NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Bortezomib and thalidomide for the first-line treatment of multiple myeloma

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Multiple myeloma is a form of cancer that occurs in a type of white blood cell (plasma cell) in the bone marrow. In people with multiple myeloma, a single plasma cell becomes cancerous to form a myeloma cell, which begins to multiply. These abnormal plasma cells, or myeloma cells, build up in the bone marrow, reducing the space available for making normal white cells, red cells and platelets. Normal blood cells are responsible for fighting infections, carrying oxygen around the body and blood clotting. Myeloma cells produce large amounts of one type of abnormal antibody, which does not work properly and is not able fight infection. Symptoms and clinical features of multiple myeloma include fatigue, bone pain and/or fracture, anaemia, infections, M-protein in serum and/or urine, and hypercalcaemia. The origin of multiple myeloma is unknown and malignant cells display a variety of cytogenetic abnormalities.

Multiple myeloma is the second most common haematological cancer in the UK. In England and Wales there are approximately 3600 new diagnoses recorded annually. In 2007 most diagnoses were recorded in people aged 75–79 years. Multiple myeloma is about 1.5 times as common in men as in women, and twice as common in people of African or Caribbean descent. In

the UK, the estimated lifetime risk of developing multiple myeloma is 1 in 148 for men and 1 in 186 for women[1]. There are currently between 10,000 and 15,000 people living with multiple myeloma in the UK.

Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy. The aim of treatment is to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects. Survival after diagnosis can vary from months to more than 10 years. Factors affecting survival and outcome include burden of disease, type of cytogenetic abnormality, the age and performance status, and response to treatment.

1.2 Current management

In England and Wales the choice of first-line treatment depends on a combination of factors. Most people with multiple myeloma are not able to withstand intensive treatment, such as high-dose chemotherapy with autologous stem cell transplantation (SCT), because of their age, specific problems or poor performance status. These people are 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 include combination therapies that incorporate drugs such as thalidomide and bortezomib.

The main objective of first-line therapy is to achieve a period of stable disease (termed the plateau phase) for as long as possible, thereby prolonging survival and maximising quality of life. After initial treatment, most people usually experience a period of remission, but almost all relapse eventually, and some have disease that does not respond (is refractory) to treatment.

[1] Derived from incidence and mortality data for 2001–2005 by the statistical information team at Cancer Research UK.

‘Bortezomib monotherapy for relapsed multiple myeloma’ (NICE technology appraisal guidance 129) recommends bortezomib monotherapy as a possible treatment for progressive multiple myeloma for people whose multiple myeloma has relapsed for the first time after having one treatment, and who have had a bone marrow transplant (unless it is not suitable for them). However, this appraisal did not consider bortezomib for first-line therapy of multiple myeloma.

The British Society for Haematology (BSH) guideline on the diagnosis and management of multiple myeloma has recommended that all people with multiple myeloma should be treated with bisphosphonates, whether or not bone lesions are present. The guideline states (page 428) that ’Although high-dose chemotherapy 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.’ The guideline recommends single agent or combination chemotherapy as a first-line treatment for people who are not able to withstand such an intensive type of treatment. The BSH guideline is currently being revised and updated. The draft of the revised guideline contains a recommendation that for older and/or less fit people in whom high-dose chemotherapy is not planned, initial therapy should consist of either a thalidomide-containing regimen in combination with an alkylating agent and steroid (such as thalidomide in combination with melphalan (MPT) or cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) or bortezomib in combination with melphalan and prednisolone (VMP).

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Bortezomib	Thalidomide
Proprietary name	Velcade	Thalidomide Pharmion
Manufacturer	Janssen-Cilag	Celgene
Dose (SPC)	1.3 mg/m^2 body surface area Cycles 1 – 4: twice weekly Cycles 5 – 9: weekly	200 mg per day
Acquisition cost (BNF edition 58)	3.5-mg vial = £762.38	50 mg x 28-capsule pack = £298.48

Bortezomib

Bortezomib (Velcade, Janssen-Cilag) is an anticancer drug that works by reversible proteasome inhibition. This inhibition leads to arrest of the cell cycle and apoptosis (cell death), which reduces tumour growth. Myeloma cells are more sensitive to the action of bortezomib than normal cells.

Bortezomib has a marketing authorisation for use in combination with melphalan and prednisone 'for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant'. Bortezomib is administered as an intravenous injection.

The summary of product characteristics (SPC) for bortezomib recommends nine 6-week treatment cycles for combined therapy with melphalan plus prednisone (VMP). During these treatment cycles bortezomib is administered over 3–5 seconds as a 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 9 mg/ml sodium chloride (0.9%) solution. In the first four cycles of treatment, bortezomib is administered twice weekly. In 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 response to treatment and the occurrence of certain adverse

events. 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.

Thalidomide

Thalidomide (Thalidomide Pharmion, Celgene) is an immunosuppressive agent. Its precise mechanism of action is under investigation and is currently unknown, but it is thought to have multiple actions, including anti-inflammatory activity and the ability to inhibit the growth and survival of myeloma cells and the growth of new blood vessels. It is also a non-barbiturate hypnotic sedative with central action.

Thalidomide has a marketing authorisation for use 'in combination with melphalan and prednisone as first-line treatment of patients with untreated multiple myeloma', aged '≥ 65 years or ineligible for high dose chemotherapy'. Because thalidomide is a known human teratogen, it must be prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme. Thalidomide is taken orally.

The SPC for thalidomide recommends an oral dosage of 200 mg per day, taken as a single dose at bedtime 'to reduce the impact of somnolence'. Treatment is usually started with a lower dose, which is gradually increased if this is tolerated. In the UK most people with multiple myeloma who are ineligible for high-dose chemotherapy and SCT are likely to receive a 100-mg 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 people with other risk factors for thrombosis. The dosage and total number of cycles may change depending on the response to treatment and the occurrence of certain adverse events.

The SPC does not recommend particular doses or dosing schedules for melphalan and prednisone when these are 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.

3 The evidence

The Assessment Group reviewed the evidence for clinical effectiveness of the two technologies in accordance with their marketing authorisations. However, the remit of this MTA also allows appraisal outside the marketing authorisations, via inclusion of data from the UK wide, MRC – sponsored Myeloma IX study. The interventions were compared with melphalan or cyclophosphamide in combination with prednisolone or dexamethasone (all for the first-line treatment of multiple myeloma). The scope of the appraisal also allows for the interventions to be compared with each other. The Assessment Group also considered interventions that used prednisone rather than prednisolone. Prednisone (not currently used in the UK) and prednisolone are equally effective, and are used in the same manner at largely equivalent doses.

The Assessment Group identified five relevant clinical trials, which informed the following comparisons:

- Myeloma IX (MMIX) study – cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP)
- Vista trial – bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (MP)
- IFM trial 99/06 – melphalan and prednisolone/prednisone (MP) plus thalidomide (MPT) Vs. versus melphalan plus prednisolone/prednisone (MP)
- IFM trial 01/01 – melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP)
- GIMEMA trial – melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP)

The Assessment Group excluded two sources of data that were included in the manufacturers' submissions; HOVON-40 (Wijermans et al, 2008[5]), and the Nordic Myeloma Study Group (NMSG) study (Waage et al, 2007[6]). They commented that it is unclear whether the the Hovon study meets the inclusion criteria for this review because patients could receive thalidomide maintenance treatment. The study reported by Waage et al, 2007 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).

3.1 Clinical effectiveness

3.1.1 Cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP)

The Assessment Group identified one randomised controlled trial (RCT) that included a non-intensive pathway and evaluated cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) against melphalan plus prednisolone/prednisone (MP) (the MMIX study). Equal numbers of participants were randomised to receive either cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) or melphalan plus prednisolone/prednisone (MP). Within each treatment arm participants were also randomised to bisphosphonate treatment either with sodium clondronate or zoledronic acid. This multicentre RCT was conducted at [redacted] in the UK and enrolled [redacted]. The MMIX study used a minimisation algorithm, stratified by centre haemoglobin level corrected serum calcium serum creatinine and platelet count.

In common with the other included RCTs, people were eligible to participate if they were newly diagnosed with symptomatic multiple myeloma or non-secretory multiple myeloma and had not received previous treatment for myeloma (other than local radiotherapy). The non-intensive pathway of the MMIX study was designed for older (generally $\geq$ 70 years of age) or less fit

participants (who could be younger than 70), but strict age restrictions were not in place to ensure that fit older participants were not excluded from the intensive therapy arm.

[redacted]

Overall survival, progression-free survival and response were the primary outcomes and power calculations were provided for both survival and response. Secondary outcomes were quality of life, skeletal-related events, height loss, adverse events, and the proportion of participants receiving bortezomib plus dexamethasone as 'early rescue' on induction chemotherapy, or at relapse. All analyses from the MMIX study were intention to treat unless stated otherwise. Intention to treat was defined as all people randomised, except those who had been misdiagnosed.

[redacted]

Table 2: Treatment response in the MMIX study

	Cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) [redacted]	**Melphalan plus prednisolone/prednisone (MP)** [redacted]	**p value**
Complete response	[redacted]	[redacted]	[redacted]
Very good response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Complete, very good or partial response	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Data from the MMIX study on overall survival, progression-free survival, time to disease progression and quality of life were not eligible for inclusion in the Assessment Group's 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.

[redacted]

3.1.2 Bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (MP)

The Assessment Group identified one relevant RCT investigating bortezomib plus melphalan and prednisolone/prednisone (VMP); (the Vista trial). This was a randomised (1:1), open-label, phase 3 trial with 682 participants conducted in 151 centres in 22 countries in Europe, North and South America, and Asia.

People were eligible to participate if they had newly diagnosed, untreated, symptomatic, measurable myeloma and were not candidates for high-dose chemotherapy plus SCT because of their 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 participants had ISS stage II or III disease,

about a third had a Karnofsky performance score of ≤70%, and over 60% had lytic bone lesions.

The primary outcome measure was time to disease progression. Secondary outcomes were the rate of complete response, duration of response time, time to subsequent myeloma therapy, overall survival and progression-free survival (defined as the time between randomisation and either disease progression or relapse from complete response criteria, or death due to any cause, whichever occurred first). Disease progression was defined by European Group for Blood and Marrow Transplantation (EBMT) criteria and assessed by the investigators. The sponsors also determined progression using of a computer algorithm that applied EBMT criteria. Time to progression and overall survival were analysed from the time of randomisation. Various rates for response to treatment are reported as secondary outcomes for bortezomib plus melphalan and prednisolone/prednisone (VMP). Statistically significantly more participants achieved a complete or partial response or better with bortezomib plus melphalan and prednisolone/prednisone (VMP) than with melphalan plus prednisolone/prednisone (MP) (table 3). This outcome was not analysed using intention to treat principles, although most analyses in this study did.

An advantage in terms of overall survival was reported for bortezomib plus melphalan and prednisolone/prednisone (VMP) compared with melphalan plus prednisolone/prednisone (MP). A statistically significant survival benefit for bortezomib plus melphalan and prednisolone/prednisone (VMP) was reported after a median follow-up of 25.9 months (hazard ratio [HR] = 0.64, p = 0.0032). More recently reported 3-year survival rates after a median follow-up of 36.7 months are 68.5% versus 54% respectively. However, it has also been reported that a survival benefit was associated with bortezomib because 45 participants (13%) in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP) had died compared with 76 (22%) in the group receiving melphalan plus prednisolone/prednisone (MP) (HR 0.61, p = 0.008) (despite the fact that 44% of participants receiving melphalan plus prednisolone/prednisone (MP) also received bortezomib after

disease progression). The most recent analyses show a median overall survival of 43.1 months for participants receiving melphalan plus prednisolone/prednisone (MP); this was not estimable in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP).

Time to subsequent myeloma therapy was reported as 20.8 months in the group receiving melphalan plus prednisolone/prednisone (MP); this was not reached in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP).

Table 3: Results from the VISTA trial

	Bortezomib plus melphalan and prednisolone/prednisone (VMP) (n = 344)	**Melphalan plus prednisolone/prednisone (MP) (n = 338)**	**Hazard ratio and p value**
Median time to progression	20.7 months	15.0 months	HR = 0.54, p < 0.001
Partial response or better (EBMT criteria)	71%	35%	p < 0.001
Complete response	30%	4%	p < 0.001
Partial response	40%	31%	p < 0.001
Minimal response	9%	22%	p < 0.001
Stable disease	18%	40%	-
Progressive disease	1%	2%	-
Median progression-free survival	21.7 months	15.2 months	HR 0.56 p < 0.001

In the VISTA trial, death rates during treatment were similar for the two groups (5% for bortezomib plus melphalan and prednisolone/prednisone [VMP] and 4% for melphalan plus prednisolone/prednisone [MP]). Treatment-related deaths were also similar (1% and 2% respectively).

Limited data on health-related quality of life were available. After the onset of best response, participants treated with bortezomib plus melphalan and prednisolone/prednisone (VMP) had a higher sustained improvement rate in 14 of the 15 European Organisation for Research and Treatment of Cancer QoL questionnaire C-30 (EORTC QLQ-C30) scores.

Adverse events occurred in participants in both arms. Although the occurrence of any adverse event and any grade 4 adverse event was similar in the two groups, there was a statistically significant increase in grade 3 adverse events in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP) (53% versus 44%, p = 0.02). Haematological events were the most frequently reported and were also similar in the two groups. Peripheral sensory neuropathy was reported more frequently in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP) 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 2 months. All grade 3 and grade 4 gastrointestinal events were more frequent in the group receiving bortezomib plus melphalan and prednisolone/prednisone (VMP)(19% versus 5%, no p value given). The incidence of deep vein thrombosis was low and similar in the two groups.

Although subgroup analyses were conducted, the Assessment Group commented that this RCT may not have been adequately powered for these analyses. Because of this the results, which indicate that the reported benefits of bortezomib interms of time to progression apply to each of the seven subgroups of participants, should be interpreted with caution.

3.1.3 Melphalan and prednisolone/prednisone plus thalidomide (MPT) Versus melphalan plus prednisolone/prednisone (MP)

The Assessment Group identified three RCTs of melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP). The number of participating centres ranged from 44 to 73. All were located in one or more European countries (France,

Belgium, Switzerland and Italy). The IFM 99/06 RCT was the largest, recruiting 447 participants; but the results from only 321 participants are reported here because the trial had a third arm (reduced-intensity SCT) which did not meet the inclusion criteria. The GIMEMA RCT enrolled 331 participants and the IFM 01/01 RCT enrolled 232 participants.

All participants in each RCT met the inclusion criteria for the systematic review. The two IFM RCTs differed in the target age range of participants: IFM 01/01 included people aged at least 75 years, whereas IFM 99/06 mainly included people aged between 65 and 75 years, with younger people being eligible for inclusion providing they were not eligible for high-dose chemotherapy. The GIMEMA study included people older than 65 years without specifying any upper age limit, but also included participants younger than 65 years providing they were unable to undergo SCT. All RCTs included people whose multiple myeloma was at stage II or III; the two IFM RCTs also included people with stage I myeloma if they met the criteria for high-risk stage I disease. The percentage of participants in the IFM and GIMEMA 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.

Overall survival was the primary outcome measure for the two IFM RCTs. Both RCTs were powered at 80% for the primary outcome but recruitment was stopped early in both because interim analyses had demonstrated a clear survival advantage. The secondary outcomes of these RCTs were response rates, progression-free survival, survival after progression, adverse events, and safety. The primary outcome measure for the GIMEMA RCT was response rates and progression-free survival. The secondary outcomes were overall survival, time to first evidence of response, prognostic factors, and frequency of any grade 3 or higher adverse events. All RCTs stated that intention to treat analyses had been conducted.

Table 4: Results from the IFM 99/06, IFM 01/01, GIMEMA trials

	MPT	MP (with or without placebo)	Hazard ratio and p-value
Number of participants			
IFM 99/06	125	196	
IFM 01/01	113	116	
GIMEMA	167 (129 followed up)	164 (126 followed up)	
Median PFS			
IFM 99/06	27.5 months	17.8 months	HR = 0.51, p = 0.001
FM 01/01	24.1 months	18.5 months	HR = 0.62, p = 0.001
OS (median survival)			
IFM 99/06	51.6 months	33.2 months	HR = 0.59, p = 0.0006
Adjustment for prognostic factors:	MPT remains superior		HR = 0.49, p = 0.0002
FM 01/01	44 months	29.1 months	HR = 0.68, p = 0.028
Complete response			
IFM 99/06	13%	2%	p = 0.008
IFM 01/01	7%	1%	p < 0.001
GIMEMA	13% difference at 6 months	-	-
Very good - partial response			
IFM 99/06	47%	7%	p < 0.001
IFM 01/01	21%	7%	p < 0.001
GIMEMA	60.4%	45.2%	-
MPT - Melphalan and prednisolone/prednisone plus thalidomide MP - Melphalan plus prednisolone/prednisone			

Both IFM RCTs reported a statistically significant difference in overall survival in favour of the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) (table 4). The Assessment Group reported that meta-analysis of the overall survival data confirmed the superiority of melphalan and prednisolone/prednisone plus thalidomide (MPT). The GIMEMA RCT

included maintenance therapy with thalidomide and therefore overall survival, which was a secondary outcome of this RCT, was not eligible for inclusion in the assessment.

The Assessment Group noted that caution must be applied in interpreting the overall survival results for IFM 99/06 because these appeared to be based on a small proportion of the participants. The Assessment Group also commented that the IFM 99/06 study stated all analyses were done on an intention to treat basis, and it is therefore unclear why response to treatment outcomes are reported for only 60% of the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) (75 of 125 participants) and 84% of the group receiving melphalan plus prednisolone/prednisone (MP)(165 of 196 participants).

Table 5: Deaths during treatment

Study	**Treatment arms**		
IFM 99/06	**MPT (n=124)**	**MP (n=193)**	***p*-value**
Toxic death	n=0	n=4 (2%), all due to infection	Not reported
Early death – in first 3 months of treatment	3/124 (2%)	13/193 (7%)	Not reported
IFM 01/01	**MPT (n=113)**	**MP + placebo (n=116)**	***p*-value**
Toxic death (intestinal perforation)	n=1	n=1	Not reported
Early death – after 1 month of treatment	n=3	n=3	Not reported
Early death – after 3 months of treatment	n=5	n=6	Not reported

The two IFM RCTs provided some information about deaths, see Table 5. However, the Assessment Group commented that, for both study arms, it is not clear whether the number of deaths reported after 3 months is a

cumulative value (that is, it includes the deaths reported after 1 month of treatment), or whether these are additional deaths that have occurred in months two and three.

The Assessment Group commented that because the GIMEMA RCT had included maintenance therapy with thalidomide few data on adverse events could be included. So most of the data on adverse events came from just two RCTs. Four types of haematological event (at grade 3 and 4) were reported from the IFM 99/06 study. There were no statistically significant differences in the occurrence of anaemia (14% both groups, p = 0.94) or thrombocytopenia (melphalan and prednisolone/prednisone plus thalidomide 14%, melphalan plus prednisolone/prednisone 10%, p = 0.29). A statistically significant difference was reported for neutropenia, which occurred in more participants receiving melphalan and prednisolone/prednisone plus thalidomide (MPT (48% versus 26%, p < 0.0001). The IFM 01/01 study showed a statistically significantly greater proportion of participants receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) experienced neutropenia (grade 3 and 4) (23% versus 9%, p = 0.003). Both IFM RCTs reported the occurrence of grade 3 and 4 thrombosis or embolism. The Assessment Group commented that the IFM 99/06 study found the greater proportion of participants with grade 3 or 4 thrombosis or embolism in the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) was statistically significant (12% versus 4%, p = 0.008). In contrast, there was no statistically significant difference in this adverse event in the IFM 01/01 study (6% versus 3%, p = 0.33). Peripheral neuropathy occurred statistically significantly more frequently in the groups receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) of both IFM RCTs, but the reporting of this differed.

The IFM 99/06 study reported no statistically significant difference in the number of patients with infections of grade 3 or 4 (16 participants receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) [13%] versus 18 participants receiving melphalan plus prednisolone/prednisone (MP) [9%]; p = 0.32). In the 6-month period of treatment in the GIMEMA study eligible for

inclusion in the review, there were statistically significantly more infections in the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) than the group receiving melphalan plus prednisolone/prednisone (MP)(10% [all within the first 4 months] versus 2%, p = 0.01). The Assessment Group commented that the IFM 01/01 study did not report this outcome, other than stating that the higher incidence of neutropenia in the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) did not translate into more frequent severe infections.

Constipation was the most commonly reported gastrointestinal adverse event. Data from the IFM 99/06 study showed that only participants receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) experienced constipation at grade 3 and 4 ($p < 0.0001$). The IFM 01/01 study reported constipation of grade 2 to 4, and found no statistically significant difference between the groups (melphalan and prednisolone/prednisone plus thalidomide (MPT)17% versus melphalan plus prednisolone/prednisone plus placebo (MP) 10%, p = 0.16). Overall, the IFM 99/06 study found that non-haematological adverse events of grade 3 or higher were statistically significantly more likely in the group receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) (42% versus 16%, $p < 0.0001$).

The conclusions on the clinical effectiveness of melphalan and prednisolone/prednisone plus thalidomide (MPT) and bortezomib plus melphalan and prednisolone/prednisone (VMP) from the two manufacturers' submissions and the Assessment Group's 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 in the Assessment Group's meta-analyses and the manufacturers' mixed-treatment comparison, the Assessment Group concluded that it was not possible to make meaningful comparisons.

3.2 Cost effectiveness

The Assessment Group's systematic search of the literature found five abstracts of economic evaluations of treatment for people with previously undiagnosed multiple myeloma who are ineligible for high-dose chemotherapy with SCT. None of the studies contained sufficient information for critical appraisal. Three abstract concluded that melphalan and prednisolone/prednisone plus thalidomide (MPT) was a cost-effective alternative to melphalan plus prednisolone/prednisone (MP) in patients in Scotland, Wales and Australia. Two abstracts concluded that bortezomib plus melphalan and prednisolone/prednisone (VMP) was cost effective compared with melphalan plus prednisolone/prednisone (MP) and melphalan and prednisolone/prednisone plus thalidomide (MPT) in Canadian and US patients. The latter study stated that bortezomib plus melphalan and prednisolone/prednisone (VMP) dominated melphalan and prednisolone/prednisone plus thalidomide (MPT) (that is, was more effective and less costly). A systematic review of studies of quality of life for people with multiple myeloma identified six studies. Only two of these studies were for the population of interest and neither included generic preference-based utility measures. The other four studies provided utility estimates for people with multiple myeloma who had intensive therapy.

The two manufacturers submitted cost-effectiveness models. The Assessment Group developed their own economic model and critiqued the economic models submitted by the manufacturers.

3.2.1 Manufacturer submissions

Two manufacturers submitted evidence to be considered for the appraisal of bortezomib and thalidomide as first-line treatment. Janssen-Cilag, the manufacturer of bortezomib, constructed a survival model that estimated overall survival and progression-free survival based on treatment effects from a mixed-treatment comparison of the RCTs. Celgene, the manufacturer of thalidomide, constructed a Markov model with health states for pre progression (with or without adverse events), post progression and death.

Both models aimed to consider the cost effectiveness of the technologies from an NHS perspective.

Janssen-Cilag – bortezomib

The decision-analytic cost-utility model from Janssen-Cilag evaluates lifetime costs and benefits for bortezomib in combination with melphalan and prednisolone/prednisone (VMP), for people with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with SCT, compared to melphalan and prednisolone/prednisone plus thalidomide (MPT), cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) and melphalan plus prednisolone/prednisone (MP). The model uses a cohort of newly diagnosed people with myeloma treated with melphalan plus prednisolone/prednisone (MP) as the baseline treatment. Treatment effects for bortezomib in combination with melphalan and prednisolone/prednisone (VMP), melphalan and prednisolone/prednisone plus thalidomide MPT), cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) are then modelled over time by adjusting the baseline patient experience via hazard ratios. The model also includes further treatment (second and third-line) to estimate the total treatment costs.

The manufacturers' model makes the following assumptions:

- Dose of thalidomide of 150 mg per day for melphalan and prednisolone/prednisone plus thalidomide (MPT) and 167 mg per day for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) .
- Adverse events are included in the model as the cost of treating them; the incidence of adverse events does not influence the treatment duration, efficacy or patient utility.
- Costs included for second- and third-line treatments.
- RCTs of thalidomide which included maintenance therapy with thalidomide were included in the meta-analysis.

Survival is divided into three different states: prior to response to treatment; response but no progression; and post progression. Death represents the final

state. The time to response or death were estimated from life tables constructed directly from the patient-level data from the VISTA trial. Progression-free survival at 6, 12, 18 and 24 months for melphalan plus prednisolone/prednisone (MP) was estimated from a meta-analysis of the melphalan plus prednisolone/prednisone (MP) arms of included RCTs. Progression-free survival was extrapolated beyond 24 months, assuming an exponential survival distribution, and using the hazard rate for all time periods beyond 24 months calculated for months 18 to 24.

Following first-line therapy, it was assumed that on disease progression second-line treatment would consist of bortezomib plus high-dose dexamethasone, cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) or high-dose dexamethasone. Most people received cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) after first-line bortezomib plus melphalan and prednisolone/prednisone (VMP) and bortezomib and high-dose dexamethasone for all other first-line therapies. All patients received lenalidomide plus dexamethasone as third-line treatment.

Health-related quality of life utility values are assigned to each of the states: prior to response to treatment; response to treatment without progression; and post progression. 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 duration of treatment with melphalan plus prednisolone/prednisone (MP) was seven cycles as in the VISTA trial. For bortezomib, 31.5 vials were used per patient (VISTA trial). The Assessment Group noted that 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, which was obtained from the five RCTs of melphalan and prednisolone/prednisone plus thalidomide (MPT) included in the meta-analysis for the manufacturers' submission. Within the cyclophosphamide, thalidomide plus attenuated dexamethasone (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 RCTs of melphalan and prednisolone/prednisone plus thalidomide (MPT).

The resource use cost for the first-line management of multiple myeloma was assumed to be the same for all regimens. There was an outpatient cost of £102 per visit and a total of nine outpatient visits. In addition, people receiving bortezomib plus melphalan and prednisolone/prednisone (VMP) had this outpatient cost each time they were administered bortezomib.

Table 6 shows the base-case results from the submission for bortezomib. The submission states that the incremental analysis shows extended dominance of melphalan and prednisolone/prednisone plus thalidomide (MPT) over cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa). However the Assessment Group found an error in the calculation of third-line costs for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) (correct cost £24,978 instead of £16,652). Correction of this error resulted in an incremental cost-effectiveness ratio (ICER) of £51,552 per QALY gained for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP).

Table 6: Base-case results from the Janssen-Cilag submission for bortezomib

	Mean QALYs	Mean cost	ICER versus MP (cost/QALY)	ICER versus next best option with lower cost (cost/QALY)
MP	2.86	£54,434	-	-
CTDa	3.07	£56,668	£10,905[a]	£10,905
MPT	3.41	£59,322	£8912	£7724
VMP	4.03	£66,676	£10,498	£11,907

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; VMP – bortezomib plus melphalan and prednisolone/prednisone

[a] - Assessment Group correction: £51,552 per QALY

One-way sensitivity analysis showed the model is most sensitive to the following parameters: underlying melphalan plus prednisolone/prednisone (MP) survival hazard, hazard ratios for overall survival, dose of thalidomide, and duration of treatment with thalidomide in the melphalan and prednisolone/prednisone plus thalidomide (MPT) arm.

A probabilistic sensitivity analysis was undertaken using Monte Carlo simulation with 10,000 iterations. All parameters in the model were included except medication costs. For the sensitivity analysis, at the £20,000 and £30,000 thresholds, bortezomib plus melphalan and prednisolone/prednisone (VMP) has the highest probability of being cost effective (64% and 75% respectively).

Two scenario analyses were conducted. The first 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 increased to £48,437, £16,956 and £21,099 per QALY gained for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa), melphalan and prednisolone/prednisone plus thalidomide and bortezomib plus melphalan and prednisolone/prednisone (VMP) compared with melphalan

plus prednisolone/prednisone (MP). The second scenario assumed the same second-line therapies as for people treated with melphalan plus prednisolone/prednisone (MP) in the VISTA RCT. For this scenario, the results were similar to the base case analyses.

Celegene – thalidomide

The submission from Celegene aims to compare the costs and benefits of melphalan and prednisolone/prednisone plus thalidomide (MPT) with those of bortezomib plus melphalan and prednisolone/prednisone (VMP) and melphalan plus prednisolone/prednisone (MP) in people with multiple myeloma who are older than 65 years or are ineligible to receive high-dose chemotherapy. The analysis takes a lifetime horizon (30 years), presenting costs and outcomes (that is, years of life gained and quality-adjusted life years [QALYs] gained) for the three treatment arms and an incremental analysis of costs and outcomes. The manufacturer's submission stated that it was not able to include the Myeloma IX Study because the Medical Research Council's response to their request was that data would not be available by the October 2009 submission deadline.

A Markov model was developed to compare the difference in the progression of multiple myeloma and the costs of treatment with the three different treatment options. Treatment effects were calculated from a random-effects Bayesian mixed-treatment comparison of data originating from three RCTs (Vista, IFM 99/06, 01/01). The mixed-treatment comparison was undertaken despite differences in the dosage used in the RCTs comparing melphalan plus prednisolone/prednisone (MP) with melphalan and prednisolone/prednisone plus thalidomide (MPT). It used measures of survival time before and after progression as the primary outcomes. Time to progression and progression-free survival were used and assumed to be equivalent. The outcome from the mixed-treatment comparison was a measure of the risk of progression, with extrapolation beyond 30 months using an exponential distribution. Resources and costs were obtained from several sources, including an unpublished

survey of UK haematologists by Celgene, NHS reference costs, the BNF 57, and Wilson and colleagues[2] with costs inflated to 2008 values.

The manufacturer's model makes the following assumptions:

- Post-progression survival is modelled to be the same across different treatment strategies, with the different arms assumed to receive the same alternative treatment after progression (that is, second- and third-line treatments).
- Patients are assumed to discontinue first-line treatment upon disease progression.
- No second- and third-line treatments costs are included.
- Deaths can only occur at or after progression and are assumed to be because of disease related deterioration.
- Adverse events included in the model incorporate a utility decrement at the time of the event and the additional cost of treating them. They are assumed to not affect the disease progression rate or overall survival, or treatment duration, efficacy or dose.
- Venous thromboembolism antithrombotic prophylaxis for 5 months for patients receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) with no increased risk of venous thromboembolism and antiviral prophylaxis for bortezomib plus melphalan and prednisolone/prednisone (VMP).

The HOVON 24 study[3], an RCT of intensive chemotherapy followed by myeloblative therapy with autologous stem cell rescue compared with intensive chemotherapy alone, provided health-related quality of life data

[2] Wilson J, Yao GL, Raftery J, et al. (2007) A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technology Assessments 11: 1.

[3] van Agthoven M, Segeren CM, Buijt I, et al. (2004) A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study. European Journal of Cancer 40: 1159.

using the EQ–5D to assess the benefits of treatment for people with multiple myeloma. 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 the same age group). A utility value of 0.77 at 24 months was used for people who continue to respond to intensive chemotherapy and whose disease has not progressed. An assumption was made that the pre-progression and post-progression states matched 'responders' and 'non-responders' in the HOVON trial. However, the Assessment Group commented that other more relevant studies show that the utility values used in the manufacturer's submission are higher than would be experienced by people with multiple myeloma, 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). The literature search for utility decrements for adverse events did not identify specific values for people with multiple myeloma and so utility values from different population groups were used (for example, people with breast, colon and rectal cancer).

Comparison of the benefits used for the model showed considerable benefit for those receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) or bortezomib plus melphalan and prednisolone/prednisone (VMP) over melphalan plus prednisolone/prednisone (MP) in terms of median time to progression, median overall survival, total life years and total QALYs. In contrast, more people receiving melphalan and prednisolone/prednisone plus thalidomide (MPT) (43.2%) or bortezomib plus melphalan and prednisolone/prednisone (VMP) (40.9%) experienced adverse events compared with those receiving melphalan plus prednisolone/prednisone (MP) (13.4%). The total costs of the different treatment strategies used within the model showed considerable variation between melphalan plus prednisolone/prednisone (MP) (£1365) and bortezomib plus melphalan and prednisolone/prednisone (VMP) (£42,616). The cost of the medications was the main reason for these differences. The base case ICERs are shown in Table 7.

Table 7: Base-case results for the Celgene submission

	Incremental life years	Incremental QALYs	Incremental costs	Incremental cost per life year gained	Incremental cost per QALY gained
MPT versus MP	1.09	0.85	£19,768	£18,188	£23,381
VMP versus MPT	0.11	0.07	£21,483	£200,237	£303,845
MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; VMP – bortezomib plus melphalan and prednisolone/prednisone					

The submission assessed uncertainty through one-way deterministic sensitivity analyses. The parameters with the greatest effect on the model results were changes in treatment efficacy with a range of £16,586 to £33,275 per QALY gained for melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP) and a range of £148,873 to £1,000,435 per QALY gained for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan and prednisolone/prednisone plus thalidomide (MPT). No probablilistic sensitivity analysis was conducted because the manufacturer stated that the efficacy of melphalan and prednisolone/prednisone plus thalidomide (MPT) and bortezomib plus melphalan and prednisolone/prednisone (VMP) was essentially the same and that the cost differences would be the key driver for the model.

Comparison of the manufacturers' results

The Assessment Group noted that 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 bortezomib plus melphalan and prednisolone/prednisone (VMP), melphalan

and prednisolone/prednisone plus thalidomide (MPT) and melphalan plus prednisolone/prednisone (MP). Janssen-Cilag also included cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) as a comparator. The ICERs produced by the Janssen-Cilag and Celgene vary considerably from £11,907 to £303,845 per QALY gained for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan and prednisolone/prednisone plus thalidomide (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.

3.2.2 Economic model from the Assessment Group

The Assessment Group developed a model to estimate the costs, benefits and cost effectiveness of melphalan and prednisolone/prednisone plus thalidomide (MPT), bortezomib plus melphalan and prednisolone/prednisone (VMP) and cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) compared with melphalan plus prednisolone/prednisone (MP), in people with newly diagnosed multiple myeloma who are ineligible for high-dose chemotherapy with SCT. The economic evaluation was from the perspective of the NHS and PSS.

The model used clinical effectiveness data from the five RCTs included in the Assessment Group's systematic review of effectiveness. A mixed-treatment comparison was not carried out because of the Assessment Group's concerns about potential differences in participant characteristics, delivery of melphalan plus prednisolone/prednisone (MP) in the comparators arms, and differences in length of follow-up. Cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) was included in the Assessment Group's analyses in order to compare all relevant comparators; however the Assessment Group commented that there are limitations to the effectiveness data, because the effectiveness estimate for overall survival was not statistically significant and the MMIX RCT included a second randomisation to thalidomide maintenance for some participants.

Health-related quality of life data were from a systematic review of studies of health-related quality of life. Costs were derived from published studies (where available) and from national and local NHS unit costs (see table 38: summary data for treatment duration, dose and unit cost in technology assessment report).

Although the Assessment Group's systematic review of studies reporting health-related quality of life did not find any generic preference-based studies of people with untreated multiple myeloma who were not eligible for high-dose chemotherapy with SCT, it did identify two studies[4,5] that assessed health-related quality of life in this group using the EORTC QLQ C-30. The Assessment Groups suggested that the most appropriate source of data for the treatment period and post treatment values are those presented in Table 8.

Table 8: EQ–5D utility values derived by mapping from EORTC QLQ-C30 health-related quality of life scores

Mapping algorithm	Reference population	Time (months)					
		0	1	6	12	24	36
McKenzie and van der Pol	0.81	0.55	0.58	0.68	0.68	0.68	0.69
Kontodimopoulos et al.	0.86	0.52	0.58	0.69	0.69	0.69	0.71

The Assessment Group developed a survival model, consisting of two survival curves that estimate 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. Because of a lack of data on subsequent therapies, it was unclear how these affected health-related quality of life and survival, Therefore second-line therapy is only included in the

[4] Kontodimopoulos N, Aletras VH, Paliouras D, et al. (2009) Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. Value Health.

[5] McKenzie L, van der PM (2008) Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. Value Health.

model as a cost. The survival curves for overall survival from the model are shown in Figure 1. The results show increased survival for melphalan and prednisolone/prednisone plus thalidomide (MPT), bortezomib plus melphalan and prednisolone/prednisone (VMP) and cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP).

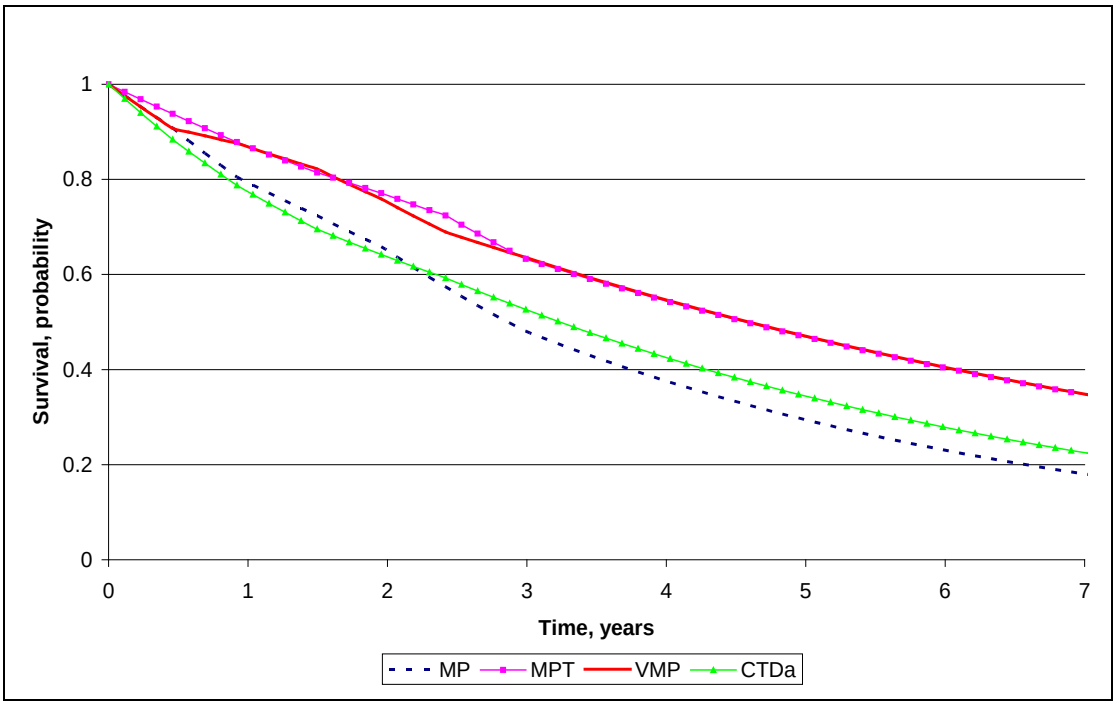


Figure 1: Overall survival curves for melphalan plus prednisolone/prednisone (MP); melphalan and prednisolone/prednisone plus thalidomide (MPT); bortezomib plus melphalan and prednisolone/prednisone (VMP); and cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa)

The summary results of the non-discounted treatment effects are shown in Table 9. In the base-case analysis, overall survival varied from 4.20 years for melphalan plus prednisolone/prednisone (MP) to 6.66 years for melphalan and prednisolone/prednisone plus thalidomide (MPT). Survival for melphalan and prednisolone/prednisone plus thalidomide (MPT) is slightly longer than for bortezomib plus melphalan and prednisolone/prednisone (VMP). The Assessment Group noted that the cost-effectiveness results for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) should be treated with caution because the MMIX trial results have not shown

a statistically significant benefit in overall survival compared with melphalan plus prednisolone/prednisone (MP).

Table 9: Summary of the duration in each health state for treatment with MP, MPT, VMP and CTDa

	Time, 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	4.69
CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; VMP – bortezomib plus melphalan and prednisolone/prednisone				

The relative effectiveness of the treatments versus MP for OS and PFS were represented as hazard ratios (tables 10 and 11). Table 12 shows the complete response for different treatments.

Table 10: Published hazard ratios for overall survival and hazard ratios derived from published Kaplan–Meier plots

Months	**IFM 99/06 (MPT)**	**IFM 01/01 (MPT)**	**Assessment Group MPT trials summary**	**Vista (MP)**	**MMIX (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]
CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; VMP – bortezomib plus melphalan and prednisolone/prednisone					

Table 11: Published hazard ratios for progression-free survival and hazard ratios derived from published Kaplan–Meier plots

Months	IFM 99/06 (MPT)	IFM 01/01 (MPT)	Assessment Group MPT trials summary	Vista (MP)	MMIX (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]

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; VMP – bortezomib plus melphalan and prednisolone/prednisone

Table 12: Complete response for different treatments

Treatment	Complete response, %
Melphalan and prednisolone/prednisone (**MP**)	2.6
Melphalan and prednisolone/prednisone plus thalidomide (**MPT**)	14.2
Bortezomib plus melphalan and prednisolone/prednisone (**VMP**)	21.7
Cyclophosphamide, thalidomide plus attenuated dexamethasone (**CTDa**)	14.4

The Assessment Group analysed health-related quality of life data from the MMIX RCT to determine whether patients with complete response had a better quality of life after response than those with other levels of response. The EORTC QLQ-C30 data were mapped to EQ–5D health utilities using the algorithm from McKenzie and van der Pol[6]. In the model, the Assessment Group estimated the utility for the post-treatment health state as a weighted average of those who had a complete response (utility value of 0.72) and those with lesser response (utility value of 0.68).

[6] McKenzie L, van der PM. Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. Value Health 2008.

The Assessment Group's model includes the following assumptions:

- For bortezomib, each person receives one vial per administration
- Costs included for second -line treatments. Most people who received bortezomib plus melphalan and prednisolone/prednisone (VMP) as first-line treatment receive cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) as second-line treatment 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.
- People discontinue first-line treatment upon disease progression.
- Health-related quality of life is better for those with complete response than those with less than complete response and is assumed to improve when people stop treatment
- Adverse events are not modelled explicitly in the model for overall survival and progression-free survival, but are included as additional cost for treating the adverse events in the model.

Table 13: Baseline cost-effectiveness results versus MP

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

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; QALY – quality-adjusted life-year; VMP – bortezomib plus melphalan and prednisolone/prednisone

Baseline ICERs results are shown in Table 13. The incremental analysis presented in Table 14 suggests extended dominance of melphalan and

prednisolone/prednisone plus thalidomide (MPT) over cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa), and that melphalan and prednisolone/prednisone plus thalidomide (MPT) dominates bortezomib plus melphalan and prednisolone/prednisone (VMP) because it is more effective and cheaper. The comparison of bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan and prednisolone/prednisone plus thalidomide (MPT) suggests that bortezomib plus melphalan and prednisolone/prednisone (VMP) and cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) are unlikely to be cost-effective treatment options at the conventional threshold of £20,000 to £30,000 per QALY gained. However there is much uncertainty around the results for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) because the overall survival estimates were not statistically significant and the results from the MMIX RCT included those of participants who had received thalidomide maintenance therapy.

Table 14: Incremental baseline cost-effectiveness results

	Quality – adjusted life-year	**Cost, £**	**Incremental cost effectiveness ratio (£/QALY)**
Melphalan and prednisolone/prednisone (**MP**)	2.42	£21,555	-
Cyclophosphamide, thalidomide plus attenuated dexamethasone (**CTDa**)	2.68	£30,147	£33,216
Bortezomib plus melphalan and prednisolone/prednisone (**VMP**)	3.62	£57,304	£28,907
Melphalan and prednisolone/prednisone plus thalidomide (**MPT**)	3.64	£32,762	Dominates VMP

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. As shown in Table 15, the model results are most sensitive to changes in the parameter values of the hazard ratios for overall survival (varied between £6,470 and £22,855 per QALY gained).

Table 15: 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 overall survival	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 overall survival 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

ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; QALY – quality-adjusted life-year

The deterministic sensitivity results for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (MP) are shown in Table 16 and varied between £20,451 and £87,716 per QALY gained. Bortezomib plus melphalan and prednisolone/prednisone (VMP) is dominated by melphalan and prednisolone/prednisone plus thalidomide (MPT) for all parameters, except overall survival (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 overall survival, the cost-effectiveness estimate of bortezomib plus melphalan and prednisolone/prednisone (VMP)

versus melphalan and prednisolone/prednisone plus thalidomide (MPT) is £33,979 per QALY gained.

Table16: 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 overall survival	[redacted]	[redacted]	[redacted]	£87,716	£20,451	£67,265
MP overall survival 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

ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; QALY – quality-adjusted life-year; VMP – bortezomib plus melphalan and prednisolone/prednisone

The deterministic sensitivity results for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP) are shown in Table 17 and varied between -£29,388 and £16,989 per QALY gained. This variation is because the estimates for overall survival are not statistically significant.

Table 17: Deterministic sensitivity analyses for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan and prednisolone/prednisone (MP)

Parameter	Baseline	Upper value	Lower value	Upper value ICER, (£/QALY)	Lower value ICER, (£/QALY)	Range
Hazard ratio for overall survival	[redacted]	[redacted]	[redacted]	-£29,388	£16,989	£46,377
MP overall survival 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

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; QALY – quality-adjusted life-year

In addition to the sensitivity analyses, four alternative scenarios were undertaken to investigate the uncertainty around structural assumptions:

Scenario A – no subsequent therapies

In this case, melphalan and prednisolone/prednisone plus thalidomide (MPT) and cyclophosphamide, thalidomide plus attenuated dexamethasone (VTDa) are slightly less cost effective than melphalan plus prednisolone/prednisone (MP) and bortezomib plus melphalan and prednisolone/prednisone (VMP) is considerably less cost effective. The cost-effectiveness estimate for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (MP) increases to £37,727 per QALY gained.

Scenario B – vial sharing

The base case scenario assumes that it is not possible for patients to share vials of bortezomib. This scenario investigates the cost effectiveness when patients do share vials of bortezomib. With vial sharing and no wastage, bortezomib becomes more cost effective versus melphalan plus prednisolone/prednisone (MP), with an ICER of £22,549 per QALY gained.

Scenario C – inclusion of thalidomide maintenance trials

The base case scenario uses the efficacy for melphalan and prednisolone/prednisone plus thalidomide (MPT) from RCTs that did not include thalidomide maintenance. This scenario investigates the cost effectiveness using the estimate for melphalan and prednisolone/prednisone plus thalidomide (MPT) efficacy from a meta-analysis that includes trials with thalidomide maintenance. Janssen-Cilag conducted a mixed-treatment comparison for melphalan and prednisolone/prednisone plus thalidomide (MPT) efficacy with trials that included thalidomide maintenance and derived a hazard ratio of [redacted] for melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP). Using this hazard ratio, makes melphalan and prednisolone/prednisone plus thalidomide (MPT)less cost effective with an ICER of £24,390 per QALY gained versus melphalan plus prednisolone/prednisone (MP). In addition, melphalan and prednisolone/prednisone plus thalidomide (MPT) no longer dominates bortezomib plus melphalan and prednisolone/prednisone (VMP), with an ICER of £32,739 for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan and prednisolone/prednisone plus thalidomide (MPT).

Scenario D –treatment effectiveness beyond the end of trial

The base case scenario extrapolates beyond the end of the trial by assuming a constant hazard ratio for the treatment effectiveness compared with melphalan plus prednisolone/prednisone (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 the three drug combinations over melphalan plus prednisolone/prednisone (MP), that is, the event rates for these treatments are the same as for melphalan plus prednisolone/prednisone (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 than melphalan plus prednisolone/prednisone (MP). The ICERs for each of the treatment options more than double to £20,698 (melphalan and prednisolone/prednisone plus thalidomide, MPT), £71,264 (bortezomib plus melphalan and prednisolone/prednisone, VMP) and £80,840 (cyclophosphamide, thalidomide plus attenuated dexamethasone, CTDa) per QALY gained versus melphalan plus prednisolone/prednisone (MP).

Table 18: Scenario analyses A to D

	ICER (Cost per QALY gained, £)		
	MPT	**VMP**	**CTDa**
Base case 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

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis estimated the probability of each of the treatments to be cost effective at the £20,000 and £30,000 thresholds. Melphalan and prednisolone/prednisone plus thalidomide (MPT) has the highest probability of being cost effective with probabilities of 0.95 and 0.95 respectively (see Figure 2).

Table 19: Baseline probabilistic sensitivity analysis cost-effectiveness results for each drug combination versus melphalan and prednisolone/prednisone (MP)

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

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; QALY – quality-adjusted life-year; VMP – bortezomib plus melphalan and prednisolone/prednisone

Figure 2: Cost-effectiveness acceptability curve from the PSA

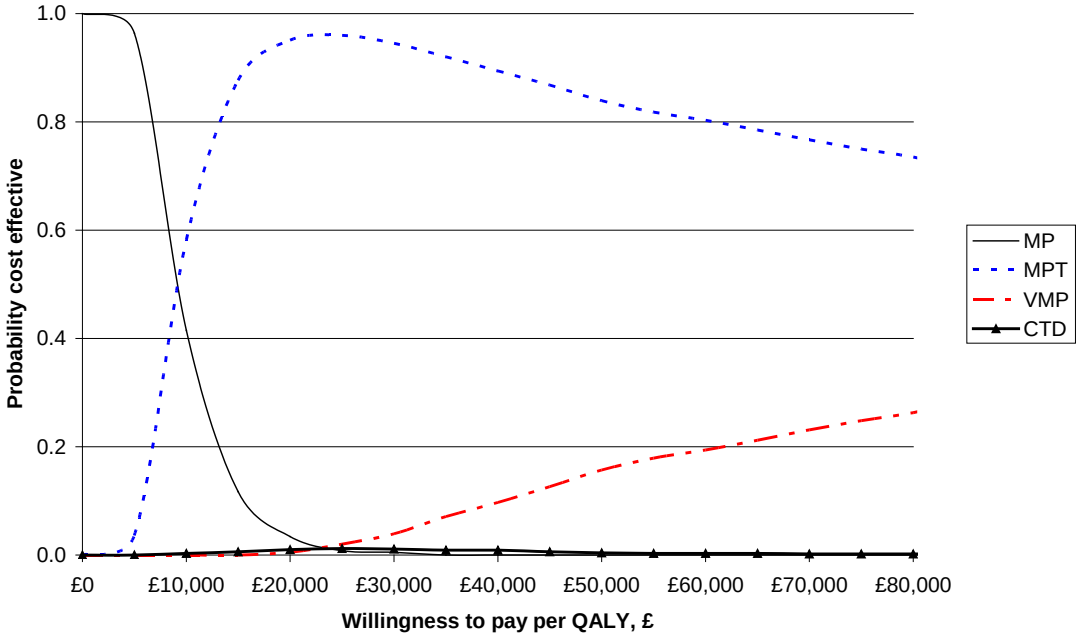
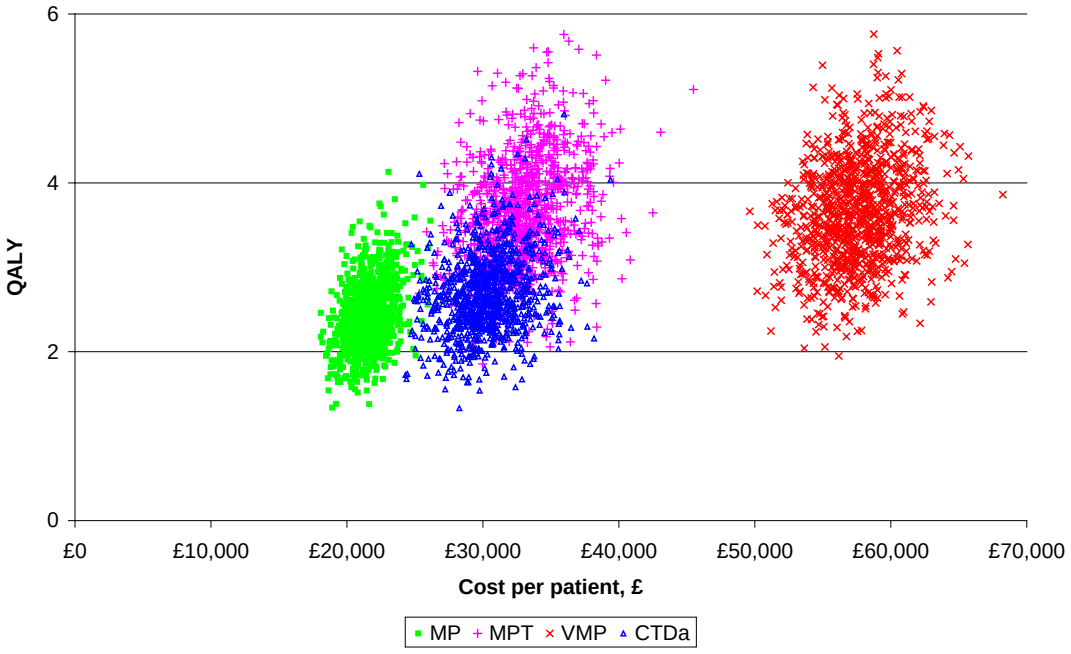


Figure 3: Scatterplots of the costs and health benefits from PSA



3.2.3 Comparison of the manufacturer and Assessment Group models

The results for the manufacturers' and Assessment Group's economic analyses are shown in Table 20. The results of the analyses vary considerably. The costs vary substantially between the analyses; for example, the cost of melphalan plus prednisolone/prednisone (MP) varies between £1365 for the Celgene submission to £54,434 for the Janssen-Cilag submission. The costs from the Celgene analysis were lower because they did not include any subsequent treatment costs, whereas the Assessment Group's analysis included costs for second-line treatment and the Janssen-Cilag analysis included costs for second- and third-line treatment.

Table 20: Comparison of costs from Assessment Group and manufacturer's economic models

	Analysis	Total cost	Total QALY	Incremental cost	Incremental QALY	ICER £ per QALY
MP	Assessment Group	£21,555	2.42	–	–	–
	Janssen-Cilag	£54,434	2.86	–	–	–
	Celgene	£1,365	2.43	–	–	–
MPT	Assessment Group	£32,762	3.64	£11,207	1.22	£9,174
	Janssen-Cilag	£59,322	3.41	£4,888	0.55	£8,912
	Celgene	£21,133	3.28	£19,768	0.85	£23,381
VMP	Assessment Group	£57,304	3.62	£35,749	1.20	£29,837
	Janssen-Cilag	£66,676	4.03	£12,242	1.17	£10,498
	Celgene	£42,616	3.35	£41,251	0.92	£44,838
CTDa	Assessment Group	£30,147	2.68	£8,592	0.26	£33,216
	Janssen-Cilag	£56,668	3.07	£2,234	0.21	£10,905
	Celgene	–	–	–	–	–

CTDa – cyclophosphamide, thalidomide plus attenuated dexamethasone; ICER – incremental cost effectiveness ratio; MP – melphalan and prednisolone/prednisone; MPT – melphalan and prednisolone/prednisone plus thalidomide; QALY – quality-adjusted life-year; VMP – bortezomib plus melphalan and prednisolone/prednisone

The incremental costs for melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP) vary between £4888 (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 bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (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 Assessment Group and Celgene economic evaluations. The incremental costs for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP)vary between £2234 (Janssen-Cilag) and £8592 (Assessment Group) and these differences are due to an error in the cost calculation for third-line therapy for cyclophosphamide, thalidomide plus attenuated dexamethasone (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 melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP) vary widely. These differences are due to the estimates chosen for the hazard ratio for overall survival compared with melphalan plus prednisolone/prednisone (MP). The incremental QALY estimates for melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP) range from 0.55 (Janssen-Cilag) to 1.22 (Assessment Group).

Within the submissions there were differences in the way adverse events were modelled:

- Janssen-Cilag: adverse events are included in the model as the cost of treating them; the incidence of adverse events does not influence the treatment duration, efficacy or patient utility.
- Celgene: adverse events 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 overall survival, or treatment duration, efficacy or dose.
- Assessment Group: adverse events are not modelled explicitly in the model for patient outcomes, that is, overall survival and progression-free survival, but are included as additional cost for treating the adverse events in the model.

The submissions also varied in their inclusion of costs after first-line treatmentin their analyses:

- Janssen-Cilag: second- and third-line treatments costs were included. Most people who received bortezomib plus melphalan and prednisolone/prednisone (VMP) as first-line received cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) as second-line treatment and most who did not receive bortezomib plus melphalan and prednisolone/prednisone (VMP) as first-line treatment received it as second-line.
- Celgene: patients were assumed to discontinue first-line treatment upon disease progression with no second- and third-line treatments costs included.
- Assessment Group: costs were included for second-line treatments. Most people who received bortezomib plus melphalan and prednisolone/prednisone (VMP) as first-line treatment received cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) as second-line treatment and most who did not receive bortezomib as first-line treatment received it as second-line.

The different assumptions and methodology described above result in a range of estimates for the cost effectiveness of the treatment options. The ICER for

melphalan and prednisolone/prednisone plus thalidomide (MPT) versus melphalan plus prednisolone/prednisone (MP) varies between £9174 (Assessment Group) and £23,381 (Celgene) per QALY gained. The ICER for bortezomib plus melphalan and prednisolone/prednisone (VMP) versus melphalan plus prednisolone/prednisone (MP)varies between £10,498 (Janssen-Cilag) and £44,838 (Celgene) per QALY gained. The ICER for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) versus melphalan plus prednisolone/prednisone (MP) varies between £10,905 (Janssen-Cilag) and £33,216 (Assessment Group) per QALY gained.

4 Issues for consideration

4.1 Clinical effectiveness

- What is the Committee's view on the appropriateness of including patients on thalidomide maintenance in the analysis?
- What is the Committee's view on the appropriateness of the data available for cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa)?
- What is the Committee's view on the inclusion of additional data from the MMIX trial for the patients randomised to receive no maintenance treatment to derive PFS, OS and TTP estimates?
- What is the Committee's view on the variable selection of studies? (e.g. the exclusion of other survival outcomes data from Palumbo, Wijermans and Gulbrandsen)
- What is the Committee's view on the appropriateness of a meta-analysis of MPT vs MP (is this possible given the data)?
- Does the Committee feel that the participants in the study investigating CTDa are representative of the UK population?

4.2 Cost effectiveness

- What is the Committee's view on the most appropriateness source of utilities for the patient group under consideration?

- What is the Committee's view on the use of dose and duration of therapy data from trials as opposed to clinical practice, as well as the average number of vials used?
- Do the Committee members think that the analyses should consider the potential for vial sharing?
- Do the committee members consider that analyses/costs after first-line treatment should be considered?
- Does the Committee think that only including second-line treatment costs lead to a bias against the more expensive treatment arm?
- What is the Committee's view on the appropriateness of not adjusting utility values for adverse events?
- What is the Committee's view on appropriateness of extrapolating the trial data and of the method for modelling this extrapolating?
- What is the committee's view on the appropriateness of using average hazard rates and ratios, and not adjusting hazard ratios based on trial population characteristics?
- Do the Committee feel that uncertainty in the models presented was sufficiently explored?
- What do the Committee consider to be the main clinical and cost-effectiveness drivers in the models?

5 Ongoing research

One NICE technology appraisal is in development, 'Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma', but the expected date of issue is not until January 2012.

The clinical effectiveness search for studies conducted by the Assessment Group identified seven abstracts and two ClinicalTrials.gov records which described four ongoing studies, each comparing MPT with MP. It was not clear to the Assessment Group whether these studies meet the inclusion criteria of this systematic review (see page 80 of the Assessment Report).

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- J Picot, K Cooper, J Bryant, AJ Clegg. The clinical and cost-effectiveness of bortezomib and thalidomide for the first-line treatment of multiple myeloma. Health Technology Assessment 2010.

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Celgene
- Janssen-Cilag

II Professional/specialist, patient/carer and other groups:

- Myeloma UK Leukaemia CARE Macmillan Cancer Support
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Myeloma Forum

C Additional references used:

1. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study. European Journal of Cancer 2004;40:1159-69.
2. Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with

cancer, especially that attributable to cancer treatment. Health Technol Assess 2007;11:1-iv.

3. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. Value Health 2009.
4. McKenzie L, van der PM. Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. Value Health 2008.
5. Wijermans P, Schaafsma M, van Norden Y. Melphalan + prednisone vs melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: first interim results of the dutch cooperative group HOVON. Abstract 2008.
6. Waage A, Gimsing P, Juliusson G, Waage A, Gimsing P, Juliusson G. Melphalan-prednisone-thalidomide (MP-T) to newly diagnosed patients with multiple myeloma: a placebo controlled randomized phase 3 trial. Abstract and slide presentation ASH. 2007.