National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit, draft scope (pre-referral) and provisional matrix

Note: The title of the draft remit and draft scope for the consultation was bortezomib for induction and consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma.

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Celgene	Yes	Comment noted. No changes to the scope required.
	CSAS	This topic is appropriate for consideration as it has the potential to improve overall management and outcomes for people with multiple myeloma (MM)	Comment noted. No changes to the scope required.
	Myeloma UK	The draft scope suggests appraising bortezomib (Velcade®) in two settings; 1. In the induction setting, prior to autologous stem cell transplantation (ASCT), in combination with 'an optimum chemotherapy regimen' 2. In the consolidation setting as a monotherapy We welcome the opportunity to comment on this draft scope. As myeloma is a very individual cancer, it is important that clinicians and patients have access to as many effective treatment options as possible so that the heterogenity of myeloma can be reflected in prescribing. Bortezomib is a well-established treatment for myeloma and is currently approved for use at first relapse and in a sub-group of patients in the upfront setting in the UK. Although current NICE guidance recommends the use of bortezomib in the first relapse setting as monotherapy, in practice, it is almost always given in combination	Comments noted.

Section	Consultees	Comments	Action
		with dexamethasone, with or without cyclophosphamide. In addition, based on clinical experience and published data, practice is moving towards a once-weekly schedule using a sub-cutaneous formulation rather than a twice-weekly, IV approach. This is more convenient and cost effective for both hospitals and patients and is associated with less severe side-effects but similar efficacy. In the upfront setting, bortezomib in combination with melphalan and prednisone is approved for use in non-transplant eligible patients who are refractory to or cannot tolerate a thalidomide based combination. This is important information to consider in this scoping exercise. With regard to the induction part of this scoping exercise, we consider this to be an appropriate topic to refer to NICE.	
	Myeloma UK	We are aware of the ongoing clinical studies using bortezomib in this setting. We note that all these studies are investigator initiated studies and we understand that neither of them were originally designed for licensing purposes or with a UK HTA submission in mind. We also note that the combinations used in these studies may not reflect either current or future upfront clinical practice in the UK but believe that a strong case can be made to approve bortezomib as part of an induction treatment combination in a way that is relevant to UK clinical practice. We believe that it is an important responsibility of NICE, wherever possible and within its remit, to approve treatments in a way that make sense to current and future UK clinical practice. In summary, we strongly believe that bortezomib should be approved as part af an induction treatment combination and we look forward to discussing how best to do this in the context of UK clinical practice in due course. In relation to the second proposed intervention, we consider the principle of consolidation treatment an important and interesting development in the treatment of	Comments noted.

Section	Consultees	Comments	Action
		myeloma. However, the role of consolidation treatment in myeloma and the data to support it is less clear. What is more, there appears to be the need for clarification about what is meant by consolidation treatment versus maintenance treatment in context of this appraisal. With this in mind and taking into consideration current UK clinical practice and clinical studies, our view would be that this part of the draft remit would not be a priority for referral at this time.	
	Myeloma UK	We also understand that Janssen are delaying their application for a licence for bortezomib as consolidation therapy after stem cell transplant and therefore it would not be appropriate to appraise it in this context.	Comments noted. It was agreed at the scoping workshop that as the manufacturer is to apply for two separate licensed indications covering two separate populations it would be appropriate for the draft remit to be split into two, one for bortezomib as induction therapy and one for bortezomib as consolidation therapy.

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	Royal College of Pathologists	We agree it is entirely appropriate that this topic be referred to NICE for appraisal but suggest that the remit is altered to cover only bortezomib induction prior to autologous stem cell transplantation, omitting consolidation therapy after transplantation	Comments noted. It was agreed at the scoping workshop that as the manufacturer is to apply for two separate licensed indications covering two separate populations it would be appropriate for the draft remit to be split into two, one for bortezomib as induction therapy and one for bortezomib as consolidation therapy.
	Royal College of Physicians	We agree it is entirely appropriate that this topic be referred to NICE for appraisal but suggest that the remit is altered to cover only bortezomib induction prior to autologous stem cell transplantation, omitting consolidation therapy after transplantation	Comments noted. It was agreed at the scoping workshop that as the manufacturer is to apply for two separate licensed indications covering two separate populations it would be

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			appropriate for the draft remit to be split into two, one for bortezomib as induction therapy and one for bortezomib as consolidation therapy.
Wording	Celgene	Yes	Comment noted. No changes to the scope required.
	CSAS	The wording is appropriate	Comment noted. No changes to the scope required.
	Janssen	The remit of this future NICE single technology appraisal should assess the clinical and cost effectiveness of bortezomib within its anticipated licensed indication: induction therapy prior to high dose chemotherapy and stem cell transplantation in patients with in multiple myeloma.	Comment noted. It was agreed at the scoping workshop that the draft remit should to be split into two and reworded to reflect the wording of the anticipated separate licensed indications: 1) for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation 2) for consolidation

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			therapy after autologous stem cell transplantation
	Royal College of Pathologists	we would suggest a change of the wording to read "Bortezomib for induction prior to autologous stem cell transplantation for the treatment of multiple myeloma".	Comment noted. It was agreed at the scoping workshop that the draft remit should to be split into two and reworded to reflect the wording of the anticipated separate licensed indications: 1) for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation 2) for consolidation therapy after autologous stem cell transplantation
	Royal College of Physicians	we would suggest a change of the wording to read "Bortezomib for induction prior to autologous stem cell transplantation for the treatment of multiple myeloma".	Comment noted. It was agreed at the scoping workshop that the draft remit should to be split into two and reworded to reflect the wording of the anticipated separate licensed

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			indications: 1) for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation 2) for consolidation therapy after autologous stem cell transplantation
Timing Issues	CSAS	Bortezomib is currently not licensed for this indication and the marketing approval is expected soon, appraisal is urgent.	Comment noted. No changes to the scope required.
	Myeloma UK	NICE, the manufacturer and consultees should all be confident about the availability of relevant data prior to undertaking the appraisal. In relation to the consolidation setting, it would be much more appropriate to undertake this part of the appraisal at a later date.	Comments noted. It was agreed at the scoping workshop that as the manufacturer is to apply for two separate licensed indications covering two separate populations it would be appropriate for the draft remit to be split into two, one for bortezomib as induction therapy and one for bortezomib as consolidation

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			therapy.
	Royal College of Pathologists	Multiple myeloma remains an incurable cancer with considerable morbidity from organ failure, and thus we consider the proposed appraisal of a technology that significantly improves disease response, and clinical outcome, to be urgent.	Comment noted. No changes to the scope required.
	Royal College of Physicians	Multiple myeloma remains an incurable cancer with considerable morbidity from organ failure, and thus we consider the proposed appraisal of a technology that significantly improves disease response, and clinical outcome, to be urgent.	Comment noted. No changes to the scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	CSAS	The figure of 3,900 diagnosed with MM in England and Wales in 2008 is similar to the latest Cancer Research UK reports stating that there were 3,562 deaths in 2007 in England and Wales.	Comment noted. No changes to the scope required.
	Janssen	The median age at Multiple Myeloma diagnosis is reported being around 70 years (Venon et al, 2009), with about 15% to 35% of patients aged under 60 years (Bird et al, 2011; Venon et al, 2011), which is consistent with the estimation that between 24% and 35% of these newly diagnosed myeloma adult patients usually receive a first-line high dose therapy with stem cell transplantation (SCT) (NICE TA228, 2011; Venon et al, 2009).	Comment noted. No changes to the scope required.
	Myeloma UK	Myeloma is most frequently diagnosed in people over 60 and is only slightly more common in men than women. NICE should not use the words consolidation and maintenance interchangably. Whilst for reasons stated above consolidation treatment should be removed from the draft remit, for future reference and clarification the definitions are: Consolidation treatment - consists of a standard dose of anti-myeloma treatment that is given over a period of a few weeks, the aim of which is to further reduce the residual myeloma. In the context of this appraisal, it can be used either after induction prior to ASCT or post transplant Maintenance treatment - consists of a low dose of anti-myeloma treatment given over a period of many months (or years) with the aim of sustaining or enhancing the response already achieved (e.g. the ongoing NICE Revlimid maintenance appraisals) TAD and PAD are regimes that are rarely, if ever, used in the UK in the induction setting.	Comments noted. The background section of the scope has been amended accordingly.

Section	Consultees	Comments	Action
	Royal College of Pathologists	The background is in general accurate and complete, however we suggest the following minor alterations. In the last paragraph of the Background, 2nd sentence. "In some people, active consolidation (maintenance) may be considered with the aim of stimulating the immune system and slowing or stopping cancer cell growth" should be changed to "In some people, for example, those who have failed to achieve a major response, active consolidation treatment may be considered with the aim of deepening disease response. Treatment after stem cell transplantation may also take the form of maintenance therapy, which is given with the aim of stimulating the immune system and slowing or stopping cancer cell growth". We do particularly endorse the statement at the end of the 4th paragraph in this section that reads "Decisions regarding the most appropriate induction treatment for individual patients will require the assessment of a number of factors such as renal function, thrombotic risk and pre-existing neuropathy".	Comments noted. The background section of the scope has been amended accordingly.
	Royal College of Physicians	The background is in general accurate and complete, however we suggest the following minor alterations. In the last paragraph of the Background, 2nd sentence. "In some people, active consolidation (maintenance) may be considered with the aim of stimulating the immune system and slowing or stopping cencer cell growth" should be changed to "In some people, for example, those who have failed to achieve a major response, active consolidation treatment may be considered with the aim of deepening disease response. Treatment after stem cell transplantation may also take the form of maintenance therapy, which is given with the aim of stimulating the immune system and slowing or stopping cancer cell growth". We do particularly endorse the statement at the end of the 4th paragraph in this section that reads "Decisions regarding the most appropriate induction treatment for individual patients will require the assessment of a number of factors such as renal function, thrombotic risk and pre-existing neuropathy".	Comments noted. The background section of the scope has been amended accordingly.
The	CSAS	Bortezomib is described accurately. The extent to which it is currently used off	Comment noted. As Guidance

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technology/ intervention		license is not described and would be useful additional information.	will only be issued in accordance with the marketing authorisation, the extent to which a technology is currently used off licence is not an issue normally discussed at the scoping stage.
	Janssen	Janssen is anticipating that Velcade as part of a 2-drug regimen or 3-drug regimen will be licensed for induction treatment in multiple myeloma adult patients likely to receive front line SCT. The regimens to be considered could include one or more of the following regimen for which data from randomised clinical studies is available: • VTD [bortezomib, thalidomide and dexamethasone] • PAD [bortezomib, Adriamycin® (doxorubicin) and dexamethasone] • Vel-Dex [bortezomib and dexamethasone] • VCD [bortezomib, cyclophosphamide and dexamethasone] At this stage we cannot confirm which bortezomib-based regimen would be covered by the anticipated license.	Comments noted. It was agreed at the scoping workshop that the comparators should be: **Induction therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for example CTD (cyclophosphamide, thalidomide and dexamethasone).**Consolidation therapy remit:** The comparators should be amended to 'watch and wait', thalidomide and lenalidomide
	Royal College of Pathologists	Yes	Comment noted
	Royal College of Physicians	Yes	Comment noted
Population	CSAS	The separate population groups for induction therapy and consolidation therapy are appropriately defined.	Comments noted. It was agreed at the scoping workshop that the definition of the population for the induction therapy remit should

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			be changed to: Adults with newly diagnosed multiple myeloma who are potentially eligible for high dose chemotherapy and who are suitable for autologous stem cell transplantation. It was agreed at the scoping workshop that the definition of the population for the consolidation therapy remit should be changed to: Adults with newly diagnosed multiple myeloma who have had high dose chemotherapy and autologous stem cell transplantation and whose disease has had a response to treatment with high dose chemotherapy.
	Janssen	Janssen would like the population in the scope to reflect the anticipated licence for bortezomib for induction treatment in multiple myeloma patients likely to receive front line SCT. At this stage we cannot provide any more information with regard to the anticipated licensed population.	Comment noted. In their discussions regarding the patient populations, attendees took account of their recommendation to split the draft remit into two separate remits relating to induction and consolidation therapy. Attendees agreed that the definition of the population for the induction therapy remit should be changed to: Adults with newly diagnosed multiple

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			myeloma who are potentially eligible for high dose chemotherapy and who are suitable for autologous stem cell transplantation. Attendees agreed that the definition of the population for the consolidation therapy remit should be changed to: Adults with newly diagnosed multiple myeloma who have had high dose chemotherapy and autologous stem cell transplantation and whose disease has had a response to treatment with high dose chemotherapy.
	Myeloma UK	It may be appropriate as data becomes available from studies to look at sub-groups (i.e. renal impairment, genetic sub-groups etc). However, it may not be possible to define these with any degree of certainty at this time.	Comment noted. It was agreed at the scoping workshop that people with renal impairment should not be included as a subgroup for either the induction or consolidation remits, because people with renal impairment, autologous cell transplantation is not normally considered to be an appropriate treatment option and they are excluded from clinical trials. However it was agreed that for the Induction therapy remit people with myeloma cell genetic

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			abnormalities should be included as a subgroup.
	Royal College of Pathologists	There are patient subgroups with specific genetic abnormalities in their cancer (myeloma) cells who have hitherto had poor outcomes on traditional regimens, and who may benefit especially from this technology. Data to confirm these preliminary observations is being accrued in clinical trials, and should be available in the coming few months to inform this appraisal. Patients presenting with renal failure (up to 30%) are at risk of becoming dialysis dependent, and represent an unmet need currently as mortality in this group of patients has not changed over the last 20 years. This technology is safe in renal failure and is particularly effective in such patients because of speed of disease response. Faster disease response increases the chances of renal recovery. This technology thus represents an important advance for this subgroup of patients as it has the potential to reverse renal failure and avoid dialysis. Avoiding dialysis improves survival, and dialysis costs >£30,000 per person per annum, thus has health economic implications.	Comment noted. It was agreed at the scoping workshop that people with renal impairment should not be included as a subgroup for either the induction or consolidation remits, because people with renal impairment, autologous cell transplantation is not normally considered to be an appropriate treatment option and they are excluded from clinical trials. However it was agreed that for the Induction therapy remit people with myeloma cell genetic abnormalities should be included as a subgroup.
	Royal College of Physicians	There are patient subgroups with specific genetic abnormalities in their cancer (myeloma) cells who have hitherto had poor outcomes on traditional regimens, and who may benefit especially from this technology. Data to confirm these preliminary observations is being accrued in clinical trials, and should be available in the coming few months to inform this appraisal. Patients presenting with renal failure (up to 30%) are at risk of becoming dialysis dependent, and represent an unmet need currently as mortality in this group of patients has not changed over the last 20 years. This technology is safe in renal failure and is particularly effective in such patients because of speed of disease response. Faster disease response increases the chances of renal recovery. This technology thus represents an important advance for this subgroup of patients as it has the potential to reverse renal failure and avoid	Comment noted. It was agreed at the scoping workshop that people with renal impairment should not be included as a subgroup for either the induction or consolidation remits, because people with renal impairment, autologous cell transplantation is not normally considered to be an appropriate treatment option and they are excluded from clinical trials. However it

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		dialysis. Avoiding dialysis improves survival, and dialysis costs >£30,000 per person per annum, thus has health economic implications.	was agreed that for the Induction therapy remit people with myeloma cell genetic abnormalities should be included as a subgroup.
Comparators	Celgene	Celgene does not agree with the inclusion of Lenalidomide as a comparator in this scope. The ongoing (referred) STA for Lenalidomide is as a maintenance treatment in the post autologous stem cell transplantation setting.	Comment noted. Attendees at the scoping workshop highlighted There have been a number of phase II trials evaluating lenalidomide in combination with dexamethasone with/or without chemotherapy as induction therapy. Lenalidomide in combination with cyclophosphamide and dexamethasone (RCD) as induction therapy is currently being evaluated in the UK Myeloma XI trial (estimated study completion date December 2012). They also noted that there is an on-going NICE appraisal of lenalidomide monotherapy for maintenance therapy is currently on the NICE technology appraisal programme It was agreed at the scoping workshop that the comparators for the consolidation therapy remit should also include

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			thalidomide as well as best supportive care ('watchful waiting') and lenalidomide.
	CSAS	Comparator regimens identified from on-going and published phase III trials should be specified in the scope for each indication. It is important to consider regimens rather than single drugs for a condition where primary therapy is given as combination therapy. The following combination regimens could be assessed: • bortezomib plus dexamethasone (VD) • bortezomib plus doxorubicin plus dexamethasone • bortezomib plus cyclophosphamide plus dexamethasone • bortezomib plus VBMCP-VBAD (VBMCP: vincristine plus carmustine plus melphalan plus cyclophosphamide plus prednisolone and VBAD: vincristine plus carmustine plus doxorubicin hydrochloride plus dexamethasone) • bortezomib plus thalidomide plus dexamethasone (VTD). • thalidomide plus dexamethasone (TD) • vincristine-based regimens may be less preferred than those that contain novel agents but could be included as comparators. For example vincristine plus doxorubicin plus dexamethasone (VAD) has been studied in non-inferiority trials. It is essential that the regimens in regular use in the NHS are compared and comments on current clinical practice should be included to highlight which combinations these are. It would be more appropriate to assess the comparative effectiveness against lenalidomide in the two technology appraisals currently in preparation or in a multiple technology assessment.	Comments noted. **Induction therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for example CTD (cyclophosphamide, thalidomide and dexamethasone). **Consolidation therapy remit**: The comparators should be amended to 'watch and wait', thalidomide and lenalidomide.
	Janssen	Janssen suggests that the appropriate comparators for bortezomib-based	Comment noted. **Induction**

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		regimens reflect the clinical guidelines (Bird et al, 2011), as various combinations of therapies are commonly used in clinical practice depending on the patient's ability to receive a high dose therapy (HDT). The following regimens should therefore be considered: • CTD [cyclophosphamide, thalidomide and dexamethasone] • TAD [thalidomide, Adriamycin® (doxorubicin) and dexamethasone] • VAD [vincristine, Adriamycin® (doxorubicin) and dexamethasone]* • Thal-Dex [thalidomide and dexamethasone]* * VAD and Thal-Dex regimens are used as main comparators in most clinical studies and should therefore be considered as relevant comparators in this submission, although they are less used in clinical practice in the UK than CTD and TAD.	**therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for example CTD (cyclophosphamide, thalidomide and dexamethasone). **Consolidation therapy remit**: The comparators should be amended to 'watch and wait', thalidomide and lenalidomide
	Myeloma UK	At present in the UK, the standard of care in the induction setting is cyclophosphamide, thalidomide and dexamethasone (CTD). This should be the main comparator if the technology is referred to NICE. As a result of the ongoing Myeloma XI study, it is likely that cyclophosphamide, Revlimid® and dexamethasone (CRD) will replace the role of CTD in this setting. Moving forward, it is important that NICE considers this data when it becomes available (likely to be late 2012 or early 2013).	Comment noted. **Induction therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for example CTD (cyclophosphamide, thalidomide and dexamethasone). **Consolidation therapy remit**: The comparators should be amended to 'watch and wait', thalidomide and lenalidomide
	Royal College of Pathologists	The comparator for induction therapy would be thalidomide with cyclophosphamide and dexamethasone (CTD) as this is the most commonly used regimen outside of clinical trials in the UK. It should be noted that the current Myeloma XI trial is examining the use of lenalidomide, cyclophosphamide and dexamethasone (RCD) as induction	Comment noted. **Induction therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for

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		therapy. Preliminary data indicate that this regimen may be associated with higher response rates and lower levels of toxicity. Preliminary results may be available in the second half of next year	example CTD (cyclophosphamide, thalidomide and dexamethasone). **Consolidation therapy remit**: The comparators should be amended to 'watch and wait', thalidomide and lenalidomide
	Royal College of Physicians	The comparator for induction therapy would be thalidomide with cyclophosphamide and dexamethasone (CTD) as this is the most commonly used regimen outside of clinical trials in the UK. It should be noted that the current Myeloma XI trial is examining the use of lenalidomide, cyclophosphamide and dexamethasone (RCD) as induction therapy. Preliminary data indicate that this regimen may be associated with higher response rates and lower levels of toxicity. Preliminary results may be available in the second half of next year	Comment noted. **Induction therapy remit**: The comparator should be chemotherapy regimens containing thalidomide for example CTD (cyclophosphamide, thalidomide and dexamethasone).**Consolidation therapy remit**: The comparators should be amended to 'watch and wait', thalidomide and lenalidomide
Outcomes	CSAS	Clinical trials assessing bortezomib have subdivided response rate into complete response (CR), near complete response (nCR) and very good partial response (VGPR). Overall survival is the most important outcome Time to response and duration of response to therapy were also included as outcomes in related clinical trials. Formal and valid assessment of quality of life is essential as MM patients often present with significant pain. Pain reduction (independent from quality of life) is also a potentially important health outcome to consider. For maintenance therapy quality of life is especially important and drug-related toxicity should be included. Neuropathy, DVT risk and herpes zoster for	Comments noted. It was agreed at the scoping workshop that the outcomes should be: **Induction therapy** remit: 'response rate', 'progression-free survival', 'proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation', 'health-related quality of life'

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		example.	and 'adverse effects'. **Consolidation therapy**: 'event-free survival', 'overall survival', 'health-related quality of life' and 'adverse effects' It was agreed at the scoping workshop that "pain reduction" could be captured under the 'health-related quality of life' outcome measure and therefore should not be included as a separate outcome.
	Janssen	In addition to the outcomes in the draft scope, we consider the following outcome as being relevant for bortezomib-based regimens for induction treatment in multiple myeloma adult patients likely to receive front line SCT: time to next therapy.	Comment noted. It was agreed at the scoping workshop that the outcome 'time to next treatment' was not relevant as it measures time off treatment.
	Myeloma UK	We agree that these outcome measures capture the most important health-related benefits of the technology. In particular, Progression Free Survival (PFS) is an important outcome measure in myeloma, which is incurable and characterised by repeated relapses and remissions. PFS is usually associated with an improved quality of life as active myeloma is slowed down or prevented from returning. To this end, Treatment Free Intervals (TFI) are also a good measurement of important health-related benefits.	Comments noted. It was agreed at the scoping workshop that 'time to next treatment' was not relevant as it measures time off treatment
	Royal College of Pathologists	Progression free survival is the most important outcome.	Comment noted. No action required.

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	Royal College of Physicians	Progression free survival is the most important outcome.	Comment noted. No action required.
Economic analysis	CSAS	For a condition where reported average survival can range from a few weeks to several years a longer time horizon is appropriate. The cost of prophylactic acyclovir for people on bortezomib should be taken into account.	Comment noted. It was agreed at the scoping workshop that the general statement contained in the scope was adequate "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".
	Royal College of Pathologists	The time horizon is appropriate. We understand that the QALY has been developed as a tool to standardise measurement of benefit between interventions in different diseases, however it may not accurately reflect patient-centred benefits in cancer, because these patients are coming from a very different level of functioning and expectation. Thus, in patients with a severe disease whose prospects of health are poor, more value and significance should be attached to smaller QALY gains. We encourage NICE to consider the use of quality modifying tools in the final evaluation	Comments noted. Section 5.12 of the Methods Guide states that "An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit".
	Royal College of Physicians	The time horizon is appropriate. We understand that the QALY has been developed as a tool to standardise measurement of benefit between interventions in different diseases, however it may not accurately reflect patient-centred benefits in cancer, because these patients are coming from a very different level of functioning and expectation. Thus, in patients with a severe disease whose prospects of health are poor, more value and significance should be attached to smaller QALY gains. We	Comments noted. Section 5.12 of the Methods Guide states that "An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health

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		encourage NICE to consider the use of quality modifying tools in the final evaluation	benefit".
Equality and Diversity	Celgene	Myeloma mostly affects the elderly population, who often face other concomitant conditions. Equality of access may be achieved by ensuring that the benefits of newer treatments reach these patients	Comment noted. Attendees at the scoping workshop did not consider this to be an equalities issue and therefore no changes have been made to the draft scope.
	Royal College of Pathologists	Myeloma is a cancer in which bone disease is a prominent feature at presentation, affecting up to 80% of patients, and causing bone pain, vertebral fractures, deformity, immobility and impaired physical functioning. Because of this considerable bone morbidity that myeloma patients suffer, any effective disease-directed therapy, will, by halting bone destruction, have a disproportionately large incremental health gain and improvement in quality of life. In addition, effective therapy at diagnosis may result in maximal benefit from other NICE approved technologies such as vertebroplasty/kyphoplasty.	Comments noted.
	Royal College of Physicians	Myeloma is a cancer in which bone disease is a prominent feature at presentation, affecting up to 80% of patients, and causing bone pain, vertebral fractures, deformity, immobility and impaired physical functioning. Because of this considerable bone morbidity that myeloma patients suffer, any effective disease-directed therapy, will, by halting bone destruction, have a disproportionately large incremental health gain and improvement in quality of life. In addition, effective therapy at diagnosis may result in maximal benefit from other NICE approved technologies such as vertebroplasty/kyphoplasty.	Comments noted.
Other considerations	Janssen	Bortezomib is currently injected via intravenous route. [redacted]	Comments noted.

Section	Consultees	Comments	Action
		[redacted]	
Questions for consultation	Myeloma UK	Bortezomib is the only licensed proteasome inihibitor in the treatment of myeloma. It continues to be a novel and innovative treatment with mechanisms of action that are different to and synergistic with other available treatments. The approval of bortezomib in the induction setting would provide a very important additional treatment option on a number of levels. We look forward to exploring these further at the scoping workshop. Emerging and evolving data suggest that bortezomib may be more beneficial in high-risk genetic groups than current standard induction treatment; however, more data is needed to support this.	Comments noted.
	Royal College of Pathologists	The technology is innovative, and represents a step-change in the management of multiple myeloma, because it is a first-in-class agent that has shown remarkable activity in the treatment of this cancer. The current standard induction regimen of CTD has the advantage over traditional regimens of being oral, however, progression free survival is equivalent to that produced by traditional (VAD-like) regimens. Regimens incorporating this technology have been shown in phase 3 studies to be superior with respect to progression free survival and overall survival. This technology has the potential to make a substantial impact on disease control and hence health-related benefits. Importantly, the technology has efficacy in the sub-group of patients with poor risk genetics who represent an unmet need because they respond poorly to currently available protocols.	Comments noted.
	Royal College of Physicians	The technology is innovative, and represents a step-change in the management of multiple myeloma, because it is a first-in-class agent that has shown remarkable activity in the treatment of this cancer. The current standard induction regimen of CTD has the advantage over traditional regimens of being oral, however, progression free survival is equivalent to that produced by traditional (VAD-like) regimens. Regimens incorporating this technology have been shown in phase 3 studies to be superior with respect to progression free survival and overall survival. This technology has the potential to make a	Comments noted. During the scoping workshop it was agreed that for the Induction therapy remit people with myeloma cell genetic abnormalities should be included as a subgroup.

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		substantial impact on disease control and hence health-related benefits. Importantly, the technology has efficacy in the sub-group of patients with poor risk genetics who represent an unmet need because they respond poorly to currently available protocols.	
Additional comments on the draft scope.	CSAS	It would be more appropriate to assess the comparative effectiveness against lenalidomide in the two technology appraisals in preparation or in a multiple technology appraisal.	Comment noted. At the scoping workshop it was acknowledged that while MTAs were useful to clinical practice they took considerably longer. It was highlighted that it was crucial for patients to have access to this treatment, particularly in regards to the proposed licensed indication for induction therapy as soon as possible. It was further noted that the STA process would allow timelines to be tailored to the regulatory schedule for each licensed indication. It was agreed at the scoping workshop that this appraisal would be suitable for the STA process.
	Janssen	At this stage we cannot provide any information with regard to potential subgroups of patients in whom bortezomib is expected to be more clinically effective and cost-effective.	Comment noted
	Royal College of Pathologists	Chemotherapy agents without a novel agent are still used in UK clinical practice as induction regimens, however this is not the rule, and would usually be because of intolerance of the novel agent, ie thalidomide. In such situations, the technology would be an important advance as it would offer	Comment noted

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		such patients the opportunity to receive an effective induction treatment.	
	Royal College of Physicians	Chemotherapy agents without a novel agent are still used in UK clinical practice as induction regimens, however this is not the rule, and would usually be because of intolerance of the novel agent, i.e. thalidomide. In such situations, the technology would be an important advance as it would offer such patients the opportunity to receive an effective induction treatment.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Cochrane Haematological Malignancies Group
Marie Curie Cancer Care

Comment 3: Provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Add African Caribbean Leukaemia Trust to Patient/Carer Groups	NICE Secretariat		Added	African Caribbean Leukaemia Trust meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group consultee.
2.	Add Anthony Nolan Bone Marrow Trust to patent/carer groups	NICE Secretariat		Added	Anthony Nolan Bone Marrow Trust meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group consultee.
3.	Add National Council for Palliative Care to patient/carer groups	NICE Secretariat		Added	National Council for Palliative Care meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group consultee.

4.	Add Sue Ryder Care to patient/carer groups	NICE Secretariat		Added	Sue Ryder Care meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group consultee.
5.	Add British Society for Blood and Bone Marrow Transplant to professional groups	NICE Secretariat		Added	British Society for Blood and Bone Marrow Transplant meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.
6.	Add British Transplantation Society to professional groups	NICE Secretariat		Added	British Transplantation Society meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.
7.	Add Allied Health Professional Federation to general commentators	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
8.	Add Leukaemia Busters to relevant research groups	NICE Secretariat		Added	Leukaemia Busters meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a relevant research group.