosed multiple myeloma who were treated in a tandem transplantation programme.

All patients were scheduled for the following treatment protocol: 2 courses of vinicristine, adriamycin and dexamethason (VAD) or vinicristine, adriamycin and methyl prednisone (VAMP) chemotherapy, high dose melphalan (HDM) and transplantation of whole blood stem cells, collection of r-met Hu G-CSF mobilised peripheral blood progenitor cells by leucapheresis and finally high-dose chemotherapy (busulfan/cyclophosphamide) followed by reinfusion of the previously collected peripheral stem cells (PSCT).

Describe the type of study and study design.

Prospective, longitudinal questionnaire study.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Patients with multiple myeloma irrespective of previous treatment regimes who were scheduled for intensive treatment between March 1997 and December 1998, whether at the start of the treatment protocol or who were undergoing treatment and had not passed the last 2 measurement points for quality of life (started between March 1995 and September 1996).

What are the characteristics of the baseline cohort for the evaluation?

Age (years)	All Patients (n=51): Mean (sd) 53(7.2); Median (min/max) 54 (31/65) Patients in analysis (n=25): Mean (sd) 53(8.2); Median (min/max) 55 (31/65)
Sex	All Patients (n=51): Male 31(61%); Female 20(39%) Patients in analysis (n=25): Male 16(64%); Female 9(36%)
Race (if appropriate)	Not reported.
Indication / disease	Multiple myeloma Stage Salmon and Durie [n(%)] All Patients (n=51): Ia 12 (24); IIa 4 (8); IIIa 32 (63); IIIb 3 (6) Patients in analysis (n=25): Ia 8 (32); IIa 1 (4); IIIa 15 (60); IIIb 1 (4)
Other characteristics (sample size)	N=51; 35 from the start of the treatment protocol and 16 partially completed treatment.
QoL instrument	EORTC QLQ-C30; EuroQol-5D. Data collected at baseline (2 weeks post induction therapy); day of hospital discharge after HDM (T2); 1 month after discharge after HDM (T3); day of hospital admission for PSCT (T4), day of discharge following PSCT (T5), 6 months post discharge for PSCT (T6), 12 months discharge post PSCT (T7).
Utility values, (Y/N)	Y
Treatment effect, if	Not reported.

reported	

Country/ setting

What is the country and setting for the evaluation?

Local referring hospitals and the academic hospital at the VU University Medical Centre, Amsterdam, Netherlands.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

A single observational study.

Results

Mean absolute scores (SD) at baseline after VAD/VAMP (baseline) and mean change scores from baseline.

	Baseline (n=25)	T2 (n=22)	T3 (n=24)	T4 (n=15)	T5 (n=14)	T6 (n=15)	T7 (n=12)
EORTC QLQ-C30 functioning scales							
Physical	50 (28)	-2	13**	13*	-19*	13*	20*
Role	41 (29)	2	18**	14	-26**	19*	20
Emotional	72 (22)	3	10*	6	0	0	1
Cognitive	76 (25)	-11	8	1	-6	3	3
Social	59 (30)	5	12	6	-23*	10	13*
Global QoL	58 (23)	-11*	3	10*	-17**	7	4
EORTC QLQ-C30 symptoms							
Fatigue	55 (29)	7	-15*	-13	10	-13	-6
Nausea/vomiting	11 (25)	26**	2	-1	27*	-1	4
Pain	37 (29)	-7	-8	-10	4	-9	-11
Appetite loss	22 (31)	40**	2	-4	43**	-4	-3
Diarrhoea	18 (31)	25**	-1	0	36**	-2	3
Disease/treatment related symptoms							
Pain in back	43 (37)	-6	-14*	-7	-21*	-7	-11
Soreness of mouth	9 (20)	26**	1	-11	36**	-2	-6
Change in taste	20 (32)	23*	6	-9	21	-4	-8
Diminished sexual interest	52 (40)	11	-1	-27*	-12	-20	-22
Pain in bones	35 (35)	-20*	-4	-7	-21*	-9	-6
EuroQol utility	0.52 (0.33)	0.03	0.14*	0.14	-0.14	0.12	0.17
* p<0.05; ** p<0.01.							

Mean absolute scores (SD) at baseline and at 12 months follow-up for the patients who proceeded to PSCT 12 months follow-up

	Baseline – Patients who proceeded to 12 months follow-up (n=12)	12 months follow-up Patients with baseline (n=12)	12 months follow-up – All patients (n=26)

EORTC QLQ-C30 functioning scales			
Physical	65 (28)	85 (15)	78 (19)
Role	53 (32)	72 (18)	71 (21)
Emotional	74 (19)	74 (20)	78 (19)
Cognitive	79 (21)	82 (21)	85 (17)
Social	69 (27)	82 (25)	82 (25)
Global QoL	66 (23)	70 (16)	69 (19)
EORTC QLQ-C30 symptoms			
Fatigue	42 (30)	35 (27)	30 (26)
Nausea/vomiting	1 (5)	6 (13)	3 (9)
Pain	28 (30)	17 (17)	15 (16)
Appetite loss	6 (13)	3 (10)	1 (7)
Diarrhoea	0 (0)	3 (10)	1 (7)
Disease/treatment related symptoms			
Pain in back	31 (39)	19 (17)	22 (19)
Soreness of mouth	11 (22)	6 (13)	4 (11)
Change in taste	14 (22)	6 (13)	7 (22)
Diminished sexual interest	56 (38)	33 (40)	40 (38)
Pain in bones	19 (30)	14 (17)	17 (7)
EuroQol utility	0.60 (0.33)	0.77 (0.13)	0.79 (0.18)

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes. The EORTC QLQ-C30 and the EuroQol 5-D are outlined as are the methods for their application.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

The authors found an improvement in subjective well-being on the EORTC QLQ-C30 and the EuroQol 5-D for patients who were able to complete the treatment programme. There was a trend towards improved functioning and reduced symptoms .There were declines associated with the provision of treatment, however improvements did occur with time.

What are the implications of the study for the model

Although the study provides utility outcomes for multiple myeloma patients, these are related to a different patient group and to different treatment regimens.

This study indicates that QoL is worse initially at diagnosis and treatment but improves after end of treatment. Long term QoL appears stable but is lower than for the reference population.

Reference

Van Agthoven and colleagues, 2004[89]

Data extracted by: KC Extraction checked by: AC

Study Characteristics

Research question

What are the stated objectives of the study?

Estimate the cost utility of intensive chemotherapy vs intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue in newly diagnosed patients with multiple myeloma

Describe the type of study and study design.

Cost utility study based on a RCT in patients ≤65 years old with previously untreated multiple myeloma. Trial of intensive chemotherapy versus intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue.
Phase 1 VAD remission-induction therapy (vincristine, doxorubicin, dexamehasone) (3-4 cycles at 28 day intervals), phase 2 cyclosphamide and autologous stem cell collection, phase 3 intensive melphalan (2 cycles at 8 week intervals), phase 4 peripheral blood stem cell transplantation for patients in myeloablative group (cyclophosphamide/total body irridation), phase 5 maintenance with interferon-α-2a.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Patients with undiagnosed and untreated multiple myeloma.

What are the characteristics of the baseline cohort for the evaluation?

Age (years)	Mean (range): Intensive chemotherapy 55 (38-65); myeloablative 55 (32-65).
Sex	Intensive chemotherapy 74 M, 55 F; myeloablative therapy 81 M, 51 F
Race (if appropriate)	Not reported
Indication / disease	Newly diagnosed multiple myeloma and stage II or II A/B disease; in intensive arm 32/129 stage IIA; 89/129 stage IIIA; 8/129 stage IIIB; myeloblative arm 26/132 stage IIA; 92/132 stage IIIA; 11/132 stage IIIB.
Other characteristics (sample size)	129 in intensive chemotherapy arm and 132 in myeloablative treatment arm
QoL instrument	EQ-5D assessed up to 24 months and then assumed to be stable until 36 months.
Utility values, (Y/N)	Y
Treatment effect, if reported	Median overall survival in myeloablative treatment group 47 months vs 50 months in intensive chemotherapy group (p=0.41)

Country/ setting

What is the country and setting for the evaluation?

Holland and Belgium

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study

Results

Authors state that patients in an undefined state following intentionally curative primary therapy would have a QoL 19.5% lower than those in the general population (0.8), ie QoL is 0.644 (0.8 - (0.195*0.8))

Utility values for the different treatment groups.

Time from randomisation	Intensive chemotherapy	Myeloablative treatment
6 months	0.81	0.65
12 months	0.80	0.62
18 months	0.81	0.69
24 months	0.77	0.75

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Limited detail given on methodology or results in present study. Reference given for more detail: Segeren C.M. Intensive therapy in Multiple myeloma, Rotterdam, Erasmus University, 2002. (thesis)

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Cost effectiveness of myeloma therapy after 3 years of follow up seems not to be favoured by myeloablative treatment with autologous stem cell rescue. Cost per QALY at 3 yrs: Intensive €37328; Myeablative €51357.

What are the implications of the study for the model

Although the study assessed the QoL in newly diagnosed and untreated people with multiple myeloma, it focused on interventions not included in the current evaluation. It provides an

indication of the QoL following curative treatment and over two year period of treatment.

Appendix 11: Cost-effectiveness data extraction forms for manufacturers' submissions

Reference

Janssen-Cilag, 2009[111]

Research question

What are the stated objectives of the evaluation?

To provide a cost effectiveness analysis, reporting the total costs associated with the interventions under consideration in the appraisal and the QALYs gained. (p49)

Funding source

Janssen-Cilag

Study population

What definition was used for [condition]?

The patient population is newly diagnosed patients ineligible for HDT-SCT in line with the scope of the appraisal.

What are the characteristics of the baseline cohort for the evaluation?

The characteristics of the baseline cohort are not specified but the authors report that they are reflective of the UK population and the trial evidence.

Interventions and comparators

What interventions/ strategies were included?

Bortezomib in combination therapy with an alkylating agent and a corticosteroid Thalidomide in combination therapy with an alkylating agent and a corticosteroid

Was a no treatment/ supportive care strategy included?

Compared with melphalan + prednisone (MP)

Describe interventions/ strategies

Bortezomib + melphalan + prednisone (VMP) Thalidomide + melphalan + prednisone (MPT) Thalidomide + cyclophosphamide + dexamethasone (CTDa)

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

UK NHS and PSS

Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost utility

Institutional setting Where is/are the intervention(s) being evaluated usually provided?

NHS inpatient care

Country/ currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

UK, £ 2008/9 costs

Effectiveness

Were the effectiveness data derived from:
a single study, a review/ synthesis of previous studies or expert opinion?

A meta-analysis was conducted to estimate the treatment effects.

Give the definition of treatment effect used in the evaluation

The treatment effects for VMP, MPT and CTDa were estimated using constant hazard ratios for Progression free survival (PFS) and overall survival (OS) relative to MP.

Give the size of the treatment effect used in the evaluation

[redacted]

Intervention Costs
Were the cost data derived from:
a single (observational) study, a review/ synthesis of previous studies expert opinion?

Treatment unit costs are based on the BNF 2009 and MIMMS 2009.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes.

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Table 53 Summary

	Dose	Duration of treatment	Unit Cost
Bortezomib	1x 3.5mg vial	Mean number of vials used in the VISTA trial: 31.5 (J&J, Velcade CSR 1)	£762
Thalidomide	CTDa arm: 167mg per day MPT arm: 150mg per day	315 days	£298 per 28 tablets
Enoxaparin as thromboprophylaxis	40mg per day	6 months (4 cycles of thalidomide)	40mg/0.4ml: 10 syringes=£40.36
Melphalan	9 mg /m^2 4 doses/cycle; 28 doses /course	*7 cycles	£11.46 for 25 tablets of 2mg
Prednisolone	60mg /m^2 4 doses/cycle; 28 doses	*7 cycles	£20 for 56 tablets of 25mg £0.98 for 28 tablets of 5mg

	/course		
Cyclophosphamide	500mg 4 doses/cycle ; 30 doses/course	**7.5 cycles	$12.44 for 100 tables of 50mg

**Median number of MP cycles administered in VISTA = 7*
***Midpoint between the minimum (n=6) and maximum (n=9) number of courses in the Myeloma IX trial protocol*
indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion.

Costs for subsequent treatment and adverse events were from previous studies. Incidence of the included AEs was from the RCTs.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

Upon disease progression, patients have 2nd line treatment. Costs for 2nd and 3rd line treatment are shown in Table 28 of the MS.

The unit costs of treating adverse events (Table 25) were applied to the incidence of AEs (Table 24) to obtain the total cost of treating adverse events (Table 26). Unit costs of AEs are mainly from NICE TA 171 for lenalidomide.

Table 54: Unit costs of AEs

AE	Cost	Care Setting
Anaemia	£430.53	Day case
Deep-venous thrombosis (DVT)	£199.00	Outpatient
Haematological	£455.00	Day case
Infection	£685.00	Day case
Leukopenia	£470.00	Day case
Lymphopenia	£470.00	Day case
Neurological	£580.00	Day case
Neutropenia	£470.00	Day case
Non-hematologic toxicity (≥ grade 3)	£97.00	Outpatient
Oedema (peripheral)	£0.85	Outpatient
Peripheral neuropathy	£97.00	Outpatient
Thrombocytopenia	£547.89	Day case

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

None

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

NA

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Single study (van agthoven 2004)

List the utility values used in the evaluation

Table 55: Utility data sets

Utilities	For prior to response to treatment state	For response state	For post-progression state
EQ5D (UK weights) – (Van Agthoven et al, 2004)	0.77	0.81	0.64

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

A cost-utility decision-analytic model was used in this economic evaluation. The model, developed using Excel, considers a cohort of newly diagnosed myeloma patients and defines a baseline response, disease progression and survival based on treatment with MP. Treatment effects for VMP, MPT, CTDa are then modelled over time by adjusting this baseline patient experience via hazard ratios. Further lines of treatment (2^{nd} and 3^{rd} line) are taken into consideration to estimate the total treatment costs. The analytic framework was based on a variant of Quality-Adjusted Analysis of Time Without Symptoms or Toxicity (Q-twist Gelber 1991) using partitioned survival analysis (PSA) and utilises the area under and the difference between time to event curves to estimate mean durations spent within the disease states of interest.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

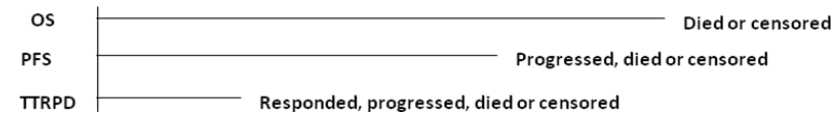
Not reported. However model needed to extrapolate trial data over patient lifetime.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Survival is partitioned into 3 different states: (1) prior to response to treatment; (2) response but no progression; and (3) post-progression. Death represents the final state. The steps to estimate the mean periods in these states are described below and the approach is presented schematically in figure 1: Step 1. Estimate mean OS (µOS) from start of treatment until death. Step 2. Estimate mean PFS (µPFS) from start of treatment until progression or death. Step 3. Estimate mean survival after progression (µPROG) as µOS - µPFS. Step 4. Estimate mean time until response (µPreRESP) from start of treatment until response,

progression, or death (include all patients, such that non-responders will either have event time as that of progression or death, or will be censored if they drop-out).
Step 5. Estimate mean time from response to progression or death (μ_{DOR}) as $\mu_{PROG} - \mu_{PreRESP}$.

Figure 15: Partitioned survival framework



TTRPD = Time to response or disease progression

To determine QALYs over the life of a patient, utilities for the following health states were assigned:

From start of treatment until response (u_{PRE})
From response to progression (u_r)
From progression to death (u_{PROG})

$$QALY = u_{PRE} \times \mu_{PreRESP} + u_r \times \mu_{DOR} + u_{PROG} \times \mu_{PROG}$$

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

What is the model time horizon?

30 year time horizon

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

3.5%

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Cost per QALY gained

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

	CTDa	MPT	MP	VMP
QALYs (discounted)	3.07	3.41	2.86	4.03

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

	CTDa	MPT	MP	VMP
Costs (discounted)	£56,668	£59,322	£54,434	£66,676

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

The ICER for VMP vs MP is estimated to be £10,498. Furthermore the ICERs of VMP vs MPT and VMP vs CTDa are estimated to be £11,907 and £10,411 respectively.

Table 56: Base-case results

	VMP vs MP	VMP vs MPT	VMP vs CTDa	MPT vs MP	MPT vs CTDa	CTDa vs MP
Incremental QALYs	1.17	0.62	0.96	0.55	0.34	0.20
Incremental cost	£12,241	£7,353	£10,007	£4,888	£2,654	£2,234
Incremental ICER	£10,498	£11,907	£10,411	£8,912	£7,724	£10,905

Give results of any statistical analysis of the results of the evaluation.

Survival curves are presented for progression free survival and overall survival.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

One way sensitivity analyses and probabilistic sensitivity analyses have been undertaken. Two alternative scenario analyses have also been undertaken.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

One way sensitivity analyses have been undertaken for a limited number of analyses, including different survival distributions for OS and PFS, alternative hazard ratios for OS, dose and duration of thalidomide, utilities, time horizon and discounting rate.

A PSA was undertaken using monte carlo simulation with 10,000 iterations. All parameters in the model were included except medication costs.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

The results are generally robust to changes in the sensitivity analyses. The model is most sensitive to the following parameters: underlying MP survival hazard, hazard ratios for overall survival, dose of thalidomide, duration of treatment with thalidomide in the MPT arm.

For the PSA, at the £20,000 and £30,000 willingness to pay thresholds, VMP has the highest probability of being cost effective: 64% and 75% respectively.

Two scenarios were conducted:
Scenario A assumes there is no subsequent therapy after 1st line treatment.

Table 57: Scenario: no subsequent therapy

	Mean QALYs	Mean cost	ICER vs MP
MP	2.86	£13,888	-
CTDa	3.07	£23,810	£48,437
MPT	3.41	£23,188	£16,956
VMP	4.03	£38,574	£21,099*

* Erroneously reported as £15,360 in MS

Scenario B assumes that the same second line therapies as those treated with MP in the VISTA trial. The results were similar for this scenario to the base case analyses.

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Base case results from the model demonstrated that VMP is more costly, but more effective than comparator treatments.

What are the implications of the evaluation for practice?

Reference

Celgene, 2009[112]

Research question

What are the stated objectives of the evaluation?

To compare the costs and benefits of adding thalidomide (T) to the combination melphalan and prenisolone (MP) with MP alone and with bortezomib in combination with melphalan and prenisolone (VMP) in patients with multiple myeloma older than 65 or who are ineligible for high dose chemotherapy.

Funding source

Celgene Ltd

Study population

What definition was used for [condition]?

Patients with untreated multiple myeloma aged 65 years and over or who are ineligible for high dose chemotherapy.

What are the characteristics of the baseline cohort for the evaluation?

The characteristics of the baseline cohort are not discussed.

Interventions and comparators

What interventions/ strategies were included?

TMP compared with MP alone and with VMP

Was a no treatment/ supportive care strategy included?

No. Comparisons as defined above.

Describe interventions/ strategies

Comparisons defined above.

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

NHS and Personal Social Services

Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost utility analysis.

Institutional setting Where is/are the intervention(s) being evaluated usually provided?

Patients were treated in several settings. Although the majority of care was provided as day case and outpatient care, there was some provision of care within the in-patient and primary care. The effect of the setting is taken into account in resources and costs.

Country/ currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

The evaluation is for England and Wales, with costs expressed as pounds sterling (£ - UK). The base year for costs appears to be 2008, although some costs are for 2007-9 and 2009.

Effectiveness

Were the effectiveness data derived from:
a single study, a review/ synthesis of previous studies or expert opinion?

Give the definition of treatment effect used in the evaluation

Treatment effects were calculated from a Bayesian mixed treatment comparison of data originating from three trials,[23,26,58] using survival time before and after progression as the primary outcomes. Progression free survival (PFS) was assumed to be equivalent to time to progression. The percentage of patients at six month intervals was used with extrapolation using an exponential distribution. Treatment interruptions/reductions were included in sensitivity analysis for MPT through reduction in average dose. AEs were included through data from two trials.[23,26] Post-progression survival (PPS) was reported as if patients had changed treatments from their original treatment to a similar but different treatment. PPS was calculated by combining the MPT, MP and MEL100 arms from IFM 99-06 trial to create an average survival curve.[23] Average survival at different time points was then extrapolated through an exponential distribution. Treatment interruptions/discontinuations were encompassed in the trial efficacy data, with no alteration to costs in the base case. Differences in costs were assessed.

Give the size of the treatment effect used in the evaluation

Meta-Analysed Odds Ratios of Progression Free Survival for MPT Compared to MP and VMP – Random Effects

Comparison	Point Estimate	95% CI
(MPT vs MP) - 6 mos.	2.63	(1.03, 7.01)
(MPT vs VMP) - 6 mos.	1.08	(0.23, 5.21)
(MPT vs MP) - 12 mos.	2.15	(0.92, 5.1)
(MPT vs VMP) - 12 mos.	1.07	(0.25, 4.47)
(MPT vs MP) - 18 mos.	2.10	(0.83, 5.24)
(MPT vs VMP) - 18 mos.	1.02	(0.22, 4.81)
(MPT vs MP) - 24 mos.	2.19	(0.9, 5.07)
(MPT vs VMP) - 24 mos.	0.85	(0.2, 3.52)
(MPT vs MP) - 30 mos.	2.70	(1.1, 6.55)

Meta-Analysed Odds Ratios of Post Progression Survival for MPT Compared to MP – Random Effects

Comparison	Point Estimate	95% CI
(MPT vs MP) - 6 mos.	1.04	(0.37, 2.81)
(MPT vs MP) - 12 mos.	1.05	(0.41, 2.66)
(MPT vs MP) - 18 mos.	1.15	(0.47, 3.03)
(MPT vs MP) - 24 mos.	0.99	(0.38, 2.68)
(MPT vs MP) - 30 mos.	1.15	(0.43, 3.06)

Intervention Costs
Were the cost data derived from:
a single (observational) study, a review/ synthesis of previous studies expert opinion?

Resources and costs were obtained from several sources. NHS resources were obtained from an unpublished survey of UK Haematologists by Celegene Ltd.[113] Inpatient, outpatient and day case hospitalisation costs were derived from NHS Reference costs.[96] Costs of medicines were from the BNF Edition 57[35] and costs of blood transfusions from Wilson et al[97] with costs inflated to 2008.[98]

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes.

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Medication and preparation costs used in model base-case

Medication	Drug acquisition cost (£)	Cost per mg (£)	*Dosing mg/day	Drug acquisition cost per cycle	Preparation costs (£)
Bortezomib	£762.40 for 1 x 3.5mg vial	217.83	1 vial	£6,099.04 [cycles 1-4], £3,049.52 [cycles 5-9]	159.93 per dose
Melphalan	£11.46 for 25 x 2mg	0.229	0.25	£16.23	0
Prednisone	£1.95 for 28 x 5mg	0.014	2	£7.87	0
Thalidomide	£298.48 for 28 x 50mg	0.213	238.1	£2,132.04	13.64 per cycle

**Dose source page 114; CSR [1] Using IFM 99-06[23] ; Drug costs from BNF 57. British National Formulary. 2009: BMJ Publishing Group Ltd[35]*

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion.

Other resource use and cost data were provided for outpatient consultations, disease monitoring and treatment of adverse events/complications. Resources and costs used and their sources are outlined below.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes. The costs of adverse events were calculated by combining resource use data from the survey of haematologists with unit costs to estimate total costs. These costs and trial data on the frequency of AEs[23] were then used to calculate a weighted average cycle cost. AE management costs were calculated for the entire time horizon for each AE through addition of the average medication and treatment cost (weighted for setting of care). This was then multiplied by the proportion of occurrence of AEs over the total number of AEs in the treatment arm. The costs per specific AE are then summed to provide an average cost per AE, which is applied at the time of the AE.

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

Unit costs and mean number of regular outpatient consultations and disease monitoring tests

	Cost (£)	Source	Frequency (mean # of assessments per year)	
			Pre-progression	Post-progression

			Active treatment	Off active treatment	
Outpatient	82	OP	12	6	12
Tests to monitor therapy response and disease status					
Routine Blood Counts (FBC)	2.99	H	10.7	7.1	20.1
Clotting	2.99	H	1.1	0.4	3.9
INR monitoring	2.99	H	2.9	0.4	2.6
Biochemistry (U&Es)	1.34	P	9.7	6.6	17.3
Liver function tests (LFTs)	1.34	P	7.6	5.1	14.6
Erythrocyte sedimentation rate	2.99	H	1.4	0.9	2.6
Plasma Viscosity	1.34	P	0.3	0.3	1.6
Uric Acid (Urate)	1.34	P	1.4	0.9	2.7
Immunoglobulin	1.34	P	6.4	4.9	9.7
Paraprotein Measurements	1.34	P	7.6	6.1	11.1
Protein Electrophoresis	1.34	P	6.7	5.1	9.6
Serum β2 microglobulin	1.34	P	3.0	2.0	5.0
Serum erythropoietin level	1.34	P	0.1	0.1	0.5
Immunofixation	1.34	P	3.4	2.9	4.8
Creatinine-clearance	1.34	P	0.7	0.4	2.3
Glomerular filtration rate	1.34	P	3.3	2.7	7.1
Serum Free Light Chains	1.34	P	2.9	1.7	4.1
Routine urinalysis	1.34	P	1.7	1.0	4.4
24-hour urine measurement (24hr)	1.34	P	1.3	1.0	3.0
24-hour urine for creatinine (24hr)	1.34	P	0.6	0.1	1.4
Total Urine Protein (24hr)	1.34	P	1.4	0.4	3.2
Urine protein electrophoresis/ light chains	1.34	P	2.7	2.1	4.9
Urine Immunofixation	61.70	Assumption	1.0	1.0	2.1
Skeletal Survey by X-Ray	18.56	Assumption	0.1	0.0	1.6
Skeletal Survey by X-Ray Individual Sites	18.56	Assumption	0.1	0.1	1.6
Bone Marrow Aspirate	1.34	P	0.2	0.1	2.1
Bone Marrow Trephine Biopsy	1.34	P	0.2	0.1	2.0
Bacterial investigation	7.52	P	0.4	0.3	1.6
Calcium	1.34	P	6.0	1.0	20
Albumin	1.34	P	6.0	1.0	20

P = Department of Health. NHS Reference Costs 2007-8 - Pathology Services Test Data (TPATH) - Specialty: Biochemistry - Specialty Code: DAP841]; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945 - accessed September 2009

H = Department of Health. NHS Reference Costs 2007-8 - Pathology Services Test Data (TPATH) - Specialty: Haematology [Excluding Anti-Coagulant Services] - Specialty Code: DAP823. accessed September 2008

M= Department of Health. NHS Reference Costs 2007-8 - Pathology Services Test Data (TPATH) - Specialty: Biochemistry - Specialty Code: DAP831; accessed September 2008

Op= NHS Reference Costs 2007-8 - Outpatient Adult Follow Up Attendance (TOPS FUA) - Specialty: Clinical Haematology - Specialty Code: 303. - accessed September 2009

Unit costs used in the model analyses

	Average Unit Cost *
Anaemia - grade 3 /4	£358.07
Thrombocytopenia - grade 3/4	£379.71

Neutropenia - grade 3/4	£772.13
Leucopenia - grade 3/4	£573.62
Lymphopenia - grade 3/4	£1480.55
Peripheral neuropathy - grade 3	£856.99
Thrombosis or embolism - grade 3/4	£661.59
Somnolence/fatigue/dizziness - grade 3/4	£147.94
Fever of unknown origin - grade 3/4	£1,195.37
Pneumonia – grade 3/4	£12734.34
Septicaemia - grade 3/4	£2,740.69
Meningitis - grade 3/4	£857.98
Herpes zoster - grade 3/4	£383.82
Constipation - grade 3/4	£1,277.13
Lung disorder - grade 5	£971.46
Septic shock - grade 5	£784.53

**weighted average of unit costs*

Source: unpublished survey of UK Haematologists by Celegene[113]

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

No.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

Not applicable.

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

The HOVON study,[89] a RCT of intensive chemotherapy followed by myeloblative therapy with autologous stem cell rescue compared to intensive chemotherapy, provided QoL data using the EQ-5D. A literature search was conducted for utility decrements for AE, with utility values from different population groups used (e.g. breast, colon and rectal cancer). Average percent reduction in utility by each AE was calculated from these values.

List the utility values used in the evaluation

Utility values were 0.64 for people not responding to treatment and 0.81 for people who did respond (using general public utility for same age group). A utility value of 0.77 at 24 months was presented for those who continue to respond to treatment with intensive chemotherapy. An assumption was made that pre progression patients and post progression patients matched responders and non-responders in the HOVON trial. [89] A 0.77 utility score was used for those who had not progressed at end of 2 years.

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

A lifetime Markov model developed from the evaluation presented by Deniz and colleagues,[71] which compared MPT to MP in first-line treatment for MM in Scotland. The model was updated to include comparison with VMP.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

Not stated.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Model Structure

The model tracks the progress of patients with MM as managed with MPT, VMP or MP through 4 Markov states, specifically (i) pre-progression without AE, (ii) pre-progression with AE, (iii) post progression, and (iv) death. Patients start in the pre-progression without AE health state and may move to a worse state or remain in the same state. Patients receive first-line treatment with MPT or MP for up to 12 six-week cycles or VMP for up to 9 cycles. If the patients experience a serious treatment related AE, patient enters pre-progression with AE state with no risk of additional AE. History of AEs does not determine progression. Death can only occur at progression or after progression and are assumed to be disease related deterioration. Cycle length 6 weeks (42 days), equivalent to dosing cycle in trials.[23,26,58]

Resources and Costs

Dose reductions, treatment interruptions and discontinuations are modelled as a reduction in costs.

When on active treatment, patients receive the mean observed treatment dose from the trials. Routine management resources were estimated by UK haematologists by progression status and costed using publicly available data and applied to relevant cohorts until the end of the time horizon.

AEs

Only costs of treatment-related serious (grade 3 and above) AEs or that occurred in ≥2% in treatment arms are included for those on active treatment. Rates are taken from the trials.[23,26] Risk of AE was estimated from the mean time alive per patient from Kaplan Meier survival curves, with average patients alive during a 6 month period calculated and average duration on treatment calculated. Progression is the point of stopping treatment.

[redacted]. The magnitude and duration of the risk reductions were used to calculate the relative reduction in utility value over the complete time horizon of the AE in cycles. These values were weighted according to relative frequency and summed to produce the average total relative disutility per AE which was applied to the cohort experiencing AEs.

Assumptions

Only patients on active treatment at risk of AEs

Costs of managing AE considered separately.

AE disutility applied at time of the event.

No discontinuation through AEs, implicitly included in dosing, duration and efficacy of treatment.

Deaths from AEs are through OS

Average treatment duration applied in the base case model was 12 months for MP and MPT, despite treatment interruptions/discontinations meaning median treatment duration was less [redacted]. This assumption increases costs not efficacy. No data on

discontinuation for VMP was available.

Progression
Post-progression survival is modelled to be the same across treatment strategies.
Patients assumed to discontinue active treatment upon disease progression
AEs assumed not to affect progression rate.

Concurrent medication
Assumes VTE antithrombotic prophylaxis for patients receiving MPT with no resultant risk in incidence of VTEs and anti-viral prophylaxis for VMP.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

No stated.

What is the model time horizon?

Lifetime horizon

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Costs and benefits were discounted at 3.5%.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Cost per life year gained and cost per QALY

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

	MPT	MP	VMP	
Summary of Clinical Outcomes (discounted model)				
Median Time to Progression (months)	26.3	13.8	27.6	
Patients Progressed (%)	100%	100%	100%	
Deaths (%)	100%	100%	100%	
Proportion of Patients with AE	43.2%	13.4%	40.9%	
Median Overall Survival (months)	51.1	37.3	52.5	
Total Life Years	4.49	3.4	4.60	
Total Quality Adjusted Life Years (QALY)	3.28	2.43	3.35	

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

	MPT	MP	VMP	
Cost Outcomes (overall population) (discounted model)				
Medication	£18,937	£192	£41,019	
Monitoring	£1,126	£1,034	£1,117	
AE Management	£439	£139	£404	
Total Cost	£21,133	£1,365	£42,616	

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Base case results calculated by model (discounted)

	MPT v MP	MPT v VMP
Incremental Life Years	1.09	0.11
Incremental QALYs	0.85	0.07
Incremental Costs	£19,768	£21,483
Incremental cost per LY gained	£18,188	£200,237
Incremental cost per QALY gained	£23,381	£303,845

Give results of any statistical analysis of the results of the evaluation.

None.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Yes

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

One-way deterministic sensitivity analysis examined time horizon (5 years), risk progression (2.5% and 97.5% confidence intervals from MTC), resource use and costs (monitoring, AE and all costs varied by +/- 100%), AE rates and utility (scores varied by +/- 10%), progression free and overall survival (expanded MTC),

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

One-way deterministic sensitivity analysis (discounted)

	MPT v MP		MPT v VMP	
	Incremental cost/LYG (£)	Incremental cost/QALY (£)	Incremental cost/LYG (£)	Incremental cost/QALY (£)
Base case	18,188	23,381	200,201	303,790
No discounting	14,892	19,355	153,339	226,033
Time horizon (5 years)	41,703	49,134	613,900	1,241,139
Efficacy				
2.5% CI MTC	25,836	33,275	482,097	1,000,435
97.5% CI MTC	12,916	16,586	106,683	148,873
Monitoring costs and AE costs				
+100%	18,538	23,831	199,749	303,103
-100%	18,005	23,145	200,427	304,133
Utility scores				
+10% increase	18,188	22,961	200,201	305,666
-10% decrease	18,188	23,816	200,201	302,045

Single trial analyses (discounted)

	MPT v MP		MPT v VMP	
	Incremental cost/LYG (£)	Incremental cost/QALY (£)	Incremental cost/LYG (£)	Incremental cost/QALY (£)
IFM 99-06	16,603	21,285	MPT dominates	MPT dominates
IFM 01-01	9,404	12,067	1,430,625	7,234,876
GIMEMA	23,648	30,882	314,357	462,088

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

The analyses indicate that MPT represents a cost-effective use of NHS resources when compared to MP in England and Wales for managing previously untreated multiple myeloma patients aged ≥ 65 years or ineligible for high dose chemotherapy.

What are the implications of the evaluation for practice?

The authors estimate that the eligible incident and prevalent population will increase from 3,196 in 2010 to 15,929 in 2014. With the assumption that MPT currently has no market share and that its market share will grow from 60% in 2010 to 70% by 2014, the authors estimate that the incremental budget impact of using thalidomide (based on the proposed total annual costs with MPT and MP minus the total annual costs of managing patients with MP alone) will rise from £32 million in 2010 to £44.8 million in 2014. As MPT is estimated to have a market share of 54% currently, the incremental budget impact of increasing the market share to 60% in 2010 and 70% by 2014 will result in an incremental total annual cost of £3.2 million in 2010 rising to £10.2 million in 2014.

Appendix 12: Critical appraisal checklist of economic evaluation

The quality of the cost-effectiveness studies was assessed using a critical appraisal checklist based on that by Drummond and Jefferson,[114] Philips and colleagues[94] and the NICE reference case.[77]

	Item	Celgene[112]	Janssen-Cilag[111]
1	Is there a clear statement of the decision problem?	Y	Y
2	Is the comparator routinely used in UK NHS?	Y	Y
3	Is the patient group in the study similar to those of interest in UK NHS?	?	Y
4	Is the health care system or setting comparable to UK?	Y	Y
5	Is the perspective of the model clearly stated?	Y	Y
6	Is the study type and modelling methodology reasonable?	Y	Y
7	Is the model structure described and does it reflect the disease process?	?	Y
8	Are assumptions about model structure listed and justified?	Y	Y
9	Are the data inputs for the model described and justified?	Y	Y
10	Is the effectiveness of the intervention established based on a systematic review?	Y	Y
11	Are health benefits measured in QALYs?	Y	Y
12	Are health benefits measured using a standardised and validated generic instrument?	Y	Y
13	Are the resource costs described and justified?	Y	Y
14	Have the costs and outcomes been discounted?	Y	Y
15	Has uncertainty been assessed?	Y	Y
16	Has the model been validated?	N	N

Y – Yes; N – No; ? – unclear / incomplete

Appendix 13: Methodology used for disease projection

The methodology used for estimating survival curves for the alternative treatments is as follows:

i) Derive a baseline survival curve for MP. This curve is derived by calculating the event probability for each time interval, by calculating a weighted average of the trial MP arms using number of participants in the trial as a weight.

ii) Derive hazard ratios for each of the treatments versus MP at different time points for each trial. Combine hazard ratios for treatments with more than one trial.

iii) Construct the baseline survival curves for MP using the event probability for each time interval.

iv) Construct the survival curves for other treatment by using the event probability for each time interval; ie event probability for MP multiplied by hazard ratio.

For MP treatment, OS and PFS at regular time points were estimated for each of the included studies from our meta-analysis of the clinical trials. The data from the trials were combined to form baseline MP OS and PFS curves through a weighted average, using number of patients in the trials as the weight. We estimated the hazard rate for MP for each six-monthly period (Table 1). The hazard rate for death for MP per cycle is estimated for each time point t_i,:

$$h(t_i) = 1 - \left(\frac{s(t_i)}{s(t_{i-1})} \right)^{\frac{1}{(t_i - t_{i-1})}}$$

where s(t) is the survival function over time t.

Table 1Baseline MP Overall Survival curve and derived death rate

Months	Cycles	Survival OS	Hazard OS
6	4.35	0.90	0.024
12	8.69	0.79	0.030
18	13.04	0.72	0.021
24	17.38	0.65	0.023
30	21.73	0.56	0.034
36	26.07	0.48	0.035
36+	26+		0.028

The treatment effects for the other interventions compared to MP were taken from our clinical review (Section 4.1.2). As the hazard ratio of the treatments versus MP varied over time, a

constant hazard ratio was not appropriate. A similar methodology was used for estimating OS and PFS, however only OS is described in this appendix.

We derived the hazard ratio for each six-monthly period for each of the treatments versus MP. The hazard rate for death for each of the treatments per cycle is estimated for each time point t_i,:

$$h(t_i) = 1 - \left(\frac{s(t_i)}{s(t_{i-1})} \right)^{\frac{1}{(t_i - t_{i-1})}}$$

where s(t) is the survival function over time t.

The hazard ratio (HR) for each intervention j versus MP at each time point t_i as,

$$HR_i = \frac{h_j(t_i)}{h_{mp}(t_i)}$$

The hazard ratio was assumed to be constant after 36 months for OS as there were few patients with more than this length of follow up in the trials. This hazard ratio was estimated for each of the treatments versus MP at 36 months follow-up for OS.

The hazard rate for death for each of the treatments per cycle was also assumed to be constant after 36 months and is given by:

$h(t) = 1 - s(t)^{1/t}$

where s(t) is the survival function where t is 36 months (26.1 cycles).

The methodology is illustrated for OS for VMP with data from the VISTA trial. Table 2 shows the hazards and the hazard ratios derived from the VISTA trial for OS.

Table 2: Hazards and hazard ratio for VMP vs MP for OS from the VISTA trial.

		Survival	s(t)	Hazard	h(t)	HR
Months	Cycles	MP	VMP	MP	VMP	
0	0	1.00	1.00			

To generate the survival curves for each of the treatments the baseline death rate in each time period for MP was multiplied by the hazard ratio to give the new death rate for the alternative treatment. This method provided a closer fit to the trial data, than approximations such as fitting distributions.

The survival curves were constructed by multiplying the survival in the previous time point by the proportion who survived in the current time interval, using the estimated hazards for MP and the hazard ratio for the other interventions.

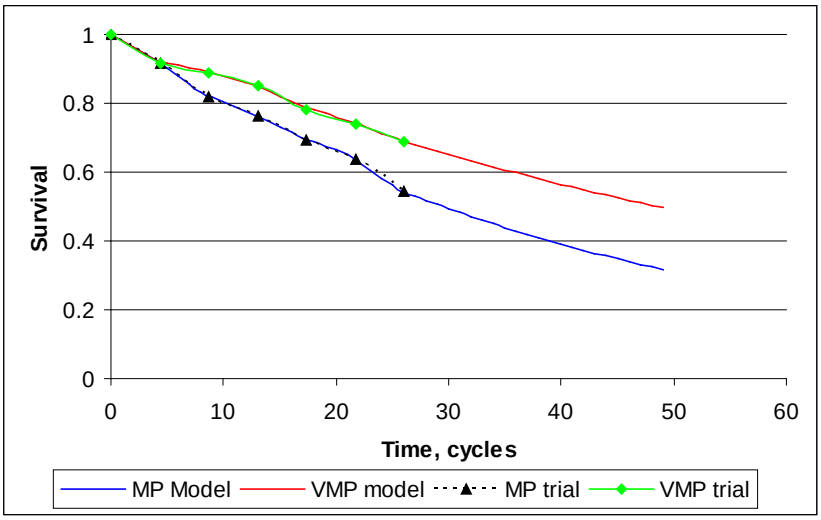
Thus the survival function s(t) is given by:

MP: $s(t_i) = s(t_{i-1}).\ (1-h(t_i)$

Other interventions: $s(t_i) = s(t_{i-1}).\ (1-h(t_i).HR_i)$

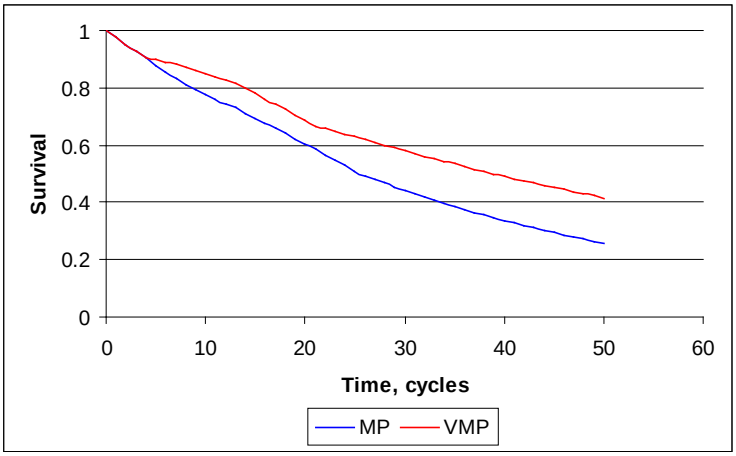
To demonstrate the fit from this method we derive the VMP survival curves using the trial MP curves and compare to the original trial curves. Figure 2 shows the MP and VMP survival curves derived for the model against the trial data from the VISTA trial. As can be seen in the Figure, the derived survival curves in the model closely match both treatments during the trial period.

[redacted]



In the model, instead of using the MP trial data, the MP baseline data is used with the same method as described above. Figure 3 shows the MP and VMP survival curves derived for the model using the baseline combined MP curves.

Figure 3: MP and VMP survival curves for the model using combined baseline MP curves



Appendix 14: Parameters included in the sensitivity analyses

The ranges used for the deterministic and probabilistic sensitivity analyses are reported in this appendix. Where appropriate, parameters were assigned a distribution in the probabilistic sensitivity analysis. Distributions were chosen, according to the methodology suggested by Briggs and colleagues.[99] They suggest that the normal distribution is a 'candidate distribution for representing the uncertainty in any parameter in the model'. Further they suggest the beta distribution for binomial outcomes, where parameters can vary between zero and one, for example probabilities, and the gamma distribution for costs where parameters are non-negative.

- Discount rates were varied between 2% and 5% for costs and benefits in the deterministic sensitivity analyses.
- The number of cycles for each of the treatments varied between 7 and 9 cycles. For each of the interventions, we assumed a range between one fewer than the mean to one more than the mean. The number of cycles was assumed to follow a normal distribution.
- Second-line treatment was varied according to the proportion who had bortezomib and HDD. For MP, MPT, and CTDa, the proportion varied between 60 and 80% and for VMP, the proportion varied between 5 and 25%.
- The range for the utility values was assumed to be +/- 10% of the mean utility values, based on the uncertainty in the utility values from the MMIX trial. We analysed the HRQoL data from the MMIX trial. [redacted] Utility values were sampled from a beta distribution.
- The complete response data was obtained from the trials and standard errors were derived. Values were sampled from a beta distribution.
- The costs for adverse events, bortezomib administration and consultation costs were assumed to vary within the range +/-30% of the mean and were sampled from a gamma distribution.
- The ranges for the hazard ratios and event rates for the MP survival curves were taken from the trial data. Values were sampled from a log normal distribution.
- The costs for adverse events, bortezomib administration and consultation costs were varied within +/-30% of the mean for the deterministic sensitivity analysis.

Table A1 Parameters and distributions for the deterministic and probabilistic sensitivity analyses

Name	Mean	Higher CI	Lower CI	standard error	distribution
Discount rate					
Discount rate costs	3.5%	5.0%	2.0%		N/A
Discount rate benefits	3.5%	5.0%	2.0%		N/A
Cycles of treatment					
cycle_MP	8	9	7	0.5102	log normal
cycle_MPT	8	9	7	0.5102	log normal
cycle_VMP	9	10	8	0.5102	log normal
cycle_CTDa	7	8	6	0.5102	log normal
Subsequent treatment, Bort.					
Sub_treat_Bort_MP	70	80	60	5.1020	log normal
Sub_treat_Bort_MPT	70	80	60	5.1020	log normal
Sub_treat_Bort_VMP	15	25	5	5.1020	log normal
Sub_treat_Bort_CTDa	70	80	60	5.1020	log normal
Utility values					
u_treatment	0.58	0.639	0.522	0.030	beta
u_response	0.72	0.792	0.648	0.037	beta
u_progression	0.68	0.748	0.612	0.035	beta
Complete response					
CR_MP	0.026	0.035	0.017	0.005	beta
CR_MPT	0.142	0.307	0.066	0.084	beta
CR_VMP	0.217	0.386	0.121	0.087	beta
CR_CTDa	0.144	0.111	0.280	-0.015	beta
Adverse events, £ per cycle					
cAE_MP	£60.31	£78.40	£42.22	9.231	gamma
cAE_MPT	£91.12	£118.45	£63.78	13.946	gamma
cAE_VMP	£88.51	£115.06	£61.95	13.547	gamma
cAE_CTDa	£96.13	£124.97	£67.29	14.714	gamma
Other					
Cost of bortezomib administration	£153.40	£199.42	£107.38	23.4796	gamma
OP appointment medical oncology	£121.11	£157.44	£84.78	18.5372	gamma
Survival curve parameters					
Multipliers					
MP OS baseline curve	0.028	0.039	0.020	0.0041	log normal
MP PFS baseline curve	0.067	0.070	0.060	0.0036	log normal
HR OS MPT	0.62	0.82	0.50	0.0714	log normal
HR OS VMP	[redacted]	[redacted]	[redacted]	[redacted]	log normal
HR OS CTDa	[redacted]	[redacted]	[redacted]	[redacted]	log normal
HR PFS MPT	0.58	0.77	0.49	0.0612	log normal
HR PFS VMP	0.58	0.76	0.48	0.0612	log normal
HR PFS CTDa	[redacted]	[redacted]	[redacted]	[redacted]	log normal
Cost of treatments					
Unit cost bortezomib	£762.38	£914.86	£609.90	77.7939	N/A
Unit cost thalidomide	£298.48	£358.18	£238.78	30.4571	N/A
Dosage thalidomide, mg/day	150	200	100	25.5102	log normal