

**Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence**

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**1. Title of the project<sup>a</sup>:**

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

**2. Name of TAR team and 'lead'**

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**3. Plain English Summary<sup>b</sup>**

Multiple myeloma is a type of cancer that occurs when a single white blood cell of a particular type becomes cancerous. The cancer (myeloma) multiplies in bones where there is bone marrow, such as the pelvis, spine, and ribs. Because the myeloma is located at several sites it is known as multiple myeloma.

Multiple myeloma is a rare cancer and there were about 3500 new cases in England and Wales in 2005. Most people who are diagnosed with multiple myeloma are aged between 60 and 65 years. Multiple myeloma is not curable, but can be treated to control the disease for a period of time and limit the symptoms. Usually the disease will become active again (relapse) after treatment. Sometimes the disease does not respond to treatment. The average survival of people with multiple myeloma is between 4 and 6 years.

The initial treatment upon diagnosis of multiple myeloma depends on their age and general health. Elderly patients and those patients who are not well enough to withstand the most aggressive type of treatment (high-dose chemotherapy plus bone marrow transplant using the patient's own cells) are given less intensive chemotherapy using one drug or a combination of drugs. Common first-line drugs used to treat multiple myeloma include an alkylating agent, such as melphalan or cyclophosphamide, in combination with a corticosteroid, such as prednisolone or

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<sup>a</sup> this will be used for the National Research Register and will appear on the HTA Programme website

<sup>b</sup> initially this will be used on the HTA Programme website, but it is anticipated that, in the near future it will also be required for use in the National Research Register

dexamethasone. Recently other drugs, either bortezomib (Velcade) or thalidomide, have been added to the alkylating agent and corticosteroid combination.

This review will systematically summarise the results of clinical trials which evaluate the use of bortezomib or thalidomide in combination with an alkylating agent and corticosteroid compared with melphalan or cyclophosphamide in combination with prednisolone or dexamethasone. The report will include a systematic review of existing cost-effectiveness studies and an independent economic evaluation will be undertaken to estimate of the cost-effectiveness of bortezomib and thalidomide for first-line treatment of multiple myeloma.

#### **4. Decision problem<sup>c</sup>**

The aim of this health technology assessment is to 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 multiple myeloma (MM).<sup>1</sup>

Initial treatments for patients with MM depend on factors such as age and performance status. Guidelines on the diagnosis and management of multiple myeloma 2005<sup>2</sup> state that “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.” Therefore for the majority of patients therefore where high-dose therapy is not planned, and the treatment recommended by the guidelines is either melphalan or cyclophosphamide given either with or without prednisolone. Since the publication of these guidelines marketing authorisations have been granted for the use of bortezomib<sup>3</sup> (Velcade, Janssen-Cilag) in combination with melphalan and prednisolone for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant, and for the use of thalidomide<sup>4</sup> (Thalidomide Pharmion, Celgene) in combination with melphalan and prednisolone as first-line treatment of patients with untreated MM, aged  $\geq 65$  years or ineligible for high-dose chemotherapy. Bortezomib and thalidomide may also be used in clinical practice in combination with other alkylating agents and corticosteroids although these combinations are not licensed.

#### **4.1. Background**

##### **Multiple Myeloma**

MM is a type of cancer that occurs when a single plasma cell (a type of white blood cell) in bone marrow becomes cancerous and begins to multiply. 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. As the abnormal myeloma cells build in number, space is reduced for the normal functions of bone marrow such as making normal white blood cells, red blood cells and platelets. Normal white blood cells produce a variety of antibodies to fight infections. Myeloma cells however produce large amounts of one type of abnormal antibody that does not function properly and does not help to fight infections. The lack of normal white blood cells means that people with MM are more susceptible to infections and less able to fight them off. Furthermore, the lack of red blood cells and platelets can

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lead to anaemia and problems with blood clotting respectively. Other symptoms that patients may experience include bone pain, bone fractures, fatigue, hypercalcaemia and kidney problems.<sup>1,5</sup>

### **Epidemiology**

Approximately 3500 new cases of MM were diagnosed in England and Wales in 2005.<sup>1</sup> The most common age at which MM is diagnosed is between the ages of 60 and 65 years; MM is rare before the age of 40. The incidence of MM is about 1.5 times as common in males as it is in females, and it is twice as common in black people than it is in white people.<sup>1,6</sup>

### **Prognosis**

MM is an incurable disease with an average survival of 4-6 years. A number of factors affect prognosis including age, stage of disease at diagnosis, which treatments are suitable for a particular patient, and how the MM responds to treatment. The aim of treatment is to alleviate symptoms and achieve disease control whilst minimising the adverse effects of the treatment.<sup>1</sup> 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.

### **Diagnosis & Staging**

MM is diagnosed in secondary care using a combination of tests such as urine tests, blood tests, bone marrow tests, and X-ray results. If necessary further tests can be conducted to find out the stage of disease which will help to determine the most appropriate treatment.<sup>5</sup> There are two systems for staging MM The Durie-Salmon staging system, and the International Staging System.<sup>2</sup>

### **Current Treatment options**

In the current management of MM<sup>2</sup> the choice of first-line treatment depends on a combination of factors including age and performance status of the patient. For suitable patients, high-dose chemotherapy (HDT) with autologous stem-cell transplantation will be offered. Where this is not a suitable treatment option, single agent or combination therapies may be offered. Combination therapies include chemotherapy with alkylating agents (such as melphalan or cyclophosphamide) and corticosteroids (such as prednisolone or dexamethasone), and more recent treatment options include drugs such as thalidomide<sup>7-9</sup> and bortezomib.<sup>10</sup> After first-line treatment patients usually experience a remission, but almost all patients will eventually relapse. Some patients will have disease which does not respond to treatment. Side effects of treatment such as peripheral neuropathy may result in discontinuation of treatment.<sup>11</sup>

In addition to chemotherapy patients also require concomitant 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 necessary in some patients receiving thalidomide.<sup>11</sup>

Newer treatment options are being investigated in ongoing clinical trials such as the MRC funded Myeloma IX study which is comparing thalidomide in combination with

cyclophosphamide and dexamethasone against the standard drug combination of melphalan with prednisolone.

#### **4.2. Definition of the Intervention**

Two interventions are being considered in this assessment,<sup>1</sup> bortezomib in combination therapy with an alkylating agent and a corticosteroid, and thalidomide in combination therapy with an alkylating agent and a corticosteroid. The interventions as stated above allow 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 thalidomide in combination with cyclophosphamide and dexamethasone.

Bortezomib is a proteasome inhibitor which is specific for the 26S proteasome of mammalian cells and it has been specifically 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.<sup>3</sup>

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.<sup>4</sup>

Details of treatment from the summary of product characteristics (SPC) are shown in Appendix 8.1.

#### **4.3. Place of the Intervention in the treatment pathway**

Bortezomib in combination with melphalan and prednisolone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. Thalidomide in combination with melphalan and prednisolone is indicated for the first-line treatment of patients with untreated MM, aged  $\geq 65$  years or ineligible for high-dose chemotherapy.

#### **4.4. Comparators**

Bortezomib or thalidomide in combination with an alkylating agent (e.g. melphalan or cyclophosphamide) and a corticosteroid (e.g. prednisolone or dexamethasone) will be compared with each other. Bortezomib or thalidomide regimens will also be compared with melphalan or cyclophosphamide in combination with prednisolone or dexamethasone.

#### **4.5. Population and relevant sub-groups**

The population under consideration is that described above in section 3.3. If sufficient evidence is available consideration will be given to the following patient subgroups:

- according to disease severity
- by cytogenetic features of MM
- according to the presence of comorbidities such as renal impairment

Additionally, if the evidence allows, consideration will be given to the number of treatment cycles and continuation rules for treatment.

#### **4.6. Outcomes**

Clinical outcomes will include: overall survival, progression-free survival, time to progression, response rates, health-related quality of life and adverse effects of treatment. Direct costs will include estimates of health care resources associated with the interventions as well as consequences of the interventions, such as treatment of adverse events.

### **5. Report methods for synthesis of evidence of clinical and cost-effectiveness**

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'.<sup>12</sup>

#### **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 is shown in Appendix 8.2. This will be adapted for other databases. Literature will be identified from several sources including electronic databases (listed in Appendix 8.2), 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<sup>13</sup> and earliest description of bortezomib as a potential cancer therapy<sup>14</sup>) 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:

	<p>Melphalan or cyclophosphamide in combination with prednisolone or dexamethasone</p> <p>(Other chemotherapy regimens or stem cell transplantation will not be included)</p>
Outcomes	<p>Studies will be included if they report on one or more of the following outcomes:</p> <p>overall survival  progression-free survival  time to progression  response rates  health-related quality of life  cost-effectiveness (such as incremental cost per QALY gained)</p> <p>Adverse effects of treatment will be reported if available within the trials that meet the inclusion criteria.</p>
Design	<p>The following types of study will be eligible for inclusion:</p> <p>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.</p> <p>Economic evaluations (such as cost-effectiveness studies, cost utility studies, cost benefit studies)</p> <p>(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)</p>

### **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 (see Appendix 8.3) 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.<sup>12</sup> Methodological quality of economic evaluations will be undertaken based on recognised criteria for appraising economic evaluations.<sup>15,16</sup> 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.

### **6. 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. Methods for the review are described in section 4.

### **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.<sup>17,18</sup> The perspective will be the NHS and Personal Social Services (PSS). Costs and benefits will be discounted using standard rates (3.5%).<sup>17</sup> 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<sup>19</sup>). 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.<sup>20</sup> 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.

## **7. 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.



**8. Competing interests of authors**

None.

**9. Appendices****9.1. Treatment details from the summary of product characteristics (SPC)****Bortezomib (Velcade) in combination with melphalan and prednisone**

The SPC for bortezomib<sup>3</sup> recommends nine 6-week treatment cycles for combined therapy with bortezomib, melphalan and prednisone (Table 1).

Bortezomib: 1.3 mg/m<sup>2</sup> body surface area administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. Cycles 1-4 Bortezomib administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, Bortezomib is administered once weekly (days 1, 8, 22 and 29)

Melphalan: 9 mg/m<sup>2</sup> administered orally on days 1, 2, 3 and 4 of the first week of each cycle.

Prednisone: 60 mg/m<sup>2</sup> 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.

Table 1: Recommended dosages for bortezomib in combination with melphalan and prednisone for patients with previously untreated MM.<sup>3</sup>

<b>CYCLES 1 to 4: Bortezomib administered twice weekly</b>												
WEEK	1				2		3	4		5		6
B (1.3 mg/m <sup>2</sup> )	Day 1	--	--	Day 4	Day 8	Day 11	RP	Day 22	Day 25	Day 29	Day 32	RP
M (9 mg/m <sup>2</sup> )	Day 1	Day 2	Day 3	Day 4	--	--	RP	--	--	--	--	RP
P (60 mg/m <sup>2</sup> )												
<b>CYCLES 5 to 9: Bortezomib administered once weekly</b>												
WEEK	1				2		3	4		5		6
B (1.3 mg/m <sup>2</sup> )	Day 1	--	--	--	Day 8		RP	Day 22		Day 29		RP
M (9 mg/m <sup>2</sup> )	Day 1	Day 2	Day 3	Day 4	--		RP	--		--		RP
P (60 mg/m <sup>2</sup> )												

B – Bortezomib; M – Melphalan; P – Prednisone; RP – Rest Period

**Thalidomide (Thalidomide Pharmion) in combination with melphalan and prednisone**

Thalidomide Celgene must be prescribed and dispensed according to the Thalidomide Celgene Pregnancy Prevention Programme. The SPC for thalidomide<sup>4</sup> recommends an oral dose of 200 mg per day, taken as a single dose at bedtime to reduce the impact of somnolence. A maximum number of 12 cycles of 6 weeks should be used.

Thromboprophylaxis should 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.

## 9.2. Search strategy

Sources of information for the clinical and cost-effectiveness searches will include:

Electronic databases including MEDLINE, EMBASE, Science Citation Index, BIOSIS, DARE, the Cochrane library; NHSEED

Grey literature and recent conference proceedings;

Contact with individuals with an interest in the field;

Bibliographies of related papers;

Research in progress databases: NIHR CRN Portfolio, Current Controlled Trials (CCT), Clinical trials.gov.

Draft Search Strategy for Medline:

Below is an example of a search strategy for bortezomib studies. This illustrative Medline strategy will be broadened to include combination chemotherapy regimens of bortezomib or thalidomide with an alkylating agent and a corticosteroid. The strategy will then be adapted for use with other databases.

- 1 Multiple Myeloma/
- 2 exp Plasmacytoma/
- 3 exp Paraproteinemias/
- 4 (myeloma\$ or (multiple adj myeloma\$) or plasmacytom\$ or plasmocytom\$ or MGUS or (monoclonal adj gammopathy)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 5 1 or 2 or 3 or 4
- 6 (bortezomib or Velcade or ps341 or ps-341 or (ps adj '341') or (proteasome adj inhibit\$5)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 7 5 and 6
- 8 randomized controlled trial.pt.
- 9 controlled clinical trial.pt.
- 10 randomized controlled trials/
- 11 random allocation/
- 12 double-blind method/
- 13 single-blind method/
- 14 exp evaluation studies/
- 15 exp clinical trials/
- 16 clinical trial.pt.
- 17 (clin\$ adj5 trial\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19 ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
- 20 exp placebos/
- 21 placebo\$.tw.

## Final Protocol

- 22 random\$.tw.
- 23 exp research design/
- 24 19 or 20 or 21 or 22 or 23
- 25 18 or 24
- 26 limit 25 to human
- 27 7 and 26
- 28 limit 27 to (humans and english language)

### 9.3. Data extraction form – Generic Example

Reference and Design	Intervention	Participants	Outcome measures
Author:	Intervention:	Number of Participants:	Primary outcomes:
Year:	Control:	Intervention:	Secondary outcomes:
Country:		Control:	
Study design:	Other interventions used:	Sample attrition/dropout:	Method of assessing outcomes:
Number of centres:		Sample crossovers:	
Recruitment dates:		Inclusion criteria for study entry:	Adverse events:
Funding:		Exclusion criteria for study entry:	Length of follow-up:
		Characteristics of participants:	
<b>Results</b>			
Primary Outcomes	Intervention	Control	P Value
Comments:			
Secondary outcomes	Intervention	Control	P value
			P=0.87
Comments:			
Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE			

**Methodological comments**

Allocation to treatment groups:

Blinding:

Comparability of treatment groups:

Method of data analysis:

Sample size/power calculation:

Attrition/drop-out:

General comments

Generalisability:

Outcome measures:

Inter-centre variability:

Conflict of interests:

**10. References**

Reference List

1. National Institute for Health and Clinical Excellence. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. Final scope. 2009.
2. Smith A, Wisloff F, Samson D, UK MF, Nordic Myeloma Study Group, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. *British Journal of Haematology* 2006;132:410-51.
3. Summary of Product Characteristics for Velcade. 2009. European Public Assessment Report No. Revision 17 - Published 20/04/09
4. Summary of Product Characteristics for Thalidomide Celgene. 2009. European Public Assessment Report No. Revision 2 - Published 16/04/09
5. Cancer Research UK. Myeloma. CancerHelp UK  
<http://www.cancerhelp.org.uk/help/default.asp?page=4746> (accessed 28 May 9 A.D.)
6. Cancer Research UK. UK Multiple Myeloma statistics. Cancer Statistics  
<http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/?a=5441> (accessed 28 May 9 A.D.)
7. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial.[see comment]. *Lancet* 2007;370:1209-18.
8. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial.[see comment]. *Lancet* 2006;367:825-31.
9. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V *et al.* Oral melphalan, prednisone, and thalidomide in elderly patients with multiple

- myeloma: updated results of a randomized controlled trial.[see comment]. *Blood* 2008;112:3107-14.
10. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.[see comment]. *New England Journal of Medicine* 2008;359:906-17.
  11. Richardson PG, Mitsiades C, Schlossman R, Munshi N, Anderson K. New drugs for myeloma. *The Oncologist* 2007;12:664-89.
  12. CRD. Systematic Reviews. CRD's guidance for undertaking reviews in health care. 2009.
  13. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P *et al.* Antitumor activity of thalidomide in refractory multiple myeloma.[see comment][erratum appears in N Engl J Med 2000 Feb 3;342(5):364]. *New England Journal of Medicine* 1999;341:1565-71.
  14. Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. The proteasome inhibitor PS-341 in cancer therapy. *Clinical Cancer Research* 1999;5:2638-45.
  15. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. 2006.
  16. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275-83.
  17. NICE. Guide to the methods of technology appraisal. *NICE, London* 2004.
  18. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:iii-xi, 1.
  19. Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV *et al.* Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004;79:867-74.
  20. Curtis L. Unit costs of health and social care. University of Kent, Canterbury: Personal Social Services Research Unit; 2008.