NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Chemotherapy acronyms

A number of acronyms are used throughout the manufacturer's submission, ERG report and premeeting briefing and these are defined here for clarity.

Bortezomib (Velcade) + dexamethasone	**VD**
Bortezomib (Velcade) +thalidomide + dexamethasone	**VTD**
Thalidomide + dexamethasone	**TD**
Cyclophosphamide + thalidomide +dexamethasone	**CTD**
Bortezomib (Velcade) + adriamycin+ dexamethasone	**PAD**
Vincristine +adriamycin + dexamethasone	**ViAD**

Key issues for consideration

- Bortezomib is indicated in combination for with thalidomide and dexamethasone (VTD), and in combination with dexamethasone (VD) for the induction therapy in people with multiple myeloma before high dose chemotherapy and autologous stem cell therapy.

- The manufacturer submitted data to NICE for 3 bortezomib regimens, VTD, VD and PAD. The final marketing authorisation granted in August 2013, only includes the VTD and VD regimens and so the PAD regimen is not a licensed regimen.
- The final marketing authorisation stipulates a discontinuation rule for VTD, where 4 cycles are received and upon at least a partial response, 2 more cycles can be administered. Subsequently, the manufacturer provided an addendum which included updated data for the VTD regimen taking into account the impact of the discontinuation rule.
- The manufacturer compared VTD with TD rather than CTD, the most commonly used induction therapy in the UK, assuming equivalence between TD and CTD.
- The manufacturer stated that a comparison of the VD regimen with a thalidomide containing regimen was not possible, and presented results comparing VD with ViAD instead. The manufacturer and the ERG both stated that ViAD is no longer used in clinical practice. Does the Committee consider that ViAD is an appropriate comparator?
- The manufacturer highlighted in its original submission that the main assumption underpinning the mixed treatment comparison was that CViAD and ViAD are clinically equivalent and that TD and CTD are clinically equivalent. The manufacturer's addendum subsequently stated a network could not be formed and an indirect comparison with CTD was not possible.

Cost effectiveness

- The ERG suggested that in the VTD versus TD model, post-induction rates from the Pethema trial are extrapolated to overall survival using data from the MRC Myeloma VII trial. However, the noted that the MRC VII survival data are categorised by maximal response to treatment which is more similar to post-stem cell transplant than post-induction response. The ERG's exploratory analysis uses post-stem cell transplant response from Pethema to provide a more consistent fit to the MRC VII data.
- The manufacturer's model extrapolated level of response after induction therapy to long term survival and time to progression using data from the MRC VII trial.

The ERG commented that the MRC VII trial is reasonably old and survival may be poorer than would be achieved currently. The ERG conducted scenario analyses using alternative data which may be more reflective of current survival.

- The ERG noted that many of the costs (drug; intervention; 2nd line treatment; 3rd line treatment; and monitoring costs) in the manufacturer's revised economic model are different from those in the original model and that these changes were not documented. In particular, the administration costs for high dose dexamethasone increased from £168 to £1,242 in 2nd line therapy, and from £168 to £1,288 in 3rd line therapy. What is the Committee's view on the appropriateness of these changes?
- One of the assumptions regarding the discontinuation rule was that patients in the Pethema trial who achieved at least partial response and received 5 or 6 cycles of VTD would have achieved at least partial response after the 4th cycle, and thus, even with the discontinuation rule, would have continued treatment with VTD beyond the 4th cycle. Is this assumption appropriate?

1 Background: clinical need and practice

1.1 Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells build up in the bone marrow and interfere with the production of normal blood cells, which are responsible for blood clotting, carrying oxygen around the body and fighting infections. They also have the ability to spread throughout the bone marrow and into the hard outer casing of the bone. The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

1.2 About 4300 people were diagnosed with multiple myeloma in England and Wales in 2009. It is most frequently diagnosed in people over 60 years.

Average survival for people with multiple myeloma is between 4 and 6 years, but can be up to 20 years. The 5-year survival rate for adults with multiple myeloma in England is estimated to be 37.1%. Factors affecting survival and outcome include burden of disease, type of cytogenetic abnormality, age and performance status, and response to treatment. In 2008, approximately 820 autologous stem cell transplants were conducted in the UK for people with multiple myeloma. The manufacturer estimated that in 2013 661 people newly diagnosed with multiple myeloma will be eligible for high dose therapy with stem cell transplant (HDT-SCT) in England and Wales. Of these, the manufacturer anticipates that approximately 33% of patients will receive a bortezomib-based induction regimen (see section 2.2 of the manufacturer's submission).

1.3 Multiple myeloma is an incurable disease. The aim of induction therapy is to achieve stable disease for as long as possible, thereby prolonging survival and maximising quality of life. First-line treatment with high-dose chemotherapy (usually melphalan) followed by stem cell transplantation may be considered for people in good general health. Induction therapy is given before high-dose chemotherapy with an aim to induce high remission rates rapidly and to preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells. After induction therapy, haematopoietic stem cells are harvested and these stem cells are reintroduced to the patient's blood (autologous stem cell transplant) following chemotherapy. This enables the bone marrow to recover quickly, so it can produce healthy blood cells again. Decisions regarding the most appropriate induction treatment require assessment of factors such as renal function, thrombotic risk and pre-existing neuropathy. NICE has not made any recommendations for induction therapies for in the treatment of multiple myeloma.

2 The technology

2.1 Bortezomib (Velcade, Janssen-Cilag) is an anticancer drug that works by reversible proteasome inhibition. By inhibiting proteasomes (multi-enzyme complexes present in all cells), bortezomib interferes with the cell cycle leading to cell death. It is administered by intravenous infusion. Bortezomib has a UK marketing authorisation 'in combination with dexamethasone (VD) or with dexamethasone and thalidomide (VTD) for the induction treatment of adult patients with previously untreated multiple myeloma, eligible for high-dose chemotherapy with haematopoietic stem cell transplantation'.

2.2 The summary of product characteristics lists the following adverse reactions for bortezomib: nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of bortezomib is £762.38 per 3.5 mg vial (excluding VAT; British National Formulary [BNF] online, May 2013). According to the marketing authorisation bortezomib should be given in combination with dexamethasone (VD – 4 cycles of 21 days) or with dexamethasone and thalidomide (VTD – 4 cycles of 28 days; 2 additional cycles of 28 days for patients with at least partial response after the 4th cycle). Four injections of bortezomib are administered per cycle, on days 1, 4, 8 and 11 of each cycle. The cost of a course of treatment with bortezomib in combination with dexamethasone is estimated to be £12,260.91 and the cost of a course of treatment with bortezomib in combination with dexamethasone and thalidomide is estimated to be £24,840.10. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of bortezomib within its licensed indication for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with newly diagnosed multiple myeloma for whom induction therapy is considered appropriate prior to high dose chemotherapy and autologous stem cell transplantation	As per final scope

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Bortezomib in combination with other chemotherapy regimens for induction therapy.	- Bortezomib in combination with dexamethasone (VD) for 4 cycles of 21 days each - Bortezomib in combination with thalidomide and dexamethasone (VTD) for 4 cycles of 28 days each; 2 additional cycles of 28 days for patients with at least partial response after the 4th cycle.

The manufacturer highlighted that bortezomib in combination with vincristine, carmustine, melphalan, cyclophosphamide and prednisone (VBMCP) and in combination with vincristine, carmustine, doxorubicin and dexamethasone (VBAD) is not reported in the submission as this combination is not licensed.

The manufacturer originally submitted evidence for three 3 bortezomib-containing regimens: VTD, VD and PAD. However, marketing authorisation was received only for the VTD and VD regimens and a discontinuation rule was applied to the VTD as part of the marketing authorisation. Therefore the manufacturer submitted an

addendum that updated the results of the manufacturer's economic evaluation to incorporate the discontinuation rule applied the VTD regimen. The VD regimen was excluded from the base-case analysis because comparison with a thalidomide containing regimen was not possible (as specified in the scope). The manufacturer presented results compared with ViAD, but acknowledged in that this was beyond the scope and also not reflective of clinical practice. The ERG was in agreement.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Comparators	Chemotherapy regimens containing thalidomide.	- The base-case analysis includes a comparison of VTD with TD. -

The manufacturer highlighted that CTD was the main comparator in the scope given its widespread use in UK clinical practice and a mixed treatment comparison was undertaken to compare the bortezomib based regimens with CTD ; however in the absence of head-to-head trials comparing the bortezomib-based regimens with CTD, the relative immaturity of the overall survival data from the pivotal trials as well as the considerable uncertainty underlying the mixed treatment comparison (see section 4.16), an economic evaluation comparing the cost-effectiveness of bortezomib-based regimens compared with CTD was not performed. The manufacturer assumed that TD would be clinically equivalent to TD and the base-case analysis focused on the comparison of VTD with TD. The ERG commented that CTD remained the most appropriate comparator, rather than TD.

The original submission also compared VD with ViAD, but the ERG noted that any comparison with the VAD regimen is outside the scope of the appraisal as it does not contain thalidomide. The manufacturer also highlighted that ViAD is no longer used in UK clinical practice and is therefore not a relevant comparator. The manufacturer confirmed in the addendum that VD cannot be linked with any thalidomide containing regimen and stated that base-case economic evaluation therefore focussed only on VTD compared with TD and an incremental analysis of VD and VTD was not possible.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • progression-free survival • response rate • proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation • overall survival • adverse effects of treatment • health-related quality of life	- Response rate post-induction (primary endpoints in most RCTs) - Response rate post-transplant - Progression-free survival and time to progression - Proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation (HDT-SCT) - Overall survival - Adverse events related to the induction treatment Health-related quality of life was not assessed during the RCTs and therefore data from the published literature is used in the economic model

The manufacturer stated that the response rate post-induction is used as the primary measure of efficacy in the economic model. The ERG commented that the outcomes included in the manufacturer's submission are appropriate and clinically meaningful.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	As per scope

	Final scope issued by NICE	Decision problem addressed in the submission
Subgroups to be considered	If the evidence allows, a subgroup of people with myeloma cell genetic abnormalities should be considered. Guidance will only be issued in accordance with the marketing authorisation	The efficacy of bortezomib-based regimens is reported for the subgroup of patients with high risk cytogenetics. However, no cost-effectiveness analysis was undertaken for this subgroup.

The manufacturer stated that cytogenetic testing performed to identify patients with high risk cytogenetics is not routine clinical practice and it is not routinely funded in the UK. This lack of funding prevents the test from being performed in some areas, and therefore clinicians are generally not able to determine whether a patient is high risk until progression. The manufacturer stated that cost-effectiveness analysis of bortezomib-based regimens in this subgroup of patients is therefore not relevant to UK clinical practice.

The ERG noted that all subgroup analyses were pre-specified but no further methodological details were provided by the manufacturer. The ERG also commented that some subgroup numbers are small and are likely to be underpowered.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of bortezomib-containing treatment compared with thalidomide-based regimens as induction therapy in people with newly diagnosed multiple myeloma before high dose chemotherapy and autologous stem cell transplantation. The manufacturer identified 9 relevant randomised controlled trials (RCTs). Four of these studies were excluded either because the dosing regimen was not appropriate or because both treatment arms contained bortezomib. The manufacturer's submission focused on 4 trials (PETHEMA, Hovon, IFM, GIMEMA). Of these, the

Hovon trial includes the unlicensed PAD regimen the results are presented here but will not be discussed in detail. The manufacturer also included the MRC Myeloma IX trial even though it did not include a bortezomib-based regimen because it was the only study that assessed the effectiveness of cyclosphosphamide, thalidomide, dexamethasone (CTD) which is considered to be the main comparator and relevant to UK clinical practice and was included in a mixed treatment comparison. The details of the regimens and comparators in the identified studies are presented in table 1.

Table 1. Interventions and comparators used in each trial included in the manufacturer's submission.

Trial	**Intervention**	**Comparator**
PETHEMA	Bortezomib, Thalidomide, Dexamethasone (**VTD**)	Thalidomide, Dexamethasone (**TD**)
GIMEMA	Bortezomib, Thalidomide, Dexamethasone (**VTD**)	Thalidomide, Dexamethasone (**TD**)
IFM	Bortezomib, Dexamethasone (**VD**)	Vincristine, Doxorubicin (Adriamycin), Dexamethasone (**ViAD**)
HOVON	Bortezomib, Doxorubicin (Adriamycin), Dexamethasone (**PAD**)	Vincristine, Doxorubicin (Adriamycin), Dexamethasone (**ViAD**)
MRC MMIX	Cyclophosphamide, Thalidomide, Dexamethasone (**CTD**)	Cyclophosphamide, Vincristine, Doxorubicin (Adriamycin), Dexamethasone (**CViAD**)

4.2 The PETHEMA trial was a randomised, open-label phase 3 study that compared the efficacy and safety of bortezomib in combination with thalidomide and dexamethasone (VTD) compared with thalidomide and dexamethasone (TD) in people with newly-diagnosed symptomatic multiple myeloma, and measurable disease (serum and/or urine M protein), who were eligible for autologous stem cell transplantation. Patients were randomised to either VTD (n=130) or TD (n=127) both of which consisted of 6 cycles of 28 days, with each cycle including 4 injections of bortezomib, oral dexamethasone (40 mg on days 1-4 and 8-

11 of each cycle, oral) and thalidomide (50 mg daily, oral). Post transplantation, patients who continued in the trial were re-randomised to receive one of three maintenance treatments (interferon alpha-2b, thalidomide or bortezomib plus thalidomide). Maintenance therapy was continued for up to 3 years, or until disease progression.

4.3 The GIMEMA trial was a randomised, open-label, Phase III study in 480 patients in people with newly diagnosed, previously untreated symptomatic multiple myeloma with measurable disease. The study was designed to compare the efficacy and safety of 3 cycles of VTD compared with 3 cycles of TD as induction treatment prior to autologous stem cell transplantation and to evaluate consolidation thereafter consisting of 2 cycles of either VTD or TD. Maintenance treatment with dexamethasone was continued until disease progression or relapse. Each cycle of induction therapy consisted of 1.3 mg/m^{2}of bortezomib on days 1, 4, 8 and 11, with 100 mg of thalidomide daily for the first 14 days and 200 mg thereafter. 40 mg of dexamethasone was administered on days 1, 2, 4, 5, 8, 9, 11, and 12.

4.4 The IFM was a randomised, open-label study designed to compare the efficacy and safety of VD (with or without intensification with dexamethasone/cyclophosphamide/etoposide or etoposide phosphate/cis-platinum [DCEP]) with ViAD (with or without intensification). Treatment with VD consisted of 4 cycles (1.3 mg/m^{2}of bortezomib and 40 mg of dexamethasone; 4 cycles of 21 days). However, the manufacturer states that the only the results without the intensification step are relevant to the decision problem. Moreover, as discussed previously, the manufacturer stated that this comparison was not in line with the decision problem as ViAD is not a thalidomide containing regimen and therefore not an appropriate comparator. The manufacturer also stated that ViAD is not routinely used in UK clinical practice and excluded this analysis from its base-case analysis.

4.5 The HOVON trial was a randomised, open-label study comparing the efficacy and safety of 3 cycles of bortezomib, doxorubicin (Adriamycin) and dexamethasone (PAD) induction therapy followed by bortezomib maintenance treatment with ViAD induction therapy followed by thalidomide maintenance treatment in multiple myeloma patients. Patients received 2 stem cell transplants prior to maintenance therapy. The PAD regimen does not have a marketing authorisation and NICE cannot make a recommendation for this regimen.

4.6 The MRC Myeloma IX trial compared cyclophosphamide, vincristine, doxorubicin (adriamycin), dexamethasone (CViAD) with CTD in 1,111 patients with newly diagnosed symptomatic myeloma. Patients were randomised to receive induction chemotherapy following either an intensive or non-intensive (attenuated treatment) pathway. In line with the scope of the appraisal, only the intensive pathway of the MRC Myeloma IX trial is considered in the manufacturer's submission. The manufacturer considered that the populations across the trials were broadly similar and there were only minor differences between patient baseline characteristics across these trials. The manufacturer highlighted that patient age was slightly higher in the MRC Myeloma IX trial compared with the bortezomib-based trials (median age of 59 compared with 57). The MRC Myeloma IX trial also included patients over the age of 65, whereas the PETHEMA, GIMEMA, IFM and HOVON trials excluded patients over 65 years of age. These patients typically have a worse prognosis than younger patients. In addition, the MRC Myeloma IX trial included fewer patients with ISS stage I multiple myeloma and a higher proportion of patients at ISS stage III compared with the bortezomib-based trials (baseline characteristics are presented in table 18, page 64 of the manufacturer's submission). Eastern Cooperative Oncology Group (ECOG) performance status was not reported for the GIMEMA and MRC Myeloma IX trials, however, in the PETHEMA trial the VTD arm had a higher proportion of people with ECOG status of 0 (44% versus 32%), but a lower proportion of people with ECOG status of 1 (44% versus 55%) compared with the TD

treatment arm. The manufacturer stated, however, that the trials were very different in many respects including the bortezomib combination regimens, the variable duration of induction, comparator arms and the differences in study design and could therefore not be combined in a meta-analysis.

4.7 The primary outcome measures in the PETHEMA, GIMEMA, IFM and MRC Myeloma IX trials were response rates reported post-induction and post-transplant. The manufacturer's submission reports 'response' in terms of:

- Complete response (CR)
- Near complete response (nCR)
- Very Good Partial Response (VGPR) (not used in the PETHEMA trial)
- Partial response (PR)
- Progressive disease
- Overall response rate (ORR)

Overall response rate is calculated from these measures combined, as the total proportion of patients who achieve partial response or better. All response rates were evaluated using the European Group of Blood and Bone Marrow Transplant (EBMT) criteria and the International Myeloma Working Group uniform criteria. Details of these criteria are presented in section 2.1 of the manufacturer's submission (pages 22 and 23).

4.8 Patients who received bortezomib (VTD) showed a statistically significant difference in the overall response rate post-induction compared with the thalidomide regimen (TD) in both PETHEMA (84.6% versus 61.4%, $p<0.001$) and GIMEMA (93.2% versus 78.6%, $p<0.0001$) trials. This difference in treatment effect on overall response rate was maintained post-transplant ($p<0.001$ and $p<0.0025$, respectively). Patients receiving bortezomib (VTD) in the PETHEMA and GIMEMA also showed statistically higher post-induction and post-transplant complete response

rates than the thalidomide containing regimen (TD). In the PETHEMA trial, 35.4% in the VTD treatment group demonstrated a post-induction complete response compared with 13.4% in the TD group ($p<0.001$). In the GIMEMA trial 18.6% demonstrated a post-induction complete response in the VTD treatment group compared with 4.6% in the TD group ($p<0.0001$). In the post-transplant period, statistically significant differences were maintained for the VTD treatment groups in both the PETHEMA and GIMEMA trials ($p<0.001$ and $p=0.0004$ respectively). Both the PETHEMA and GIMEMA trials reported a statistically significant lower proportion of patients experiencing disease progression when treated with VTD compared with patients treated with TD induction therapy in the post-induction period (6.2% and 23.6% $p=0.0004$ in the PETHEMA trial; and 0% and 5.0%, $p<0.0005$ in the GIMEMA trial).

Table 2. Response rates post-induction and post-transplant from the PETHEMA, GIMEMA, and IFM trials

Study name	Induction regimen	% (n/N)	P value	% (n/N)	P value
		ORR post-induction		**ORR post-transplant**	
Pethema	VTD	**84.6 (110/130)**	**<0.001**	**77.7 (101/130)**	**<0.001**
	TD	**61.4 (78/127)**		**56.7 (72/127)**	
Gimema	VTD	**93.2** (220/236)	**<0.0001**	**93.2 (220/236)***	**0.0025**
	TD	**78.6** (187/238)		**84.5 (201/238)***	
IFM	VD	**77.1 (185/240)**	**<0.001**	79.6 (191/240)	0.179
	ViAD	**60.7 (147/242)**		74.4 (180/242)	
		CR post-induction		**CR post-transplant**	
Pethema	VTD	**35.4 (46/130)**	**<0.001**	**46.9 (61/130)**	**<0.001**
	TD	**13.4 (17/127)**		**23.6 (30/127)**	
Gimema	VTD	**18.6 (44/236)**	**<0.0001**	**37.7 (89/236)***	**0.0004**
	TD	**4.6 (11/238)**		**22.7 (54/238)***	
IFM	VD	**5.4 (13/240)**	**0.010**	**18.3 (44/240)**	**0.011**
	ViAD	**1.2 (3/242)**		**10.3 (25/242)**	
		Near CR post-induction		**Near CR post-transplant**	
Pethema	VTD	13.8 (18/130)	-	8.5 (11/130)	-
	TD	3.9 (5/127)		11.0 (14/127)	
Gimema	VTD	12 (29/236)	-	14 (34/236)*	-
	TD	6 (16/238)		8 (20/1238)*	
IFM	VD	9.2 (22/240)	-	19.2 (46/240)	-
	ViAD	5 (12/242)		12.8 (31/242)	
		VGPR post-induction		**VGPR post-transplant**	
Pethema	VTD	25 (33/130)	-	Not reported	-
	TD	15 (19/127)		Not reported	
Gimema	VTD	31 (73/236)	-	27 (63/236)*	-
	TD	17 (39/238)		27 (63/238)*	
IFM	VD	22.5 (54/240)	-	25.0 (60/240)	-
	ViAD	8.7 (21/242)		21.9 (53/242)	
		Partial response post-induction		**Partial response post-transplant**	
Pethema	VTD	35.4[b] (46/130)	-	22.3 (29/130)	-
	TD	44.1[c] (56/127)		22.0 (28/127)	
Gimema	VTD	31 (74/236)	-	14 (34/236)*	-
	TD	51 (121/238)		26 (64/238)*	
IFM	VD	40 (96/240)	-	17.1 (41/240)	-
	ViAD	45.9 (111/242)		29.3 (71/242)	
		Progressive disease post-induction		**Progressive disease post-transplant**	
Pethema	VTD	**6.2 (8/130)**	**0.0004**	1.5 (2/130)	-
	TD	**23.6 (30/127)**		0.8 (1/127)	
Gimema	VTD	**0.0 (0/**236)	**0.0005**	<1 (1/236)*	-
	TD	**5.0 (12/**238)		7 (17/238)*	
IFM	VD	5.0 (12/240)	-	0.4 (1/240)	-
	ViAD	4.1 (10/242)		0.0 (0/242)	

* GIMEMA trial included 2 autologous stem transplantations in its study design therefore the values presented here are for 'post-1st transplant' for GIMEMA

[a] ORR for PETHEMA is defined as CR+nCR+PR, ORR for GIMEMA is defined as CR+nCR+VGPR+PR

[b] 25% in the trial publication

[c] 33% in the trial publication

Table 3. Response rates post-induction and post-transplant from HOVON and MRC Myeloma IX trials

Study name	Induction regimen	% (n/N)	P value	% (n/N)	P value
		ORR post-induction		**ORR post-transplant**	
Hovon	PAD	**84.2 (351/417)**	**<0.001**	**77.5 (323/417)**	**<0.001**
	ViAD	**61.3 (255/416)**		**65.9 (274/416)**	
MRC MIX	CViAD	**71.2** (396/556)	**<0.0001**	61.3 (341/556)	0.45**
	CTD	**82.5** (458/555)		61.1 (339/555)	
		CR post-induction		**CR post-transplant**	
Hovon	PAD	**11 (46/417)**	**<0.001**	**22.5 (94/417)**	**<0.001**
	ViAD	**2.9 (12/416)**		**12.3 (51/416)**	
MRC MIX	CViAD	**8.1 (45/556)**	**0.0083**	**25.4 (141/556)**	**0.00052****
	CTD	**13.0 (72/555)**		**33.3 (185/555)**	
		Near CR post-induction		**Near CR post-transplant**	
Hovon	PAD	7.2 (30/417)	-	10.1 (42/417)	-
	VAD	3.4 (14/416)		7.5 (31/416)	
MRC MIX	CViAD	-	-	-	-
	CTD	-		-	
		VGPR post-induction		**VGPR post-transplant**	
Hovon	PAD	31.9 (133/417)	-	25.2 (105/417)	-
	ViAD	13.2 (55/416)		19.2 (80/416)	
MRC MIX	CViAD	**19.4 (108/556)**	**0.00003**	**17.1 (95/556)**	0.73**
	CTD	**30.3 (168/555)**		**15.9 (88/555)**	
		Partial response post-induction		**Partial response post-transplant**	
Hovon	PAD	34.1 (142/417)	-	19.7 (82/417)	-
	ViAD	41.8 (174/416)		26.9 (112/416)	
MRC MIX	CViAD	43.7 (243/556)	0.14	**18.9 (105/556)**	**0.0017****
	CTD	39.3 (218/555)		**11.9 (66/555)**	
		Progressive disease post-induction		**Progressive disease post-transplant**	
Hovon	PAD	1.0 (4/417)	-	1.2 (5/417)	-
	ViAD	3.6 (15/416)		2.6 (11/416)	
MRC MIX	CViAD	2.7 (15/556)	0.6	1.6 (9/556)	0.51**
	CTD	3.2 (18/555)		2.2 (12/555)	

**P values compare the two induction regimes within the study using modified patient N as stated in the publication (number of patients who received transplant rather than ITT N; CVAD N=379 ; CTD N=370) Percentages were back calculated from the raw data using ITT N values

Bold text means that data are statistically significant at 0.05 level; ORR= PR or above

'-' indicates that the information was not reported

4.9 The manufacturer stated that because the marketing authorisation for the VTD regimen incorporated a discontinuation rule, additional patient-level analyses were presented in the addendum to evaluate the impact of the discontinuation rule on treatment durations. The manufacturer provided a

breakdown of the number of patients by final post-induction response, and by the total number of cycles they received for both VTD and TD arms of the Pethema trial (Table 4, see also page 15 of manufacturer's addendum). Fewer people received the full 6 cycles of induction therapy in the TD arm than in the VTD arm ([redacted] vs. [redacted]) mainly because discontinuation due to disease progression occurred more frequently in the TD arm than in the VTD arm ([redacted] vs. [redacted]). The manufacturer assumed the TD regimen is not subject to the same discontinuation rule as for VTD. This data was incorporated in the economic evaluation.

Table 4: Post-induction response and number of cycles in the Pethema trial

Final response during trial	**Number of cycles received in VTD arm**						
	1	**2**	**3**	**4**	**5**	**6**	**TOTAL**
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**46**
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**18**
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**46**
MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2**
NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**7**
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**8**
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2**
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1**
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**130**
Final response during trial	**Number of cycles received in TD arm**						
	1	**2**	**3**	**4**	**5**	**6**	**TOTAL**
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**17**
nCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**5**
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**56**
MR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**9**
NC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**7**
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**30**
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1**
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1**
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**126**

4.10 Secondary outcomes reported in the PETHEMA, GIMEMA, IFM and MRC Myeloma IX trials included:

- progression-free survival,

- time to progression (TTP)
- overall survival,
- proportion of patients who underwent stem cell transplantation
- adverse events.

Progression-free survival was measured from the date of randomisation to the date of disease progression or death from any cause, whichever occurred first. Time to progression was calculated from the date of randomisation to the date of disease progression or death due to disease progression. Overall survival was calculated from the date of randomisation to the date of death from any cause for the intention-to-treat populations. Table 5 reports the unadjusted hazard ratios for progression-free survival for the PETHEMA, GIMEMA,. Median follow-up of the trials were 35.9 months (PETHEMA), 36 months (GIMEMA), 33 months (IFM) and 47 months (MRC Myeloma IX). Progression-free survival was longer in the bortezomib (VTD) arm of both the PETHEMA and GIMEMA trials compared to the TD arm, and the difference was statistically significant (PETHEMA hazard ratio [HR] 0.65, 95% CI 0.45 to 0.92, p=0.015; GIMEMA HR 0.63, 95% CI 0.45 to 0.88, p=0.0061).

Table 5. Progression-free survival results (months)

Study name	Induction regimen	ITT N	Median (95% CI; p values NR)	Setting adjustment	HR (95% CI; p value)
Pethema	VTD	130	55.5 (31.2, Not reached)	Unadjusted	**0.65 (0.45, 0.92; p=0.015)**
	TD	127	27.9 (19.8, 34.6)		
Gimema	VTD	236	Not reported	Unadjusted	**0.63 (0.45, 0.88; p=0.0061)**
	TD	238	42 (not reported, not reported)		
IFM	VD	240	36.1 (32.5, 41.1)	Unadjusted Read from survival curve	0.88† (0.70, 1.11; p=NR)
	ViAD	242	29.7 (26.3, 37.2)		
Hovon	PAD	417	34.5 (30.7, 38.3)	Unadjusted with censoring Read from survival curve	**0.82† (0.69, 0.98; p=NR)**
	ViAD	416	28.6 (25.2, 31.8)		
MRC MIX	CTD	555	27** (24, 29)	Unadjusted	0.94 (0.81, 1.09; p=0.56
	CViAD	556	25** (23, 26)		

† Data read from PFS Kaplan-Meier plot

PFS values are without SCT censoring unless otherwise stated

** Per protocol analysis

Bold text indicates that data are statistically significant at 95% confidence level

4.11 The manufacturer's submission reported the median time to progression and time to progression hazard ratios from the PETHEMA and IFM trials. In the PETHEMA study there was a statistically significant lower hazard of progression in patients treated with VTD compared with TD (HR 0.64, 95% CI 0.44 to 0.93, p=0.017). No statistically significant difference in median time to progression was reported.

4.12 The manufacturer's submission reported unadjusted overall survival hazard ratios for the PETHEMA and IFM trials. Median overall survival was not reached in either the PETHEMA or IFM trials and there was no statistically significant difference in the overall survival between the treatment arms in each study (table 6). The manufacturer's submission

highlighted clinical specialist opinion that the duration of the trials were too short to allow differences in overall survival and progression-free survival differences between treatment groups to be sufficiently captured, given the relatively long survival in this patient population following an autologous stem cell transplant.

Table 6. Overall survival results

Study name	Induction regimen	ITT N	Median (95% CI)	Setting	HR (95% CI; p value)
Pethema	VTD	130	55.5 (55.5, not reached)	Unadjusted	0.80 (0.48, 1.34; p=0.393)
	TD	127	Not reached (50.6, not reached)		
IFM	VD	240	Not reached	Unadjusted Read from survival curve	0.8† (0.54, 1.19; p=NR)
	ViAD	242	Not reached		
Hovon	PAD	417	Not reached (63.9, not reached)	Unadjusted Read from survival curve	0.8† (0.62, 1.02; p=NR)
	ViAD	416	Not reached (59.9, not reached)		
MRC MIX	CTD	555	Not reached (61, not reached)	Unadjusted	0.92 (0.75, 1.13; p=0.29)*
	CViAD	556	63* (59, not reached)		

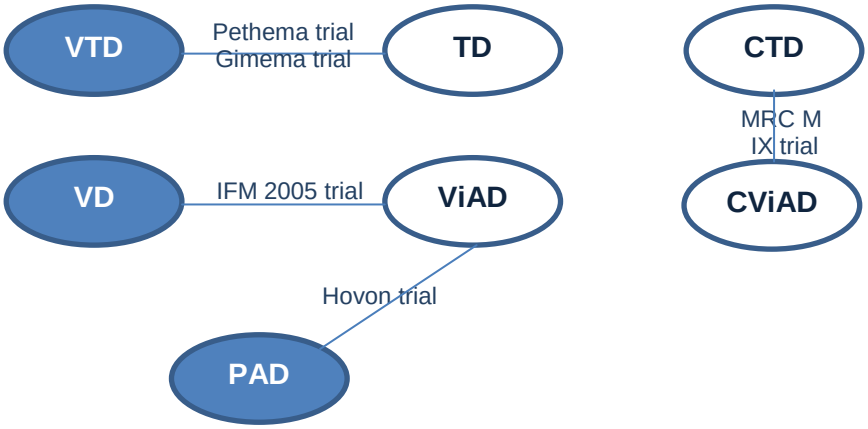
†data read from PFS Kaplan-Meier plot (figure 14B, page 86 of manufacturer's submission)

4.13 The manufacturer's submission presented results for the proportion of patients who, following induction treatment, were able to receive an autologous stem cell transplant although the studies were not powered for this endpoint. The bortezomib-containing arms of the PETHEMA and GIMEMA trials (VTD) reported higher proportions of patients undergoing stem cell transplantation compared with the TD arms (80.8% versus

61.4% in PETHEMA and 88.0% versus 82% in GIMEMA). However, no statistical tests were reported.

4.14 The manufacturer presented subgroup analyses based on cytogenetic risk. Response rates post-induction were available for Pethema and IFM trials, while progression-free survival data were available for the Pethema, Gimema (high risk only) and IFM trials. There was no statistically significant differences between patients treated with VTD or TD for PFS, TTP or OS, with the exception of the high risk group in the Gimema trial where progression-free survival was significantly longer in the VTD group compared with TD (hazard ratio 0.51, 95% confidence intervals 0.29 to 0.88; p=0.0174). Additional subgroup analyses based on age, ISS staging and creatinine clearance are presented in appendix 17 of the manufacturer's submission.

Figure 1. Evidence network of trials used to inform the mixed treatment comparison



= induction regimen stated in the decision problem, = induction regimen not stated in the decision problem

4.15 In the absence of head-to-head trials comparing bortezomib-based regimens with CTD, the manufacturer originally presented a mixed treatment comparison which was based on the PETHEMA, GIMEMA, HOVON, IFM and MRC Myeloma IX randomised controlled trials. The

PAD regimen (used in the HOVON trial) was included in the original submission but the manufacturer considered its inclusion in the MTC to be inappropriate in light of the marketing authorisation. In the addendum, the manufacturer stated that a network could not be formed between the available trials and an indirect comparison with CTD was not possible. In addition, VD could not be linked to a thalidomide containing regimen. The manufacturer highlighted that assumptions to overcome the network limitations would generate considerable uncertainties and unreliable results. The manufacturer stated that an incremental analysis of the 2 licensed bortezomib regimens was therefore also not possible and focussed the base case on the comparison of VTD compared with TD. A brief explanation of the manufacturer's original mixed treatment comparison is presented below (please see page 99 of the manufacturer's submission for further details).

4.16 Figure 1 shows the network diagram of the 5 trials that were available for the mixed treatment comparison in the manufacturer's original submission. In order to link to CTD, the manufacturer assumed that CViAD and ViAD are clinically equivalent and that TD and CTD are clinically equivalent (Section 6.7.3 of the manufacturer's submission). The manufacturer highlighted that this assumption combined with the heterogeneity across the trials means that the results of the mixed treatment comparison should be treated with the caution. The data included in the MTC are summarised in table 7.

Table 7. Overview of the data included in the MTC for TTP and OS

Trial comparison	Data used/ assumption	HR	95% lower bound	95% upper bound	Source
TTP					
PAD vs. ViAD	TTP	0.79	0.66	0.95	Hovon
VD vs. ViAD		0.82	0.63	1.06	IFM
CTD vs. CViAD		0.94†	0.81†	1.09†	MRC MIX
VTD vs. TD		0.64	0.44	0.93	Pethema
VTD vs. TD		0.63†	0.45†	0.88†	Gimema
OS					
PAD vs. ViAD	OS	0.8	0.62	1.02	Hovon

Trial comparison	Data used/ assumption	HR	95% lower bound	95% upper bound	Source
VD vs. ViAD		0.8	0.54	1.19	IFM
CTD vs. CViAD		0.92	0.75	1.13	MRC MIX
VTD vs. TD		0.8	0.48	1.34	Pethema*

4.17 The manufacturer presented the mixed treatment comparison results for time to progression and overall survival in terms of simultaneous assessment ranking of superiority, pairwise comparisons of superiority, and pairwise assessment of hazard ratios. Superiority was demonstrated by a lower hazard ratio (of death). In terms of time to progression, the results (presented in table 35, page 100 of the manufacturer's submission) suggested that VTD had the highest probability of being the most effective treatment (91.0%) and that VTD a probability close to 100% of being superior to CTD. Patients treated with VTD had a significantly lower hazard of progression or death due to progression compared to people treated with CTD. With respect to overall survival, VTD had the highest probability of being the most effective treatment (41.8%), followed by VD (27.7%) and PAD (22.6%), CTD/TD (1.6%) and ViAD/CViAD (0%) (table 37, page 100 of the manufacturer's submission). However, the manufacturer stated in the addendum that a network could not be formed from the available trials in order to directly link between bortezomib-based regimens and CTD, the current standard of care in the UK. The manufacturer also emphasised the considerable uncertainties generated by assuming equivalence between TD and CTD and between ViAD and CViAD, combined with the heterogeneity across the trials, means that the results of the mixed treatment comparison are unreliable.

4.18 The manufacturer presented a summary of results for adverse events for the Pethema, Gimema, IFM and MRC Myeloma IX trials. Only adverse events for the post-induction phase were reported because the adverse events for the post-transplant phase were considered not to be relevant by the manufacturer. Across all trials a similar proportion of patients reported any adverse event, grade 3/4 adverse events, and serious

adverse events in both the bortezomib and comparator treatment arms. However, in the Pethema trial a statistically significantly greater number of total treatment-related adverse events were reported during induction with VTD compared with TD (Relative risk [RR]=1.42; 95% Confidence intervals [CI] 1.17-1.73). In the Gimema trial a statistically significantly greater proportion of patients receiving VTD experienced any grade 3/4 adverse event compared to those receiving TD (RR=1.69; 95% CI 1.36 to 2.08). The two most common treatment-related adverse events in the Pethema trial (pneumonia and peripheral neuropathy) occurred more frequently in the VTD arm compared to the TD arm. The manufacturer's submission highlights that in the four bortezomib-based studies, bortezomib was given through the intravenous route. A subcutaneous formulation of bortezomib was recently approved, and the manufacturer claims that the incidence of peripheral neuropathy is expected to decrease. In terms of tolerability, total withdrawals and withdrawals due to disease progression were statistically significantly less in the VTD arm compared to the TD arm in the Pethema trial (HR 0.51 [95% CI 0.34 to 0.77] and HR 0.45 [95% CI 0.25 to 0.84] respectively)

4.19 No health-related quality of life data were collected in the bortezomib-containing RCTs. For the purposes of the informing the cost effectiveness evidence, the manufacturer conducted a systematic literature search to identify publications relevant to the decision problem in relation to health-related quality of life. See section 6.10 below

ERG Comments

4.20 The ERG stated that the manufacturer's search strategy was clear and comprehensive. The ERG noted that 5 trials were included in the manufacturer's original submission, but highlighted that only two trials (Pethema and Gimema) met the NICE scope and focussed its critique on these trials. This was in line with the manufacturer's addendum. The ERG stated that and both trials were unblinded and therefore at risk of

detection bias. The ERG agreed with the manufacturer that the baseline characteristics were generally similar across the trials. The ERG's clinical expert commented that the trials are fairly representative of patients in the UK, with the exception of ISS stage. The proportion of patients with ISS stage III in both trials (16-25%) is lower than would be seen in clinical practice where around one third of patients have ISS stage III. The ERG also noted that patients in the TD arm of the Pethema trial had a slightly worse Eastern Co-operative Oncology Group (ECOG) performance status than patients in the VTD arm. The TD arm had a higher proportion of patients with an ECOG performance status of 1 (55% TD vs 44% VTD) and a lower proportion of patients with an ECOG performance status of 0 (32% TD vs 44% VTD), while the VTD arm also had a higher proportion of patients with immunoglobulin-G type compared to the TD arm (66.2% vs 58.3% in manufacturer's subbmission but 65% vs 55% in publication). The ERG also highlighted that the Pethema and Gimema trials excluded patients over 65 years which is not reflective of UK clinical practice.

4.21 The ERG commented the manufacturer's submission reported all relevant outcomes from the trials. However, the ERG noted that there was a discrepancy between the primary outcome reported in the manufacturer's submission (complete response +nCR +PR), and the Pethema publication (complete response). The manufacturer stated that it was unclear why the publication had reported the primary outcome differently. In addition, the ERG noted that the Gimema trial did not include strictly ITT analyses as they did not include all randomised patients, but rather only those who received induction treatment. However, the ERG stated that as the number of patients not included in these analyses is small, this is unlikely to have affected the results. It agreed with the manufacturer's view that response rate is an endpoint that can influence prognosis, however the ERG noted that age, ISS stage and type of cytogenetic abnormality are also prognostic factors. The clinical expert consulted by the ERG suggested that although achieving a good post-induction response rate is beneficial to patients, progression-free survival and overall survival are

more important endpoints as these relate to longer-term outcomes post-treatment, which are more meaningful to patients. The ERG commented that overall, the manufacturer's approach to the trial statistics was appropriate and reasonably well reported. However, the ERG commented that long-term outcomes such as progression-free survival and overall survival may be confounded by post-induction consolidation and maintenance therapies which do not reflect current UK clinical practice. The ERG also noted that there is uncertainty in the robustness of the progression-free survival and overall survival results because of the high censoring of data the VTD and TD arms of the Pethema trial (57.7% and 44.9% respectively in the progression-free survival analysis, and 80.0% and 74.8% respectively in the overall survival analysis).

4.22 The ERG expressed concerns over the mixed treatment comparison analysis conducted by the manufacturer. The ERG stated that, to be included in a mixed treatment comparison, trials are required to be homogeneous enough to allow pooling. However, there was inconsistency in the manufacturer's submission as no standard pairwise meta-analysis was presented for reasons of heterogeneity between trials. Therefore, the ERG stated that the homogeneity assumption was not met due to the differences in trial designs and effect modifiers (such as post-induction treatment and follow-up) on the time-to-event outcomes chosen for the mixed treatment comparison. The ERG also stated that the creation of the network relied heavily on assumptions CViAD and ViAD are clinically equivalent, and TD and CTD are clinically equivalent rather than direct evidence through any common comparator. However, the ERG clinical expert stated that this assumption was reasonable in the absence of trial data. Overall, the ERG stated the analysis was flawed because the network was not supported by evidence from trials; andit may not be meaningful to generalise over the set of included studies as they may not be sufficiently similar. Therefore, the ERG emphasised that the results may not be reliable. In addition, the ERG stated that limited data available in terms of the number of trials and missing outcomes further added to the

uncertainty. The ERG noted that the manufacturer had highlighted that the results from the mixed treatment comparison were subject to substantial uncertainty and were therefore not included in the economic modelling. The ERG agreed with this approach.

4.23 The ERG stated that the manufacturer had presented some new data in the addendum on treatment duration in the form of numbers of patients achieving the different levels of post-induction response, as well as progressive disease and death, according to the number of cycles of treatment they received. Data sets were presented for the VTD and TD arms of the Pethema trial only. The ERG stated that it had not been able to check the accuracy of the data as this is commercial in confidence data and the original source of data was not provided.

5 Comments from other consultees

5.1 Professional groups stated that as long as patients can tolerate it, standard treatment for newly diagnosed multiple myeloma is induction chemotherapy, followed by autologous stem cell transplant. It was noted that the most widely used induction regimen in the UK is cyclophosphamide, thalidomide and dexamethasone (CTD) and can be delivered as an oral regimen without the need for intravenous therapy. It was also highlighted that induction regimens such as ViAD are no longer used and have been replaced by more effective thalidomide, bortezomib or lenalidomide containing regimens. In addition, professional groups stated that that induction regimens using thalidomide produced higher response rates, but this had not resulted in longer remission periods. Therefore, bortezomib-containing induction regimens are used increasingly especially when thalidomide is contra-indicated or not tolerated..

5.2 Professional groups stated that bortezomib has been associated with rapid disease control, with a higher proportion of patients proceeding to autologous stem cell transplant and achieving longer progression-free

survival, noting that progression-free survival is the most important outcome at this stage of treatment. Professional and patient groups stated that an important benefit is the increased rate of renal recovery in patients presenting with renal failure who receive bortezomib regimens, when compared with those receiving either thalidomide or lenalidomide. Recovery of renal function has important implications for health resources as well as patient quality of life. The toxicity profile of bortezomib (neuropathy, fatigue and constipation) is broadly similar to that of thalidomide, with the exception of the risk of thrombo-embolic disease with thalidomide. However, bortezomib-related toxicity has been significantly reduced with the use of careful dose adjustment schedules, and the switch to subcutaneous mode of administration..

5.3 Professional groups stated that bortezomib has been in use for many years in the relapsed setting; therefore it is unlikely that any additional education or training resources will be required. They also stated that implementation of bortezomib will reduce the number of patients requiring thromboprophylaxis and the associated burden of anticoagulation monitoring and bleeding complications.

5.4 Patient groups highlighted that myeloma is an incurable, complex and debilitating cancer and its complications include severe bone destruction, bone fractures, fatigue, frequent infection and kidney failure. Patient groups stated that while survival rates for myeloma have historically been poor, the introduction of ‘novel’ drugs such as thalidomide, bortezomib and lenalidomide has transformed the treatment of myeloma and improved both survival and quality of life. However, the complex relapsing and remitting nature of myeloma means that patients require a range of treatment options and clinicians need a degree of flexibility to choose the most appropriate treatment.

6 Cost-effectiveness evidence

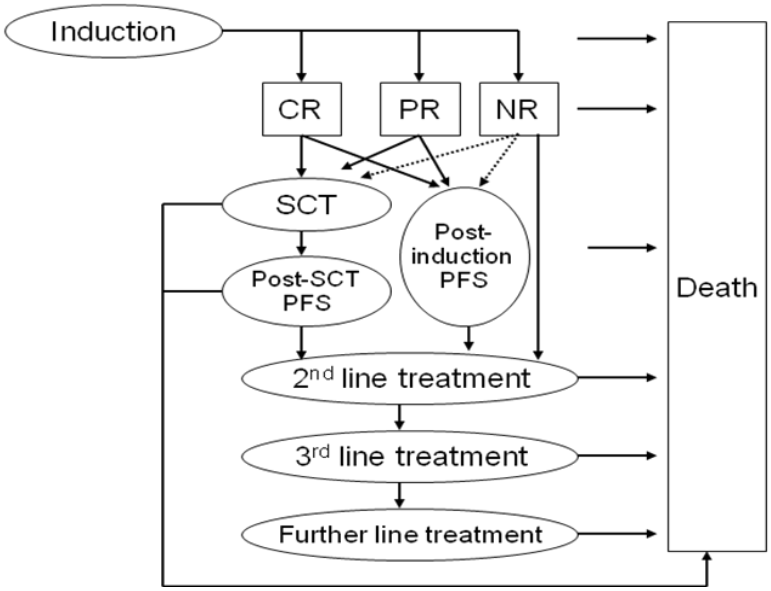
6.1 The manufacturer conducted a systematic search of the literature and identified 3 cost-effectiveness studies relevant to the decision problem. The manufacturer conducted a quality assessment of these studies but did not discuss them further in the submission.

6.2 The manufacturer developed an Excel-based economic model to assess the cost-effectiveness of bortezomib-based regimens compared with thalidomide-based induction regimens. As discussed previously, the manufacturer's base-case analysis focussed on the cost-effectiveness analysis of VTD compared with TD. The revised model in the addendum reflects the discontinuation rule in the marketing authorisation for VTD and this model and results based on it are presented below. In addition, the manufacturer also presented a cost-effectiveness analysis of VD compared with ViAD in the original submission and the results from this are presented briefly below (section 6.17), but this comparison is beyond the NICE scope and the manufacturer also highlighted that ViAD is no longer used in clinical practice. No comparisons of the VD regimen with relevant thalidomide-containing regimens were possible using indirect mixed treatment comparisons. The sections below focus largely on the analysis of VTD compared with TD.

6.3 The manufacturer chose a state-transition Markov model, with a cycle length of 1 month, to reflect the length of a course of treatment with VTD (28 days) and because clinical outcomes are reported in months. The model did not include a half-cycle correction because the cycle length was short relative to the time horizon used in the model. Costs and QALYs were discounted over a lifetime (30 years) time horizon at 3.5% per annum. The manufacturer stated that the model captured the two most important outcomes: post-induction response rate and overall survival. However, the manufacturer clarified that given the pivotal trials were not powered to detect a statistically significant difference in overall survival,

the model was based on response rate and the relationship between response rate and overall survival was quantified using long term survival from older trials in the same patient population. Patients entered the model at the start of the induction therapy. Post-induction, patients in the model entered one of 3 health state: complete response, partial response, or non-responders defined as minimal response, stable disease and progressive disease respectively. Depending on their post-induction response rate, patients subsequently proceeded to HDT-SCT or post-induction progression-free survival health state (non-stem cell transplant group). Post-induction, all patients were assumed to incur the same survival benefit which is dependent only on the response rate they achieve following the induction phase and is independent of the actual induction regimen that they received. On progression of disease, patients would then receive a 2nd treatment, followed by a 3rd line and subsequent lines of treatment following further progression.

Figure 2: diagram of the manufacturer's economic model structure



6.4 The manufacturer presented additional patient-level analyses in the addendum to evaluate the impact of the discontinuation rule for VTD on treatment durations. The manufacturer assumed that patients in the

Pethema trial who achieved less than partial response, and received 5 or 6 cycles of VTD in the original model would not have received the 5th and 6th cycles of VTD with the discontinuation rule and the manufacturer therefore excluded these patients from the revised analysis. The manufacturer stated this assumption was plausible unless patients who achieved partial response or better after the 4th cycle were likely to deteriorate to below partial response during the 5th and 6th cycle. The manufacturer also assumed that patients in the Pethema trial who achieved at least partial response and received 5 or 6 cycles of VTD would have achieved at least partial response after the 4th cycle, and thus, even with the discontinuation rule, would have continued treatment with VTD beyond the 4th cycle. The manufacturer therefore included these patients to the number of patients who received at least 5 and all 6 cycles. The manufacturer stated that this assumption was less plausible and explored it in the sensitivity analysis (see section 4.8 of the clinical effectiveness section). Overall, under these assumptions, the number of patients eligible to receive all 6 cycles would be [redacted] instead of [redacted] as observed in the trial.

6.5 For the base-case comparison of VTD with TD, clinical data was taken from the clinical study report for the Pethema trial. Post-induction response rates were used as the main measure of efficacy in the model (table 8). Stem cell transplant rates for each response category in each treatment arm were used in the model (Table 9). The model also included mortality rate during induction period (table 10), and mortality rates during the transplant period (table 9).

Table 8. Post-induction response rates used in the economic model (from the Clinical study reports for the Pethema,IFM and Hovon trials)

Pethema	**VTD** **N=130**	**TD** **N=127**
CR (CR+nCR+VgPR)	64 (49.2%)	22 (17.3%)
PR	46 (35.4%)	56 (44.1%)

NR (MR+SD+PD)	20 (15.4%)	49 (38.6%)
IFM	**VD N=121**	**ViAD N=121**
CR (CR+nCR+VgPR)	49 (40.8%)	19 (15.7%)
PR	44 (36.7%)	53 (43.8%)
NR (MR+SD+PD)	27 (22.5%)	49 (40.5%)
Hovon	**PAD N=417**	**ViAD N=416**
CR (CR+nCR+VgPR)	209 (50.1%)	81 (19.5%)
PR	142 (34.1%)	174 (41.8%)
NR (MR+SD+PD)	66 (15.8%)	161 (38.7%)

Table 9. SCT rate by post-induction response category (Pethema trial)

Post-induction response categories	**Pethema**	
	VTD % (n/N)	**TD % (n/N)**
CR category (CR+nCR)	96.9 (62/64)	95.5 (21/22)
PR category	82.6 (38/46)	89.3 (50/56)
NR category (MR + No change + PD + Death + not evaluable)	25.0 (5/20)	14.3 (7/49)
Total	80.8 (105/130)	61.4 (78/127)

6.6 The manufacturer stated that in the Pethema trial, a significantly higher proportion of patients in the VTD arm achieved complete response post-induction compared to the TD arm (table 8) and that a higher proportion of patients received a stem cell transplant in the VTD arm than in the TD arm (80.8% versus 61.4% in PETHEMA, table 9). The manufacturer's original submission used total stem cell transplant rates from the Pethema, IFM and Hovon trials (table 52 of the manufacturer's submission for the respective comparisons. In response to clarification the manufacturer subsequently used the stem cell transplant rates categorised by post-induction response and these more detailed figures (table 9) were applied

in the economic model submitted as part of the manufacturer's addendum. The manufacturer highlighted that the discontinuation rule for VTD would not alter VTD's post-induction response rates as input parameters for the economic model. It stated that this was because the discontinuation rule would not change the final post-induction responses for those who received 4 or fewer cycles of VTD.

Table 10. Mortality rate during induction period and during stem cell transplant

	Mortality rate during induction (6 months)	Monthly probability of death during induction	Mortality rate during SCT (3 months)	Monthly probability of death during SCT
VTD	3.8% (5/130)	0.7%	0.8% (1/130)	0.3%
TD	4.8% (6/126)	0.8%	0.0% (0/126)	0.0%
VD	0.7% (1/135)	0.2%	0.7% (1/106)	0.3%
ViAD	3.7% (5/136)	0.9%	0.7% (1/100)	0.3%
PiAD	4.6% (19/410)	1.6%	1.2% (5/352)	0.5%
ViAD	5.6% (23/411)	1.9%	1.0% (4/347)	0.4%

6.7 In order to model long-term survival based on the post-induction response rates, the manufacturer extracted overall survival data from the MRC VII trial (table 11) because overall survival data from the Pethema trial was considered immature. The MRC VII trial randomised a total of 407 previously untreated multiple myeloma patients over 65 years of age, to conventional chemotherapy (n=200), or HDT followed by autologous SCT (n=201). The five-year survival in the HDT-SCT group was 88.6 months [95%CI: 61.4-upper CI not reported] for patients who had a complete response, 39.8 months [95%CI: 33.8-61.4] for patients who had partial response, and 25.6 months [95% CI: 7.0-31.3] for patients who had no response. The manufacturer also used long-term survival data from the IFM90 trial in their scenario analyses.

Table 11. Overall survival by category of post-induction response

	5 year survival rate			Monthly survival probability	Monthly probability of death
	Number of months	95%CI min	95% CI max		
CR	88.6	61.4	Not reported	99.2%	0.8%
PR	39.8	33.8	61.4	98.3%	1.7%
NR	25.6	7.0	31.3	97.3%	2.7%

6.8 The manufacturer used post-transplant time to progression from the Pethema trial to determine the transition probabilities from the post-transplant progression-free health state to the start of 2nd line therapies. The manufacturer assumed that time to progression is affected by the interventions because it is modelled using separate parametric curves by treatment and response category. In the base-case, time-to-progression transition probabilities were derived from exponential curves fitted to the Pethema data. Constant transition probabilities were used from the 2nd to 3rd line health states between the two interventions, the estimates for which were derived from the APEX trial (which compared bortezomib monotherapy with high dose dexamethasone in patients with relapsed multiple myeloma), from the subgroups of patients with one or two lines of treatment respectively. Transition probabilities from 3rd to further lines of treatment were derived by applying an exponential distribution to the time-to-progression data from the APEX trial.The overall survival data from the MRC VII trial was used to determine the duration of time that patients remain in the further lines of treatment health state before transitioning to death state.

6.9 The manufacturer conducted a systematic search of the literature to identify publications that identified health-related quality of life data relevant to the decision problem. Five relevant studies were identified of which 3 reflected the current UK patient population and clinical practice. The manufacturer selected the van Agthoven as the base-case source of utility values because the utility values were obtained using EQ-5D. The study by van Agthoven *et al*. compared chemotherapy (n=129) versus

intensive chemotherapy followed by myeloablative chemotherapy with SCT (n=132) and total body irradiation treatment regimens in patients in the Netherland and Belgium under the age of 65 years with newly diagnosed and untreated multiple myeloma. Patients received 3-4 cycles of VAD and two cycles of intermediate dose melphalan, after which they were randomised to either receive SCT and interferon maintenance, or interferon maintenance only. With regard to adverse events the manufacturer applied a disutility of 0.02 to each patient experiencing an adverse event associated with induction therapy.

Table 12. Summary of the utility values for the cost-effectiveness analysis

UTILITIES	Utility value	Confidence interval	Reference
1st line treatment			
From start treatment until post-induction response	0.57	0.34-0.78	Segeren
From post-induction to post-SCT response	0.65	0.38-0.88	Segeren
SCT patients	Up to 3 mos =0.59	0.35-0.81	Segeren
	3-6 mos =0.65	0.38-0.88	Van Agthoven et al.
	6-9 mos =0.68	0.39-0.91	Segeren
	9-12 mos =0.62	0.37-0.84	Van Agthoven et al.
	12-18 mos =0.69	0.39-0.92	
	18+ mos =0.75	0.41-0.97	
Non-SCT patients	CR =0.83	0.67-0.94	Beusterien et al.
	PR =0.76	0.64-0.87	
	NR = 0.65	0.56-0.73	
2nd and 3rd line treatments	0.69	0.39-0.92	Van Agthoven et al.
Further lines	0.644	0.38-0.87	
Disutility 1st line treatment	0.02	0.013-0.029	ScHARR HTA report

6.10 The costs applied in the model were taken from the BNF 64 (2012) and from the 2012-13 Chemotherapy Regimens List. Administration of chemotherapy drugs, outpatient visits and tests as part of disease and treatment monitoring and the costs relating to stem cell transplantation were taken from the 2011-12 National Schedule Reference costs. The costs associated with treating adverse events were based on inpatient outpatient or day case visit National Schedule Reference costs. The

manufacturer presented unit costs associated with each of the 1st line induction therapies as well as drugs for prophylaxis, administration and monitoring (summary presented in table 13).

Table 13. Summary unit costs associated with 1st line induction therapies (drugs, prophylaxis, administration and monitoring)

	VTD	**TD**
Average cost of a course of treatment	£24,840	£8,720
Prophylaxis	£353.54	£298.97
Administration cost	£1,645.00	£828.00
Monitoring cost	£1,050.00	£1,050.00
TOTAL	£28,034	£8,865
	VD	**ViAD**
Average cost of a course of treatment	£12,261	£898.34
Prophylaxis	£80.65	£71.15
Administration cost	£1069	£1069
Monitoring cost	£693.42	£693.42
TOTAL	£14,104	£2,732
	PAD	**ViAD**
Average cost of a course of treatment	£9,692.09	£705.17
Prophylaxis	£80.65	£53.37
Administration	£781.00	£781.00
Monitoring cost	£520.06	£520.06
TOTAL	£11,073.80	£2,059.60

6.11 The total cost of a stem cell transplant was estimated to be £20,510.72, including the cost for mobilisation (£547.68), harvest (£823), ablation (£451.50), transplant (£17,813) and post-transplant (£875.56). For 2nd line treatment, the weighted average treatment cost (for bortezomib plus high dose dexamethasone, CTD, high dose dexamethasone) is £24,440 for a mean duration of 9.8 months. For 3rd line treatment, the weighted average treatment cost (for lenalidomide plus dexamethasone, CTD, high dose dexamethasone) is £34,271. All unit costs are presented in Tables 68 to 72 of the manufacturer's submission.

6.12 The manufacturer presented the model outputs presented by the manufacturer are in table 14.

Table 14. Model outputs by clinical outcomes (discounted)

	LY	QALY	Cost (£)	LY	QALY	Cost (£)
Outcome	**VTD**			**TD**		
Induction treatment	0.49	0.28	£25,167	0.49	0.27	£7,265
Stem cell transplant	0.19	0.12	£16,691	0.14	0.09	£12,405
Post-induction PFS	2.63	1.89	£2,611	1.80	1.29	£1,782
Post-progression survival	2.72	1.73	£31,706	2.14	1.36	£34,042
Overall survival	6.03	4.02	£76,174	4.57	3.01	£55,493
Outcome	**VD**			**ViAD**		
Induction treatment	0.33	0.19	£13,669	0.33	0.19	£2,536
Stem cell transplant	0.21	0.14	£17,488	0.20	0.13	£16,010
Post-induction PPT	2.64	1.90	£2,616	1.71	1.21	£1,700
Post-progression survival	2.46	1.57	£29,101	2.19	1.39	£29,918
Overall survival	5.64	3.79	£62,874	4.42	2.91	£50,163
Outcome	**PAD**			**ViAD**		
Induction treatment	0.24	0.14	£10,669	0.24	0.14	£2,190
Stem cell transplant	0.20	0.13	£16,302	0.19	0.13	£15,916
Post-induction PPT	2.49	1.80	£2,473	1.75	1.24	£1,737
Post-progression survival	2.78	1.78	£30,187	2.22	1.41	£29,515
Overall survival	5.72	3.84	£59,632	4.41	2.91	£49,359
LY, life years; QALY, quality-adjusted life year; TD: thalidomide and dexamethasone; TTP: time to progression; VTD: Velcade® (bortezomib), thalidomide and dexamethasone,						

6.13 The manufacturer estimated a base-case incremental cost-effectiveness ratio (ICER) of £20,468 per QALY gained for VTD compared with TD (table 15).

Table 15. Manufacturer's base-case cost effectiveness estimates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) incremental (QALYs)
VTD	£76,174	6.03	4.02	+£20,682	+1.47	+1.01	£20,468
TD	£55,493	4.57	3.01				
VD	£62,874	5.64	3.79	+£12,710	1.22	0.88	£14,446
ViAD	£50,163	4.42	2.91				
PAD	£59,632	5.72	3.84	+£10,274	1.31	0.93	£11,041
ViAD	£49,359	4.41	2.91				

6.14 The deterministic sensitivity analyses highlighted that the results are most sensitive to the mortality rate for patients with complete response after the induction therapy, and to VTD drug costs. If the complete response mortality rate is varied within its 95% confidence interval, other things being equal, the ICER ranges from £17,018 to £28,867 per QALY gained. For the VTD drug costs, sensitivity analyses was conducted using 4, 5 and 6 cycles of induction therapies. This was based on clinical opinion that the number of cycle will vary from one patient to another. The ICER range for the sensitivity analysis varying VTD drug costs was £15,761 to £25,662 per QALY gained. For all other parameters varied in the sensitivity analyses, the ICER remained between £16,000 and £25,000 per QALY gained.

6.15 The manufacturer presented for 24 scenarios (manufacturer's submission, table 95). The ICERs generally remained below or close to £30,000/QALY with the exception of the following scenarios:

- 10 year time horizon (ICER £31,507 per QALY gained)
- 2 VTD response rate variation scenarios (with CR<41%) which had ICERs of £24,624 and £21,477 per QALY gained.
- 2 TD response rate scenarios (with CR>24%) which had ICERs of £25,898 and £33,166)

6.16 The results of the manufacturer's probabilistic sensitivity analysis showed that, at thresholds of £20,000 and £30,000 per QALY gained, there is a 35.4% and 71.3% probability, respectively, of the VTD regimen being cost-effective when compared with TD.

6.17 The manufacturer adopted the same model structure and assumptions for the comparison of VD with ViAD, incorporating clinical data from the IFM trial. Details on the estimates included are presented in the manufacturer's original submission (page 193, section 7.7.6). The manufacturer estimated an ICER of £14,446 per QALY gained for VD

compared with ViAD (table 15). Deterministic sensitivity analyses highlighted that the results are most sensitive to the mortality rate for patients with complete response after the induction therapy with ICERs ranging from £10,961 to £18,354 per QALY gained. The manufacturer presented probabilistic sensitivity analysis for the VD regimen compared with ViAD. At £20,000 and £30,000 per QALY thresholds, the manufacturer estimated that there is a 68.9% and and 83.2% probability, respectively, of VD being cost-effective compared with ViAD.

6.18 The ERG stated that the structure of the model is consistent with the clinical pathway of care for multiple myeloma and was clearly presented. However, the ERG highlighted that the manufacturer's analysis of VD compared with ViAD is outside of the of the scope and also that given that the comparator in routine use in UK clinical practice is CTD, the comparison of VTD with TD is also not entirely relevant to clinical practice.

6.19 The ERG also expressed some concerns that the model extrapolated level of response after induction therapy to long term survival and time to progression based on data from the MRC VII trial. The ERG cautioned that the MRC VII trial was old and outcomes may not be reflective of the advances available today. Moreover, the ERG stated that data from the MRC VII trial related to maximal response to treatment rather than post-induction response rate, and the resulting survival curves may be confounded to some extent with post-stem cell transplant response. The ERG clinical expert agreed that response rate at induction predicts progression-free survival and overall survival. However, the ERG stated that other surrogate outcomes, such as post stem cell transplant response rate, may offer a better prediction of progression-free survival and overall survival. The ERG observed that though the model had separate states for those who receive a stem cell transplant and those who do not, the model attaches no explicit survival benefit to a stem cell transplant other than that achieved by delaying the transition to the post-induction/post-SCT progression-free survival state for the duration of the stem cell

transplant period. The ERG clinical expert stated that stem cell transplant offers a survival benefit of 12-18 months compared with no transplant and the ERG stated that it would have been more transparent to distinguish the separate effects of post-induction response and stem cell transplant on survival. Alternatively post-stem cell transplant response rate would factor this in because it is more significantly associated with overall survival than post-induction response rate. Overall, the ERG stated that external validity would have been strengthened if the model had been based on overall survival and time to progression Kaplan Meier curves or post-SCT response, rather than post-induction response. The ERG was concerned that in the absence of this the results were systematically biased in favour of VTD.

6.20 The ERG stated that, in contrast to the manufacturer's description in the submission, the model implicitly assumed a continuing effect of induction treatment after induction is complete, because separate time to progression curves were used for each induction treatment arm and stem cell transplant mortality was also applied separately by treatment arm. The ERG also highlighted that, contrary to statements in the manufacturer's submission, the probability of receiving a stem cell transplant is not dependent on post-induction response, but only on treatment received.

6.21 The ERG noted the discontinuation rule for the VTD regimen, and agreed with the manufacturer that it reduced the costs associated with the VTD regimen and that it would not alter VTD's post-induction response rates (page 22 of the manufacturer's addendum). However, the ERG considered that the assumption that 100% of patients who achieved at least partial response and received 5 or 6 cycles of VTD achieved at least partial response after the 4th cycle may not be fully met. The ERG stated that if this assumption was not met, a number of patients with a partial response or higher after 6 cycles will be lost from the final response numbers for partial response and the post-induction response rates in the

model will not be the same as seen in the Pethema trial. This then has implications for the proportion of patients who receive a stem cell transplant as the likelihood of a patient receiving a stem cell transplant is positively associated with the depth of response to induction therapy.

6.22 The ERG noted the manufacturer's approach to calculating transition probabilities (section 7.3.2 of the manufacturer's submission), and stated that the exponential distribution fitted to the Pethema Complete Response time to progression data for VTD patients resulted in a shorter median survival time (approximately 61 months) than the exponential distribution fitted to Complete Response time to progression data for patients receiving TD (median survival approximately 98 months). The ERG stated that this contrasts with overall findings for progression-free survival in the trial publication where median progression-free survival was significantly higher with VTD than with TD. The ERG noted that the manufacturer derived transition probabilities for 3rd and further lines using data from the APEX trial which compared bortezomib monotherapy with high dose dexamethasone in patients with relapsed multiple myeloma. The ERG commented that because the APEX trial used bortezomib as a monotherapy treatment, it may have different survival outcomes to those seen with bortezomib combination therapy.

6.23 The ERG noted that study selected by the manufacturer to inform the utility values in the model included patients that were largely representative of patients in this appraisal although they were not from the UK, received different treatments and were also likely to be younger (54 years). The ERG clinical expert stated that total body irradiation is much more toxic conditioning than high dose melphalan currently used in the UK, and so the utility values from this study may not be representative of patients in the UK.

6.24 The ERG considered that the costs included in the model were reasonable. However, the ERG identified a number of changes to the

updated economic model submitted as part of the addendum, which were not documented in the manufacturer's addendum. Although the addendum refers to the original submission for discussion of resource identification, measurement and valuation (manufacturer's addendum Section 7.5), the ERG notes that many of the costs in the revised model are different from those in the original model. These include costs for drugs; induction; stem cell transplant; 2nd line treatment; 3rd line treatment; and some monitoring costs. The ERG noted that these changes were generally minor, but some were substantial. For example, the administration costs for high dose dexamethasone increased from £168 to £1,242 in 2nd line therapy, and from £168 to £1,288 in 3rd line therapy. The ERG stated that when considering only model changes and assumptions which are documented in the addendum, the ICER is £23,958 per QALY gained for VTD compared with TD regimen, compared to £20,468 per QALY gained reported in the addendum.

6.25 The ERG commented that comparison of model overall survival with observed Pethema trial overall survival reveals that the model consistently underestimates overall survival, and that this underestimation is worse for TD than it is for VTD.

6.26 The ERG noted that the manufacturer addressed methodological uncertainties in the model by running alternative versions of the model with different assumptions. Discount rates were varied for costs and outcomes and alternative time horizons were examined.

6.27 The ERG considered that alternative values used by the manufacturer in scenario analysis may not fully explore the uncertainty in the model and may therefore not fully reflect the uncertainty in final ICER. Two alternative scenarios for overall survival by post-induction response are explored by the ERG in scenario analysis

6.28 The ERG conducted exploratory additional work. The ERG utilised the relevant economic model outputs from table 3 (manufacturer's original

base-case cost effectiveness results) of the manufacturer's submission and calculated the ICERs for all treatments compared with TD and CTD, the latter of which is a more relevant comparator in a UK population (tables 16 and 17). The ERG commented that all results should be treated with extreme caution as they compare individual arms of separate trials, without adjusting for trial populations. Furthermore there are differences in the trial designs. For these reasons, the results should not be directly compared. (See section 4.3 of the ERG report for more details of these analyses).

Table 16. ERG additional work: cost-effectiveness results compared with CTD and TD, using the manufacturer's original economic models

Scenario	Treatment	Total costs, £	Total QALYs	Incremental Costs vs. CTD	Incremental QALYs vs. CTD	ICER vs CTD (£/QALY)	ICER vs TD (£/QALY)
Base case results	CTD	£48,237	3.90	-	-	-	Dominates
	TD	£49,414	3.06	£1,177	-0.85	Dominated	-
	PAD	£59,632	3.84	£11,396	-0.06	Dominated	£13,026
	VD	£62,874	3.79	£14,637	-0.11	Dominated	£18,318
	VTD	£72,815	4.00	£24,579	0.10	£242,776	£24,683
Dominated treatments are more expensive and less effective than alternative treatment. Results are illustrative and should not be directly compared.							

Table 17. ERG additional work: cost-effectiveness results compared with CTD and TD, using the manufacturer's addendum model for VTD and TD and the original models for CTD, PAD and VD

Scenario	Treatment	Total costs, £	Total QALYs	Incremental Costs vs. CTD	Incremental QALYs vs. CTD	ICER vs CTD (£/QALY)	ICER vs TD (£/QALY)
Base case results	CTD	£48,237	3.90	-	-	-	Dominates
	TD	**£55,493**	**3.01**	**£7,256**	**-0.89**	**Dominated**	**-**
	PAD	£59,632	3.84	£11,396	-0.06	Dominated	£5,014
	VD	£62,874	3.79	£14,637	-0.11	Dominated	£9,512
	VTD	**£76,174**	**4.02**	**£27,938**	**0.12**	**£228,159**	**£20,468**
Dominated treatments are more expensive and less effective than alternative treatment. Results are illustrative and should not be directly compared.							

6.29 The ERG also conducted the following additional analyses:

- Two alternative scenarios for post-induction mortality (VTD vs. TD model)
- Post-SCT response rate from Pethema trial used instead of post-induction response rate

6.30 In order to model long-term survival, the manufacturer extracted overall survival data from the MRC Myeloma VII trial. The ERG considered that the data from the MRC Myeloma VII trial to be reasonably old and that the survival of patients would be poorer than would be seen in similar patients today. Therefore the ERG conducted two further scenarios using data obtained from the meta-analysis by van de Velde et al (2007) for the comparison of VTD with TD. These data were from the NMSG 5/94 study and a study by Alvares *et al*. The NMSG 5/94 study shows less difference in median survival between the response categories than is seen in the base case MRC VII data. This leads to a much higher ICER of £110,727 per QALY gained for VTD compared with TD. The median overall survival for complete responders in the Alvares *et al*. study was similar to the MRC VII study (88.8 months compared to 88.6 months respectively). However, overall median survival for partial and non-responders in this study was much better than MRC VII and this resulted in an increase in the ICER for VTD compared with TD to £38,750 per QALY gained (Table 18 (a), 19(a)). The ERG considered that the Alvares study data provide a better fit to the Pethema overall survival data than the NMSG or MRC VII data.

6.31 The ERG observed that the MRC VII trial survival data are categorised by maximal response to treatment, which is arguably more similar to post-stem cell transplant response than post-induction response, and so use of post-stem cell transplant response from Pethema would provide a more consistent fit to MRC VII data. Results for the post-stem cell transplant

response rate scenario in the VTD vs. TD model are given in table 20. The ERG observes that the attribution of patients with inevaluable or unknown outcome after stem cell transplant to the 'no response' category is a non-conservative assumption and that if some of these patients achieved PR or better the ICER would be higher than £35,915 per QALY, that is, VTD would become less cost-effective compared to TD (see table 18 (b), 19 (b) below).

6.32 The ERG combined the Alvares study data and the examination of the effect of using post-SCT response rates rather than post-induction response rates as the starting point for extrapolation to overall survival. This resulted in an ICER of £57,172 per QALY gained for VTD compared with TD, while VTD was dominated by CTD, that is, VTD was more expensive and less effective than CTD. Furthermore, in this scenario analysis, PAD and VD were dominated by CTD.

6.33 The ERG conducted some additional scenario analysis using post-SCT response rates by varying the assignment of the VGPR response rate category in the economic model. In the manufacturer's original models VGPR is added to the complete response category for the CTD, PAD and VD treatments. The ERG added VGPR to the PR category as an alternative scenario. Since this assumption was not required for TD and VTD (because no VGPR category was used in Pethema) this did not alter the ICER in this case. However, this did increase the ICERs for VD compared with TD to £48,124 per QALY gained and £49,040 per QALY gained when combined with the inclusion of the Alvares overall survival data (table 19).

Table 18. ERG scenario analysis using OS from Alvares and post-SCT response rates (with VGPR assigned to CR) based on the manufacturer's original model

Scenario	Treatment	Total costs, £	Total QALYs	Incremental Costs vs. CTD	Incremental QALYs vs. CTD	ICER vs CTD (£/QALY)	ICER vs TD (£/QALY)
(a) Median	CTD	£52,138	4.59	-	-	-	Dominates

overall survival follows Alvares et al (2005)	TD	£55,076	4.07	£2,939	-0.52	Dominated	-
	PAD	£63,438	4.45	£11,300	-0.14	Dominated	£22,017
	VD	£67,678	4.54	£15,541	-0.05	Dominated	£26,495
	VTD	£76,605	4.62	£24,467	0.03	£775,597	£38,750
(b) Post-SCT response rates (with VGPR assigned to CR)	CTD	£48,306	4.74				Dominates
	TD	£50,378	3.43	£2,072	-1.31	Dominated	-
	PAD	£62,075	4.46	£13,769	-0.27	Dominated	£11,320
	VD	£63,849	4.13	£15,543	-0.60	Dominated	£19,129
	VTD	£73,716	4.08	£25,410	-0.66	Dominated	£35,915
Both (a) and (b)	CTD	£50,127	5.06				Dominates
	TD	£54,851	4.24	£4,724	-0.82	Dominated	-
	PAD	£63,993	4.77	£4,724	-0.82	Dominated	£17,414
	VD	£67,625	4.72	£13,866	-0.29	Dominated	£26,701
	VTD	£77,203	4.63	£17,498	-0.34	Dominated	£57,172
Dominated treatments are more expensive and less effective than alternative treatment. Results are illustrative and should not be directly compared.							

Table 19. ERG scenario analysis using OS data from Alvares and post-SCT response rates based on the manufacturer's VTD vs. TD addendum model

Scenario	Treatment	Total costs, £	Incremental Costs vs. CTD	Incremental QALYs vs. CTD	Incremental QALYs	ICER (£/QALY)
(a) Median overall survival follows Alvares et al (2005)	TD	£60,485	4.03	-	-	-
	VTD	£79,586	4.66	£19,101	0.63	£30,368
(b) Post-SCT response rates	TD	£56,497	3.39	-	-	-
	VTD	£77,639	4.20	£21,142	0.80	£26,292
Both (a) and (b)	TD	£60,280	4.20	-	-	-
	VTD	£80,402	4.72	£20,122	0.52	£38,985
Results are illustrative and should not be directly compared.						

7 Equalities issues

7.1 One consultee highlighted that myeloma mostly affects the elderly population, who often have other concomitant conditions and so there may be an impact on the equality of access for these patients. Attendees at the scoping workshop did not consider this to be an issue of the equality legislation. No additional issues related to potential equality issues have been identified during the scoping process.

7.2 No equality issues were highlighted in the evidence submitted for the appraisal.

8 Innovation

8.1 No statements were received from the manufacturer or other consultees on the innovative nature of bortezomib.

9 Authors

Christian Griffiths
Technical Lead

Raisa Sidhu
Technical Adviser

with input from the Lead Team (Dr. Janice Kohler, Greg Fell and Judith Wardle).

Appendix A: Supporting evidence

Related NICE guidance

Published

Bortezomib and thalidomide for the first line treatment of multiple myeloma.. NICE technology appraisal guidance 228 (2011).

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000539/WC500147837.pdf