Appendix G -Professional organisation statement template

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Kwee L Yong

Name of your organisation: UK Myeloma Forum

Are you (tick all that apply):

 a specialist in the treatment of people with the condition for which NICE is considering this technology?

 a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Additional note:
I am lead Clinician for multiple myeloma for the North London Cancer Network and head up the myeloma service at UCLH. I am advocacy lead on the UK Myeloma Forum executive committee, and a member of the MyelomaUK Clinical Trials Network. I am Chief Investigator on commercial and NCRI investigator-led academic studies in myeloma, including several that employ the technology. I have written this statement on behalf of the Royal College of Pathologists, and the UK Myeloma Forum.

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What is the expected place of the technology in current practice?

Current treatment of multiple myeloma in the NHS

Introduction

Multiple myeloma (MM) is a plasma cell cancer that has its peak incidence in the 8th decade of life, with a higher incidence in men. The disease is preceded by a prodromal condition termed monoclonal gammopathy of uncertain significance (MGUS), that progresses (usually over years) through asymptomatic MM before symptomatic disease develops. Symptomatic MM is characterised by disease progression causing organ dysfunction, in the form of bone marrow failure, bone destruction, hypercalcaemia and renal failure, impaired immunity or symptoms related to the presence of the paraprotein. The paraprotein, or M-protein, is produced by the MM plasma cells, and, in most patients, can be used to monitor disease response to therapy, as well as subsequent relapse. Because MM is incurable, treatment is only initiated once symptomatic disease develops. Most patients are diagnosed at the stage when they develop symptoms, and the most common presentations include anaemia, recurrent infections, bone pain (especially back pain) and fractures, and renal failure.

Treatment of newly diagnosed patients

The broad aims of treatment are to achieve disease control, usually by reducing the bulk of the tumour, aiming to ameliorate symptoms (e.g. bone pain) through managing and preventing further end-organ damage, and prolonging survival whilst maintaining quality of life. A more aggressive strategy is adopted in patients who are younger and fitter at the time of diagnosis, in the expectation that prompt and maximal tumour reduction will also maximise length of first remission (termed plateau phase). This 'frontline' strategy consists of induction chemotherapy, followed by autologous stem cell transplantation (ASCT), an evidence-based strategy considered as "gold standard" (1-3). This is the approach that is recommended for patients who are considered young and fit enough (eligible) for ASCT; the age limit is generally around 65-70 years, but biological (the consideration of co-morbidity risk), rather than chronological age is considered to be key. Exploratory strategies of consolidation and/or maintenance therapy post-ASCT are only employed as part of clinical trials; these are not standard of care, nor are they licensed. This is the patient group that is relevant to the technology under consideration.

In the last few years, the availability of newer, more effective anti-MM agents ("novel" or biological agents) has meant that the traditional infusional VAD (vincristine, Adriamycin and dexamethasone)–type induction regimens have been replaced, almost everywhere in the world, by induction regimens containing thalidomide, bortezomib or lenalidomide. These agents are all licensed in the relapsed setting, and thalidomide and bortezomib are licensed for the frontline therapy of patients who are *not* eligible for ASCT.

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Natural history of MM

The recent inclusion of novel agents into induction regimens means that the majority of patients (80-90%) will respond (deemed to be a partial response or greater) to frontline therapy, and enter a period of disease remission, or stability (plateau phase). The natural history of the disease is repeated relapses, followed by increasingly shorter 'plateau phases', until the disease enters a refractory and aggressive end-stage, when patients die of overwhelming disease burden, or organ failure (Figure 1)(4) At each relapse, some patients will be unable to receive effective salvage, so that a decreasing proportion of patients are treated at each subsequent relapse.

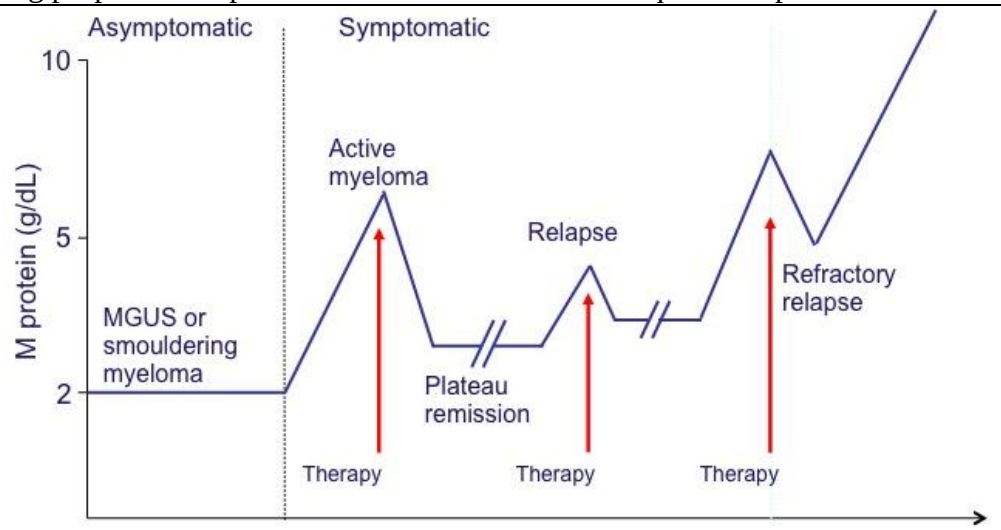

Figure 1. Disease course in multiple myeloma.
Patients typically have a pre-malignant phase of disease (termed MGUS, smouldering or asymptomatic myeloma), and treatment is only initiated when there is evidence of organ damage, usually also heralded by a rise in the paraprotein. Initial response to chemotherapy results in a period of 'remission' or plateau' followed by further relapses and subsequent disease responses that are usually less deep, and of shorter duration, until refractory end-stage disease.

Expected place of the technology in UK practice

Current UK practice in patients eligible for ASCT, including use of the technology and geographical variation in the NHS

Cyclophosphamide, thalidomide and dexamethasone (CTD) is the most widely used induction regimen in the UK, following the demonstration by the Myeloma IX study that this oral regimen can be delivered safely and effectively without the need for intra-venous therapy (5). Up to 6 cycles are administered, followed, in responding patients, by stem cell harvesting. Provided a sufficient number of stem cells are obtained, patients proceed to high dose melphalan and ASCT. There are no consolidation or maintenance strategies that are currently used in the UK, as part of standard care although these are currently being investigated in the Myeloma XI trial. Induction regimens using thalidomide produce higher response rates, but this has not resulted in longer remission periods (ie prolonged progression free survival, or PFS) (5, 6). Thus bortezomib-containing induction regimens (the technology) are used

increasingly in situations where thalidomide is contra-indicated, or not tolerated by the patient. At present, under the Cancer Drugs Fund (CDF), Bortezomib as induction therapy preceding ASCT is routinely funded in 3 of the 9 CDFs including the London area (Added to the list in March 2012: http://www.nlcn.nhs.uk/interim-cancer-drugs-fund), considered but not routinely funded in 1of 9 and is not considered by 4 of 9 (in the baseline commissioning of 1 CDF: Midland & East CDF).

High risk subgroups

Considerable clinical heterogeneity in this cancer is underpinned by distinct genetic lesions, some of which impart a significantly shorter survival. Such patients are considered to have 'high risk' disease, however, other factors such as disease burden, renal failure and aggressive morphological features may also impart a worse prognosis. Thus, a proportion of patients (15-40%) are considered to have 'high risk' disease, depending upon which genetic factors are used in the definition (7, 8). Varying definitions of high risk disease are used, but in general, the following are considered by most to be high risk features: the t(4;14) and t(14;16) translocations, loss of 17p (p53 gene) and high ISS score(9-11). There are emerging data to suggest that the technology may be able, in part, to overcome the poor prognosis of such high risk groups of patients, however, the outcome data are not sufficiently mature, and very few centres outside the major teaching hospitals have the resources to undertake routine testing for such genetic lesions. Thus, it is not clinically possible to identify a subgroup of patients who would definitely benefit from the technology, to the exclusion of the remainder.

Available guidelines

The UKMF guidelines state that "induction regimens should contain at least one novel agent… CTD, TAD, bortezomib/dexamethasone and PAD produce superior response rates to VAD. Decisions regarding the most appropriate induction regimen for individual patients will require the assessment of… renal function, thrombotic risk, pre-existing neuropathy …."(12). The IMWG Consensus statement concludes that "… recommend using one of the bortezomib-containing triplet regimens as upfront induction therapy in a transplantation-eligible MM patient." (13)

Current use of the technology in the relapse setting, variations in use, and appropriate healthcare setting

Bortezomib is approved for the treatment of patients with first relapse of their myeloma, under the VRS (velcade response scheme, Guidance TA129). Bortezomib for 2nd and subsequent relapse is routinely commissioned by 2 of 9 CDFs, considered but not routinely funded by 2 of 9 CDFs and is not considered by 5 of 9 CDFs if they are Bortezomib naïve or have previously responded well to first exposure. When used in the relapse setting, bortezomib is seldom used within its licensed indication, ie as a monotherapy. Instead, it is almost always used with dexamethasone, and often with a third agent e.g. cyclophosphamide (VCD regimen), or doxorubicin (PAD regimen. Bortezomib is usually administered as an outpatient therapy, in haematology or

oncology departments with expertise in managing and preventing the most common side effects: peripheral neuropathy, low blood counts, constipation and fatigue. UK experience in managing these toxicities has grown enormously over the last 5 years, reflected in the comprehensive guidance contained in the recently published UKMF Guidelines for the management of myeloma (12). Recently, the license has been amended to allow a change from intravenous to subcutaneous route of administration, a safer mode of delivery with equivalent efficacy (14). This means that the technology is now employed safely and to maximal efficacy in the UK.

The advantages and disadvantages of the technology

The evidence base for the technology as induction therapy prior to ASCT

The main goal of induction therapy in patients who are fit enough to receive ASCT is to achieve maximal disease control as rapidly as possible, so as to minimise any further organ damage, whilst aiming for maximal tumour reduction and preservation of (normal haematopoietic) stem cell function. The depth of response of MM to therapy is correlated with durability of response (15, 16). The technology has been demonstrated, in 4 high quality randomised RCT, to produce superior results (higher rates of disease response, improved progression free survival) when compared with standard therapies (traditional VAD regimens, and thalidomide-containing regimens (17-20)).

Table 1. Summary of major RCTs evaluating the technology with main parameters of benefit

Study	**Arm (number of patients)**	**Response to induction (pre-ASCT) %**		**Response post-ASCT %**		**PFS (months)**	**HR of PFS (95%CI)**	**% proceeding to ASCT**
		CR	ORR	CR	ORR			
HOVON-65/GMMG-HD4	**PAD (417)**	**11**	**84.2**	**22.5**	**77.5**	**35.0**	**0.74 0.62, 0.89 p=0.001**	85
	VAD (416)	2.9**	61.3	12.3**	65.9**	28.1		84
IFM 2005-01	**Vel/Dex (240)**	**5.4**	**77.1**	**18.3**	**79.6**	**36.1**	0.88 0.7-1.11	86
	VAD (242)	1.2*	60.7	10.3*	74.4	29.7		81
PETHEMA/ GEM trial	**VTD (130)**	**35.4**	**86**	**46.9**	**77.7**	**55.5**	**0.65 0.45-0.92 p=0.015**	81
	TD (127)	14.2**	62	23.6**	56.7	27.9		61
GIMEMA	**VTD (236)**	**18.6**	**93.2**	**33.7**	**93.2**	**NR**	**0.63 0.45-0.88 p=0.0061**	88
	TD (238)	4.6**	78.6	22.7*	84.5	42		82

* p<0.01
** p<0.001

In each of these studies, complete response and overall response rates were higher in the bortezomib-containing arms, both post-induction, and following ASCT. This is important because increased depth of response (CR rate) is correlated with superior PFS and OS, in many reports of the outcome of upfront ASCT(16). On the other hand, some patients who never achieve a complete response can enjoy a prolonged plateau phase (21). Hence clinically, the most important outcome of frontline treatment is progression free survival (PFS), because it is in the first plateau phase that QOL is highest (22). PFS was superior in 3 of the 4 studies in Table 1 (highlighted in bold), and in the HOVON study, a survival benefit was also seen in the bortezomib arm. Overall survival benefit in the other studies may emerge with longer follow up, as the increasing number of new and effective salvage therapies result in longer survival for most patients with MM. Another important outcome is the percentage of patients proceeding to ASCT, as a major goal of induction therapy is to achieve sufficient disease control in order that the patient can benefit from high dose chemotherapy and ASCT. In all these studies, a higher proportion of patients were able to proceed to ASCT in the bortezomib arms.

Relevance of these RCTs to UK MM patients and clinical practice

Whilst these RCTs were on-going, the Myeloma IX study compared the intravenous induction regimen, C-VAD, with the oral regimen, CTD. Although response rates were deeper and higher in the CTD arm, there was no difference in PFS. The patient populations studied in these RCTs were broadly similar to UK patients entered into the national Myeloma IX study, except that the Myeloma IX study included a small percentage of patients older than 65 years, and a greater proportion of patients with ISS stage 3. These factors may account for a generally lower proportion of patients proceeding to ASCT in the Myeloma IX study (67%). On the other hand, a similar proportion of patients in the control (TD) arm of the PETHEMA study proceeded to ASCT (62%), with very similar PFS outcome (28.2 months) compared to patients treated on the CTD arm of Myeloma IX (27 months). These figures suggest that the population of patients studied in at least the Spanish PETHEMA study, is similar to the UK population.

All 3 regimens (bortezomib/dexamethasone, PAD and VTD) are familiar to UK specialists treating patients with MM. As stated above, bortezomib is commonly used in conjunction with dexamethasone in the relapsed setting, and the addition of a third agent such as doxorubicin, cyclophosphamide or thalidomide, in order to improve disease response and response durability, is increasing. The PAD regimen has been used in the Myeloma X (n=297) study, as salvage prior to a second ASCT in suitable patients, where over 90% of patients demonstrated at least a PR (results to be presented at the EBMT Annual Scientific Conference, April 2013, London, UK).

Advantages, disadvantages and practical implications of the use of the technology

A clear clinical advantage of the technology is the ability to produce rapid disease control, with a higher proportion of patients proceeding to ASCT and hence achieving longer PFS. The benefit of improved PFS when compared with traditional and thalidomide-containing regimens has already been noted. 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(23). Recovery of renal function has important implications for health resources as well as patient quality of life. Bortezomib-related toxicity has been significantly reduced with the use of careful dose adjustment schedules, and the change-over to subcutaneous mode of administration (14). Indeed with increasing experience with the technology, adverse reactions in current clinical practice are generally lower than reported in the phase 3 clinical trials, that were conducted using the intravenous route of administration (24). Disadvantages include the inconvenience of hospital attendance for the injections, however, these attendances are brief and far shorter than with intravenous regimens. 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. When used together, e.g. in the VTD regimen, the risk and incidence of neuropathy is not increased, and the need for thrombo-prophylaxis is similar.

Effect of NICE guidance on the delivery of care for patients with MM

NICE guidance on the technology will permit clinical decision-making to direct treatment on an individual patient need basis rather than cohort health economic modelling. For example, when patients present with a large tumour load, on-going end-organ damage or evidence of aggressive disease tempo, the clinical need to gain rapid tumour control could be most effectively achieved with a Bortezomib-containing regimen. The importance of bortezomib therapy in renal failure has already been explained. Additionally, the thalidomide-associated risk of venous thrombo-embolism is primarily associated with first line therapy(25), hence the need for effective thrombo-prophylaxis; however where patients are at high risk of bleeding on anti-coagulation, the use of a bortezomib-containing regimen would be clinically recommended. Thus NICE guidance would permit a different order of delivery of lines of therapy to the current status quo (Thalidomide-based, followed by Bortezomib-based followed by Lenalidomide-based), enabling clinicians to exercise clinical judgement in a patient-centred approach to therapy.

Implementation issues

Because the technology has been in use for many years in the relapsed setting, it is unlikely that any additional education or training resources will be required. It may increase the number of patients being treated on day-care units, however, home delivery schemes are under evaluation, and, because of the greater convenience and impact on quality of life may prove to be popular. Implementation of the technology will reduce the number of patients requiring thromboprophylaxis, and the attendant burden of anticoagulation monitoring and bleeding complications. It will also reduce

the hidden costs of health care caused by adverse events on Thalidomide eg thromboembolism, cardiac arrhythmias.

Equality

There is no particular implication for people protected by the equality legislation. We wish to point out that a negative recommendation would have an adverse impact on patents who are unable to receive thalidomide as part of their induction therapy, because they are contra-indicated to receive, or are intolerant of thalidomide. The lack of an effective induction therapy for such patients would significantly reduce their chances of receiving an ASCT. Another such group of patients are those already alluded to earlier, who present with a particularly aggressive disease and marked organ damage (e.g. Renal failure) who need rapid disease control.

Summary

The main goal of therapy in patients with newly diagnosed MM who are fit and young enough is to achieve maximal disease control as rapidly and safely as possible, thus enabling the patient to proceed to and benefit from ASCT. The technology being appraised represents a major advance in providing an effective therapy that achieves this in >80% of such patients, and has proved to be superior in this respect, as well as in prolonging PFS (and OS), when compared to current standard therapies, including, we believe, the CTD regimen. We believe that a positive recommendation will significantly improve the outlook for this patient group with MM.

References

1. Cook G, Jackson GH, Morgan GJ, Russell N, Kirkland K, Lee J, et al. The outcome of high-dose chemotherapy and auto-SCT in patients with multiple myeloma: a UK/Ireland and European benchmarking comparative analysis. Bone Marrow Transpl. 2011 Sep;46(9):1210-8.

2. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. The New England journal of medicine. [Clinical Trial
Clinical Trial, Phase III
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2003 May 8;348(19):1875-83.

3. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. The New England journal of medicine. [Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 1996 Jul 11;335(2):91-7.

4. Shah N, Lonial S. Evidence-based mini-review: treatment options for patients with relapsed/refractory myeloma previously treated with novel agents and high-dose

chemotherapy and autologous stem-cell transplantation. Hematology Am Soc Hematol Educ Program. [Research Support, Non-U.S. Gov't
Review]. 2010;2010:310-3.

5. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro Coy N, et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. [Clinical Trial, Phase III
Multicenter Study
Randomized Controlled Trial
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2012 Mar;97(3):442-50.

6. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. [Clinical Trial, Phase III
Randomized Controlled Trial]. 2010 Feb 11;115(6):1113-20.

7. Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. [Research Support, Non-U.S. Gov't]. 2012 Feb;26(2):349-55.

8. Chang H, Qi XY, Samiee S, Yi QL, Chen C, Trudel S, et al. Genetic risk identifies multiple myeloma patients who do not benefit from autologous stem cell transplantation. Bone Marrow Transpl. [Research Support, Non-U.S. Gov't]. 2005 Nov;36(9):793-6.

9. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. [Comparative Study
Multicenter Study
Research Support, Non-U.S. Gov't]. 2005 May 20;23(15):3412-20.

10. Neben K, Jauch A, Bertsch U, Heiss C, Hielscher T, Seckinger A, et al. Combining information regarding chromosomal aberrations t(4;14) and del(17p13) with the International Staging System classification allows stratification of myeloma patients undergoing autologous stem cell transplantation. Haematologica. [Research Support, Non-U.S. Gov't]. 2010 Jul;95(7):1150-7.

11. Fonseca R, Bergsagel P, Drach J, Shaughnessy J, Gutierrez N, Stewart A, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210-21.

12. Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. British journal of haematology. 2011 May 14.

13. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of

multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood. 2011 Jun 9;117(23):6063-73.

14. Arnulf B, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, van de Velde H, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica. [Research Support, Non-U.S. Gov't]. 2012 Dec;97(12):1925-8.

15. Harousseau JL, Avet-Loiseau H, Attal M, Charbonnel C, Garban F, Hulin C, et al. Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 Trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009 Dec 1;27(34):5720-6.

16. Harousseau J, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. Blood. 2009;114(15):3139-46.

17. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. [Clinical Trial, Phase III
Comparative Study
Multicenter Study
Randomized Controlled Trial]. 2010 Oct 20;28(30):4621-9.

18. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. [Clinical Trial, Phase III
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2012 Aug 20;30(24):2946-55.

19. Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. [Clinical Trial, Phase III
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2012 Aug 23;120(8):1589-96.

20. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. [Clinical Trial, Phase III
Comparative Study
Multicenter Study
Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2010 Dec 18;376(9758):2075-85.

21. Pineda-Roman M, Bolejack V, Arzoumanian V, Anaissie E, van Rhee F, Zangari M, et al. Complete response in myeloma extends survival without, but not with history of prior monoclonal gammopathy of undetermined significance or smouldering disease. British journal of haematology. [Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2007 Feb;136(3):393-9.

22. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer. 2013 Feb;21(2):599-607.

23. Dimopoulos MA, Roussou M, Gkotzamanidou M, Nikitas N, Psimenou E, Mparmparoussi D, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2012 Jul 5.

24. Moore S, Atwal S, Sachchithanantham S, Streetly M, Khan I, Percy L, et al. Weekly intravenous bortezomib is effective and well tolerated in relapsed/refractory myeloma. European journal of haematology. 2013 Jan 7.

25. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2007 Dec 20.