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## **Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide, lenalidomide or bortezomib- containing regimens**

Shaji Kumar, Sergio Giral, Edward A. Stadtmauer, Jean L. Harousseau, Antonio Palumbo, William Bensinger, Raymond L. Comenzo, Suzanne Lentzsch, Nikhil Munshi, Ruben Niesvizky, Jesus San Miguel, Heinz Ludwig, Leif Bergsagel, Joan Blade, Sagar Lonial, Kenneth C. Anderson, Patrizia Tosi, Pieter Sonneveld, Orhan Sezer, David Vesole, Michele Cavo, Hermann Einsele, Paul G. Richardson, Brian G.M. Durie and S. Vincent Rajkumar

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**Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide, lenalidomide or bortezomib – containing regimens**

Shaji Kumar, MD<sup>1</sup>; Sergio Giralt, MD<sup>2</sup>; Edward A. Stadtmauer, MD<sup>3</sup>; Jean L. Harousseau, MD<sup>4</sup>; Antonio Palumbo, MD<sup>5</sup>; William Bensinger, MD<sup>6</sup>; Raymond L. Comenzo, MD<sup>7</sup>; Suzanne Lentzsch, MD<sup>8</sup>; Nikhil Munshi, MD<sup>9</sup>; Ruben Niesvizky, MD<sup>10</sup>; Jesus San Miguel, MD<sup>11</sup>; Heinz Ludwig, MD<sup>12</sup>; Leif Bergsagel, MD<sup>1</sup>; Joan Blade, MD<sup>13</sup>; Sagar Lonial, MD<sup>14</sup>; Kenneth C. Anderson, MD<sup>9</sup>; Patrizia Tosi, MD<sup>15</sup>; Pieter Sonneveld, MD<sup>16</sup>; Orhan Sezer, MD<sup>17</sup>; David Vesole, MD<sup>18</sup>; Michele Cavo, MD<sup>19</sup>; Hermann Einsele, MD<sup>20</sup>; Paul G. Richardson, MD<sup>9</sup>; Brian G.M. Durie, MD<sup>21</sup>; S. Vincent Rajkumar, MD<sup>1</sup>; On behalf of the IMWG\*

*<sup>1</sup>Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA; <sup>2</sup>Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; <sup>3</sup>Bone Marrow and Stem Cell Transplant Program, University of Pennsylvania Abramson Cancer Center, Philadelphia, Pennsylvania, USA; <sup>4</sup>Department of Hematology, Institute de Biologie, Nantes, France; <sup>5</sup>Divisione di Ematologia dell Università di Torino, Azienda Ospedaliera S. Giovanni Battista, Ospedale Molinette Torino, Italy; <sup>6</sup>Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; <sup>7</sup>Department of Clinical Laboratories, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; <sup>8</sup>Division of Hematology/Oncology University of Pittsburgh UMPC Cancer Pavilion,*

Pittsburgh, PA, <sup>9</sup>Department of Medical Oncology, Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; <sup>10</sup>Weill Cornell Medical College, New York, NY, USA, <sup>11</sup>Department of Hematology, Servicio de Hepatología, Hospital Universitario de Salamanca. CIC, IBMCC (USAL-CSIC). Spain; <sup>12</sup>1<sup>st</sup> Medical Department, Center for Oncology and Hematology, Wilhelminenspital, Wien, Vienna, Austria; <sup>13</sup>Department of Hematology, Hospital Clinic, IDIBAPS, Barcelona, Spain; <sup>14</sup>Department of Hematology & Medical Oncology, Emory University, Atlanta, Georgia, USA; <sup>15</sup>Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; <sup>16</sup>Erasmus MC, Department of Hematology, Rotterdam, The Netherlands; <sup>17</sup>Department of Hematology/Oncology, University of Berlin, Germany; <sup>18</sup>David Vesole, Division of Hematology/Oncology, Loyola University, Chicago, Illinois, USA; <sup>19</sup>Institute of Hematology and Medical Oncology Seragnoli, Bologna, Italy; <sup>20</sup>Department of Internal Medicine University of Wurzburg, Wurzburg, Germany; <sup>21</sup>Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Los Angeles, California, USA,

**Corresponding Author:** Dr. Shaji Kumar, M.D., Associate Professor of Medicine, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55906  
Phone: (507) 266-0523; Fax: (507) 284-4972; kumar.shaji@mayo.edu

For a complete list of IMWG participants, see the Supplemental Appendix.

## **ABSTRACT**

The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide and bortezomib, leading to improved outcomes. High dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Prior to the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given their potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group was convened to examine the implications of these therapies on stem cell collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferably within the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization.

## **High Dose Therapy and Autologous Stem Cell Transplantation for multiple myeloma (MM)**

High Dose Therapy and autologous stem cell transplantation (ASCT) remains an integral component of the myeloma treatment algorithm for patients considered eligible for the procedure. The majority of the randomized clinical trials have demonstrated a superior progression free survival among patients receiving ASCT compared to those treated with only conventional therapies and ASCT was associated with superior overall survival in three of those.<sup>1-7</sup> Subsequent randomized trials have further defined the role of ASCT by demonstrating equivalent overall survival for delayed transplant compared to upfront ASCT, albeit with some compromise in the quality of life parameters.<sup>8</sup> Introduction of novel agents such as thalidomide, lenalidomide and bortezomib have resulted in a paradigm change in the therapy of myeloma.<sup>9-14</sup> The high response rates with these agents, hitherto seen only in the context of high dose therapy, have once again raised questions regarding the utility of ASCT in the setting of myeloma. Given the lack of long term follow up of patients treated with these new agents, the durability of these responses as well as their potential long term adverse effects remain unknown and ASCT continues to be an important part of myeloma therapy.

Despite the increased use of the newer drugs for the initial treatment of myeloma, there is a continuous increase in the number of ASCTs reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), highlighting its continued important role. Currently, the novel agents appear best suited to be employed as first line therapy enhancing the quality of responses prior to proceeding to ASCT and diminishing early

mortality from the disease, or in selected patients as primary therapy moving ASCT to a second line position or as adjuncts to transplant conditioning regimens or as maintenance therapy in patients undergoing ASCT.<sup>15-23</sup> Furthermore, in a randomized trial evaluating single versus double ASCT a survival advantage with tandem ASCT was demonstrated in an unplanned subset analysis for those patients not obtaining at least a very good partial response (VGPR) after the first ASCT. This observation has increased the number of ASCT being performed for patients not achieving VGPR after the first ASCT.<sup>24</sup> In addition, ASCT can also be employed as part of second-line therapy after relapse especially among patients who achieved a durable response after the first ASCT.<sup>6,23</sup>

The traditional approach to patients with newly diagnosed myeloma, considered to be a candidate for ASCT, has been to provide initial therapy with 4-6 cycles of a non-alkylator containing regimen followed by collection of stem cells and high dose therapy. The initial therapy for the disease allows time to obtain necessary insurance approvals as well as control disease related symptoms, simultaneously controlling toxicity by limiting the number of cycles. In addition, adequate disease control provides an opportunity to reverse disease related complications where feasible, and generally improve the functional status of the patient, allowing for a safer transplant. Until the advent of the novel agents, the initial therapy regimens commonly used were VAD or single agent dexamethasone, both of which shared the advantage of having little impact stem cell mobilization and collection. Previous studies had shown that alkylating agents

can potentially affect the stem cell pool and thus interfere with the ability to collect adequate numbers of stem cells.<sup>25-28</sup>

The number of CD34<sup>+</sup> cells collected for ASCT is dependent on a number of factors, most importantly the number of intended transplants. The cell collection target usually depends on patient age, upfront vs. delayed ASCT, patient preference, patient performance status and presence of co-morbidities among others. Traditionally, the target for CD34 cell collection for a single ASCT has been 4-6x10<sup>6</sup> CD34<sup>+</sup> /kg with studies showing a deleterious impact on engraftment characteristics once the number falls below 2x10<sup>6</sup> CD34<sup>+</sup> /kg.<sup>29,30</sup> Use of more CD34 cells has not been consistently associated with any significant benefit in the parameters studied. Patient age is an important factor from several perspectives. Clearly there is decreasing use of SCT with increasing patient age, although selected patients with good performance status may be transplanted into their mid-seventies. The target for stem cell collection is usually based on single transplantation in the United States, since Medicare reimburses only single SCT for myeloma. Finally, there is a clear impact of age on the ability to collect stem cells with decreasing yield with advancing age.<sup>31</sup> In the majority of patients undergoing an ASCT for myeloma, stem cells are collected from the peripheral blood following mobilization using growth factor administration with or without preceding chemotherapy. A minority of patients undergoes ASCT with stem cells collected through a bone marrow harvest. Use of cyclophosphamide or other chemotherapy regimens for myelosuppression to achieve rebound CD34<sup>+</sup> cell spillover into the blood with enhanced effects of myeloid growth factors during the recovery phase of peripheral blood counts

allows for a more rapid stem cell collection and higher numbers of collected CD34<sup>+</sup> cells compared to myeloid growth factor alone.<sup>32-35</sup> Institutions differ in their standard approach for collecting stem cells, there being pros and cons to either approach. Use of cyclophosphamide, while allowing better stem cell collection and less likelihood of a collection failure (less than the 2x10<sup>6</sup> CD34<sup>+</sup> /kg), prolongs the collection process while awaiting count recovery and increases the risk of febrile neutropenia and other infectious complications.

One of the recent advances in the field of stem cell mobilization strategies has been the introduction of AMD3100 (Plerixafor®), a receptor chemokine receptor 4 (CXCR4) inhibitor. Previous studies have highlighted the role of CXCR4 in the stem cell mobilization induced by G-CSF and cyclophosphamide. Levesque et al showed that mobilization of stem cells by G-CSF coincides in vivo with the cleavage of the N-terminus of the chemokine receptor CXCR4 on the stem cells in the BM, leading to loss of chemotaxis in response to the CXCR4 ligand, the chemokine stromal cell-derived factor-1 (SDF-1/CXCL12).<sup>36</sup> In addition, accumulation of serine proteases led to cleavage and inactivation of SDF-1. Originally developed as an anti-HIV drug, the ability of this drug to enhance peripheral mobilization of CD34<sup>+</sup> cells was subsequently recognized. AMD3100, a reversible inhibitor of the binding of stromal cell derived factor - 1α (SDF-1α, also known as CXCL12) to its cognate CXCR4, has been shown to increase the number of circulating CD34<sup>+</sup> cells in healthy volunteers when administered alone or with G-CSF prior to treatment.<sup>37-39</sup> Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemo-attractant effect of SDF-1α that is

produced locally by bone marrow stromal cells. Once in the marrow, it is also believed that stem cell CXCR4 can act to help “anchor” these cells to stromal cell surface SDF-1 $\alpha$ . AMD3100-induced leukocytosis and elevations in circulating hematopoietic progenitor cell levels are thought to result from a disruption of the CXCR4/CXCL12 interaction and cell adhesion effects, resulting in the appearance of both mature and pluripotent cells in the systemic circulation. AMD3100 has been shown to exert an additive effect on the number of circulating hematopoietic stem and progenitor cells when administered with G-CSF. AMD3100-3102 was a multi-center randomized, double-blind, placebo-controlled comparative trials designed to examine the ability of 240  $\mu$ g/kg AMD3100 plus G-CSF vs. placebo plus G-CSF to mobilize CD34<sup>+</sup> stem cells in patients with MM, who had not previously failed stem cell collections and had not received prior stem cell transplant. The primary endpoint, the percentage of patients who achieved  $\geq 6 \times 10^6$  CD34<sup>+</sup> cells/kg in 2 or less apheresis days, was met in 106/128 (72%) patients in the AMD plus G-CSF group and 53/154 (34%) patients in the placebo plus G-CSF group,  $p < 0.0001$ . Fifty four percent of study patients reached target after 1 day of apheresis in the AMD + G-CSF group compared to 17.3% in the placebo plus G-CSF group. After 4 days of apheresis, these numbers were 86.8% and 56% respectively.<sup>40</sup>

### **Thalidomide, lenalidomide or bortezomib based regimens as initial therapy for multiple myeloma**

Introduction of thalidomide represented the first major therapeutic advance in myeloma in several decades. Following the initial trials in relapsed myeloma, several randomized

phase III trials of thalidomide and dexamethasone in patients with previously untreated myeloma were performed.<sup>15,18,41,42</sup> Thalidomide combinations were associated with superior response rates and improved response duration with no definite impact on the overall survival compared to dexamethasone alone or VAD. This was followed by introduction of the thalidomide analogue, lenalidomide, that in phase II trials resulted in very high response rates as well as deeper responses than were seen with previous approaches.<sup>11,43</sup> Subsequent phase III trials of lenalidomide and dexamethasone demonstrated its superiority compared to dexamethasone alone as well as its ability to spare high doses of steroids and simultaneously improving survival.<sup>12,19</sup> More recent clinical trials have examined the efficacy and tolerability of lenalidomide combined with cyclophosphamide (CTX), bortezomib, and clarithromycin, as well as other combinations.<sup>44-46</sup> Another major advance in the field had been the introduction of the proteasome inhibitor bortezomib, which along with dexamethasone or in combination with conventional chemotherapy agents is increasingly being used in the setting of newly diagnosed disease with high efficacy. Phase III trials of bortezomib in combination with dexamethasone with or without doxorubicin has shown excellent tolerability and improved response rates and progression free survival when compared to traditional VAD in the setting of initial therapy prior to SCT.<sup>17,20,47</sup> Both lenalidomide and bortezomib have been combined with cyclophosphamide in the setting of transplant eligible patients in phase II studies with excellent response rates.<sup>48,49</sup> Recently reported phase II trials have examined the efficacy of combining bortezomib with lenalidomide or thalidomide with or without cyclophosphamide in the setting of newly diagnosed MM.<sup>50-53</sup> These combinations have led to very high complete and very good partial response

rates and will undoubtedly become integral components of the initial treatment choices in the future. This in turn has led to renewed interest in the potential impact of initial therapy on the ability to collect adequate numbers of stem cells for one or more transplants.

### **Impact of thalidomide, lenalidomide and bortezomib on peripheral blood stem cell collection**

A large volume of data, albeit limited to single institution reports and less detailed data from phase III trials, have appeared in the past few years evaluating the effect of these new drugs on the stem cell collection process (**Table 1**). While there is contradictory data on the impact of thalidomide on stem cell mobilization and collection, the effect if any appears to be relatively small with limited impact on the ability to proceed with SCT.<sup>15,18,33,54</sup> In addition, there is no evidence to suggest that initial therapy with thalidomide containing regimens prior to stem cell collection adversely impacts the engraftment potential of the collected stem cells.

In contrast to thalidomide, one of the common adverse effects of lenalidomide has been hematological toxicity, especially myelosuppression. This finding raised concern that use of lenalidomide could adversely affect the ability to mobilize and collect adequate numbers of CD34<sup>+</sup> cells for ASCT. In two large studies from Mayo Clinic and MD Anderson, the most significant factor influencing the ability to collect adequate numbers of stem cells appeared to be initial therapy with lenalidomide (**Table 1**).<sup>33,55</sup> In addition to lenalidomide therapy, other important factors impacting the stem cell collection

appeared to be the patient age and the duration of lenalidomide therapy.<sup>33,55</sup> The failure rate of mobilization following lenalidomide therapy has varied significantly between the different studies, likely a reflection of the lenalidomide treatment duration, age of the patient population undergoing stem cell collection, mobilization regimens and collection targets employed. However, data so far do not indicate any impact on the quality of stem cells collected, as reflected in the engraftment kinetics as well as success.<sup>12,56,57</sup>

The effect of bortezomib on the ability to collect stem cells has also been examined in the context of phase II and III trials examining the combinations (**Table 1**).<sup>17,21,49,58</sup> While no definite impact of initial therapy on stem cell harvest was demonstrated in the smaller phase II studies of bortezomib and dexamethasone,<sup>21</sup> in the IFM 2005/01 trial comparing bortezomib/ dexamethasone to VAD there was a trend towards lower CD34 numbers among those receiving bortezomib.<sup>17</sup> In contrast, in the HOVON-65/GMMG-HD4 randomized phase III trial comparing Bortezomib, Adriamycin, Dexamethasone (PAD) vs. VAD as induction treatment, no impact of the regimen was seen on the ability to collect stem cells.<sup>59</sup> No significant impact of initial therapy has been seen in other trials that have combined the novel agents, bortezomib in combination with either lenalidomide or thalidomide.<sup>51,60</sup> Addition of alkylating agents to the initial therapy, especially in combination may increase the risk of collection failures, but no comparative data is available.<sup>48,49</sup> In a phase II study looking at the combination of lenalidomide with cytoxan and dexamethasone for newly diagnosed myeloma, we observed 8/30 failures at mobilization.<sup>48</sup> In contrast, in a phase II study of cytoxan, bortezomib, and

dexamethasone by Reeder et al, all patients who attempted stem cell collection were able to get enough cells for at least one transplant.<sup>49</sup>

While there has been a wide spectrum of reported data on the initial therapy with a novel agent and the ability to collect stem cells, some common themes have emerged. In the two larger experiences published to date of lenalidomide therapy prior to harvest, the number of cycles of therapy appear to be important.<sup>33,55</sup> While none of the patients with less than 6 cycles of lenalidomide failed to collect stem cells in the Mayo Clinic series, more than 3 cycles of lenalidomide was associated with a higher risk in the MD Anderson series. While the smaller studies have not demonstrated such a relationship, and in the absence of detailed data from the larger prospective studies, it would be reasonable to assume that longer duration of therapy will increase the risk of failure. Another common finding has been the age of the patients, with more than one study demonstrating increased likelihood of failure in the older patients.<sup>33,55</sup> In these two studies no relationship was noted between the time off lenalidomide prior to stem cell harvest. Another important finding across the studies has been the low incidence of collection failure among patients mobilized with chemotherapy, typically cyclophosphamide, and G-CSF.<sup>61,62</sup> Among 28 treatment-naive patients treated with the combination of clarithromycin, lenalidomide, and dexamethasone (BiRD) reported by Mark et al, sufficient stem cells for 2 autologous stem cell transplants were collected from all patients mobilized with CTX plus G-CSF, versus 33% mobilized with G-CSF alone demonstrating that this approach can potentially overcome the impairment in stem cell mobilization associated with lenalidomide.<sup>61</sup> For patients failing initial attempts

at stem cell mobilization with G-CSF alone, chemotherapy + G-CSF approach appears to have a reasonable efficacy. Five of seven patients failing G-CSF alone was successfully mobilized with CTX + G-CSF in one study<sup>63</sup> and 18/21 patients were remobilized successfully with a chemotherapy + G-CSF approach in another study.<sup>55</sup> Mazumder et al also reported three patients who failed to collect successfully despite undergoing mobilization with the CXCR4 inhibitor Plerixafor, but were subsequently collected using a combination of cyclophosphamide and G-CSF.<sup>56</sup>

### **Potential mechanisms of the impact of lenalidomide treatment on stem cell collection**

The exact mechanism why lenalidomide inhibits stem cell mobilization is not clear. Lentzsch et al. investigated the effects of lenalidomide, pomalidomide (CC4047) (IMiDs) and thalidomide on CD34+ hematopoietic progenitors. They showed in human Colony Formation Assays and Long-Term Culture-Initiating Cell tests (LTC-CIs) that IMiDs and thalidomide are not toxic to hematopoietic stem cells and do not inhibit self renewal capacity of stem cells.<sup>64</sup> This makes it less likely that a direct toxic effect of lenalidomide on hematopoietic progenitors explains the limitation in stem cell collection. The group further showed that IMiDs promote myelopoiesis with a concomitant maturation stop of neutrophil granulocytes by down regulation of critical transcription factors such as PU.1. This leads to an accumulation of immature granulocytes within the bone marrow compartment and neutropenia in the peripheral blood.<sup>65</sup> Interestingly the group also observed that the G-CSF secretion is highly up-regulated in cultures of hematopoietic progenitors treated with IMiDs (day 3 of treatment: control 140 pg/mL, Lenalidomide

800 pg/ml, CC4047 1500pg/mL).<sup>64</sup> (*personal communication, S.Lentzsch*) The biological reason for the strong up-regulation of G-CSF is unknown. It is likely that self-regulatory mechanisms up regulate G-CSF in order to overcome the maturation stop of granulocytes. Higher levels of G-CSF might lead to a tachyphylactic response resulting in resistance to G-CSF mobilization. These findings are also supported by our observation that all other “non-G-CSF based” mobilization approaches such as CTX and AMD3100 are successful in mobilizing a sufficient CD34<sup>+</sup> cell number.

### **Suggested approach to stem cell collection in patients undergoing initial therapy with novel agents**

In June, 2008 a panel of experts was convened by the International Myeloma Foundation to address issues regarding stem cell collection for autologous transplantation in patients receiving therapy with lenalidomide. The following statements reflect the considerations of the panel and the consensus recommendations formulated by the panel. The recommendations take into account the existing data suggesting compromised collection with the newer agents in some of the patients as well as the data, although limited, examining alternate approaches to stem cell mobilization. These recommendations will be revised when additional data becomes available enabling us to make more specific recommendations.

First attempt: Given the potential for the novel agents to impact the ability of the stem cell collection, we recommend early stem cell mobilization when SCT is being contemplated immediately or later in the course of disease. Such an approach, after 3-4

cycles of initial therapy is quite feasible given the rapid response seen with the new combinations. However, there exists considerable confusion at this point in terms of the mechanisms mediating the decreased collection as well as the best approaches to prevent this problem and every effort should be made to enroll these patients in clinical trials evaluating these questions.

Among patients undergoing initial therapy with thalidomide or bortezomib in combination with dexamethasone or among those treated with lenalidomide and dexamethasone who have received < 4 cycles of therapy and are younger than 65 years, G-CSF alone is considered adequate for the initial attempt at mobilizing stem cells although many centers will continue to use cyclophosphamide and G-CSF as their standard protocol. Among those who have received > 4 cycles of lenalidomide therapy, one should consider the initial use of cyclophosphamide and G-CSF for mobilization. This suggestion is based on the findings of increased failure risk in this population as well as the reduced risk of failure associated with the use of cyclophosphamide and G-CSF. While the use of cyclophosphamide in all patients is likely to decrease the risk of failure at first attempt, the recommendation to use G-CSF alone in the former group is driven by the low risk of failure in that group, the increased risks and delay associated with use of cyclophosphamide and finally the ability to successfully collect with cyclophosphamide and G-CSF in the few patients who fail the initial attempt with G-CSF alone. In patients > 65 years old we recommend consideration of reduced-dose Cy with G-CSF or G-CSF alone with addition of AMD-3100 before the second leukapheresis if the first leukapheresis results in less than 2 million CD34+ cells/kg. In patients receiving

other myelosuppressive drugs in combination with lenalidomide, cyclophosphamide and G-CSF should be considered for the initial attempt as the rate of failure increases in these situations. There is no data supporting additional time off therapy prior to mobilization enhancing the likelihood of a successful mobilization. We do not recommend a minimum period that patients have to be off lenalidomide prior to starting G-CSF for mobilization.

Failed stem cell collection: Among patients receiving initial therapy with lenalidomide containing regimens failing to collect with G-CSF alone, there are three options for the subsequent attempt. The majority of the patients can be collected with cyclophosphamide priming and G-CSF. These patients will be candidates for use of AMD3100, which in combination with G-CSF has been very successful in mobilizing stem cells. Another approach includes the use of a combination of G-CSF and GM-CSF (GM-CSF 10 mcg/kg/day SC for 2 days, followed by G-CSF 16 mcg/kg/day SC until stem cell collection is complete).

Upfront use of Plerixafor (AMD3100) in lenalidomide treated patients: The panel discussed the question of routine use of Plerixafor for mobilization in this patient group. It was felt that at this time, without a detailed cost benefit analysis such a recommendation cannot be made and additional clinical trials specifically addressing its use in these patients will allow us to answer this question. Prospective trials should be conducted to study the use of plerixafor in patients failing to reach certain thresholds for peripheral blood CD34 counts.

## Author Contributions

Kenneth Anderson attended Ad Board, Collected Data, and wrote paper. Paul Richardson attended Ad Board, collected data, and wrote paper. Ruben Niesvizky attended Ad Board, collected data, and wrote paper. Shaji Kumar attended Ad Board, wrote paper (Lead Author), and revised paper. Antonio Palumbo attended Ad Board, Collected Data, and Wrote Paper. Edward Stadtmauer attended Ad Board, Collected Data, and Wrote Paper. P. Leif Bergsager attended Ad Board, Collected Data, and Wrote Paper. Sagar Lonial attended Ad Board, Collected Data, and Wrote Paper. Nikhil Munshi attended Ad Board, Collected Data, and Wrote Paper. Brian Durie attended Ad Board, Collected Data, and Wrote Paper. Vincent Rajkumar attended Ad Board, Collected Data, and Wrote Paper. Sergio Giralt Contributed Comments and Edited Paper. Jean Luc Harousseau contributed Comments and Edited Paper. William Bensinger contributed Comments and Edited Paper. Ray Comenzo contributed Comments and Edited Paper. Suzanne Lentzsch contributed Comments and Edited Paper. Jesus San Miguel contributed Comments and Edited Paper. Heinz Ludwig contributed Comments and Edited Paper. Joan Blade contributed Comments and Edited Paper. Patrizia Tosi contributed Comments and Edited Paper. Pieter Sonneveld contributed Comments and Edited Paper. Orhan Sezer contributed Comments and Edited Paper. David Vesole contributed Comments and Edited Paper. Michele Cavo contributed Comments and Edited Paper. Hermann Einsele contributed Comments and Edited Paper.

## Conflict of Interest Disclosure

S. Giralt: Advisory Board for Celgene, Millennium, Novartis, and Genzyme; E. Stadtmauer: Advisory Board for Genzyme; J. Harousseau: Received Honoraria from Genzyme and Amgen, Advisory Board for Celgene and Janssen-Cilag; A. Palumbo: Advisory Board for Ortho Biotech and Celgene; W. Bensinger: Advisory Board for Celgene and Millennium, Research funding from Genzyme, Millennium, Celgene, AstraZeneca and Novartis; R. Comenzo: Advisory Board for Millennium and Ortho Biotech; S. Kumar: Clinical trial funding from Celgene, Millennium, Genzyme; N. Munshi: Advisory Board for Celgene; R. Niesvizky: Clinical trial funding from Celgene; J. San Miguel: Advisory Board for Millennium, Janssen-Cilag, and Celgene; H. Ludwig: Clinical trial funding from Schering-Plough, Janssen-Cilag, and participation in Speaker's Bureau for Amgen, Roche, Janssen-Cilag; J. Blade: Honorarium for lectures and Advisory Board for Celgene, Janssen-Cilag. Research grant from Celgene; S. Lonial: Consultant for Millennium, Celgene, Novartis, and BMS; H. Einsele: Advisory Board for Celgene and Ortho Biotech; P. Tosi: No disclosures; P. Sonneveld: Advisory Board for Ortho Biotech and Celgene; O. Sezer: Clinical trial/ research funding from Janssen-Cilag, Merck, and Novartis. Speaker's Bureau for Amgen, Celgene, Merck, Novartis, Ortho Biotech, Pharmion, and Roche; M. Cavo: No disclosures; P. Richardson: Advisory Board for Celgene and Millennium; SV. Rajkumar: No disclosures; B. Durie: Advisory Board for Celgene and Millennium

## References

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med.* 1996;335:91-97.
2. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol.* 2006;24:929-936.
3. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood.* 2005;106:3755-3759.
4. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348:1875-1883.
5. Femand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol.* 2005;23:9227-9233.
6. Femand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood.* 1998;92:3131-3136.
7. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood.* 2004;104:3052-3057.

8. Femand JP, Ravaud P, Chevret S, et al. Early versus late high dose therapy (HDT) and autologous peripheral blood stem cell transplantation in multiple myeloma (MM): Results of a prospective randomized trial. *Blood*. 1996;88 (Suppl 1):685a.
9. Rajkumar SV, Blood E, Vesole DH, Fonseca R, Greipp PR. Phase III Clinical Trial of Thalidomide Plus Dexamethasone Compared With Dexamethasone Alone in Newly Diagnosed Multiple Myeloma: A Clinical Trial Coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006;24:431-436.
10. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol*. 2002;20:4319-4323.
11. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106:4050-4053.
12. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2007 ASCo Annual Meeting Abstracts 2007;25 (18S):LBA8025.
13. Richardson P, Chanan-Khan A, Schlossman R, et al. A Multicenter Phase II Trial of Bortezomib in Patients with Previously Untreated Multiple Myeloma: Efficacy with Manageable Toxicity in Patients with Unexpectedly High Rates of Baseline Peripheral Neuropathy. *ASH Annual Meeting Abstracts*. 2005;106:2548-.
14. Richardson P, Jagannath S, Raje N, et al. Lenalidomide, Bortezomib, and Dexamethasone (Rev/Vel/Dex) as Front-Line Therapy for Patients with Multiple Myeloma (MM): Preliminary Results of a Phase 1/2 Study. *ASH Annual Meeting Abstracts*. 2007;110:187-.
15. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly

diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006;24:431-436.

16. Rajkumar SV, Jacobus S, Callander N, et al. Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome wi. *J Clin Oncol (Meeting Abstracts)*. 2008;26:8504-.

17. Harousseau JL, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial. *J Clin Oncol (Meeting Abstracts)*. 2008;26:8505-.

18. Cavo M, Zamagni E, Tosi P, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood*. 2005;106:35-39.

19. Zonder JA, Crowley J, Hussein MA, et al. Superiority of Lenalidomide (Len) Plus High-Dose Dexamethasone (HD) Compared to HD Alone as Treatment of Newly-Diagnosed Multiple Myeloma (NDMM): Results of the Randomized, Double-Blinded, Placebo-Controlled SWOG Trial S0232. *ASH Annual Meeting Abstracts*. 2007;110:77-.

20. Sonneveld P, van der Holt B, Schmidt-Wolf IGH, et al. First Analysis of HOVON-65/GMMG-HD4 Randomized Phase III Trial Comparing Bortezomib, Adriamycine, Dexamethasone (PAD) Vs VAD as Induction Treatment Prior to High Dose Melphalan (HDM) in Patients with Newly Diagnosed Multiple Myeloma (MM). *Blood (ASH Annual Meeting Abstracts)*. 2008;112:653-.

21. Jagannath S, Durie BG, Wolf J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. *British journal of haematology*. 2005;129:776-783.

22. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
23. Abdelkefi A, Ladeb S, Torjman L, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood*. 2008;111:1805-1810.
24. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma.[see comment]. *New England Journal of Medicine*. 2003;349:2495-2502.
25. Knudsen LM, Rasmussen T, Jensen L, Johnsen HE. Reduced bone marrow stem cell pool and progenitor mobilisation in multiple myeloma after melphalan treatment. *Med Oncol*. 1999;16:245-254.
26. de la Rubia J, Blade J, Lahuerta JJ, et al. Effect of chemotherapy with alkylating agents on the yield of CD34+ cells in patients with multiple myeloma. Results of the Spanish Myeloma Group (GEM) Study. *Haematologica*. 2006;91:621-627.
27. Boccadoro M, Palumbo A, Bringhen S, et al. Oral melphalan at diagnosis hampers adequate collection of peripheral blood progenitor cells in multiple myeloma. *Haematologica*. 2002;87:846-850.
28. Jansen J, Thompson J, Dugan M, et al. Impaired PBPC collection in patients with myeloma after high-dose melphalan. *Cytotherapy*. 2004;6:498-504.
29. Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. *J Clin Oncol*. 1995;13:2547-2555.
30. Desikan KR, Tricot G, Munshi NC, et al. Preceding chemotherapy, tumour load and age influence engraftment in multiple myeloma patients mobilized with granulocyte colony-stimulating factor alone. *Br J Haematol*. 2001;112:242-247.

31. Morris CL, Siegel E, Barlogie B, et al. Mobilization of CD34+ cells in elderly patients ( $\geq$  70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. *Br J Haematol.* 2003;120:413-423.
32. Alegre A, Tomas JF, Martinez-Chamorro C, et al. Comparison of peripheral blood progenitor cell mobilization in patients with multiple myeloma: high-dose cyclophosphamide plus GM-CSF vs G-CSF alone. *Bone Marrow Transplant.* 1997;20:211-217.
33. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia.* 2007;21:2035-2042.
34. Arora M, Burns LJ, Barker JN, et al. Randomized comparison of granulocyte colony-stimulating factor versus granulocyte-macrophage colony-stimulating factor plus intensive chemotherapy for peripheral blood stem cell mobilization and autologous transplantation in multiple myeloma. *Biol Blood Marrow Transplant.* 2004;10:395-404.
35. Hiwase DK, Bollard G, Hiwase S, Bailey M, Muirhead J, Schwarzer AP. Intermediate-dose CY and G-CSF more efficiently mobilize adequate numbers of PBSC for tandem autologous PBSC transplantation compared with low-dose CY in patients with multiple myeloma. *Cytotherapy.* 2007;9:539-547.
36. Levesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by G-CSF or cyclophosphamide. *J Clin Invest.* 2003;111:187-196.
37. Donzella GA, Schols D, Lin SW, et al. AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. *Nature medicine.* 1998;4:72-77.
38. Liles WC, Broxmeyer HE, Rodger E, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist. *Blood.* 2003;102:2728-2730.

39. Devine SM, Flomenberg N, Vesole DH, et al. Rapid mobilization of CD34+ cells following administration of the CXCR4 antagonist AMD3100 to patients with multiple myeloma and non-Hodgkin's lymphoma. *Journal of clinical oncology*. 2004;22:1095-1102.
40. DiPersio J, Stadtmauer EA, Nademanee AP, et al. A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (Plerixafor)+G-CSF vs. G-CSF+Placebo for Mobilization in Multiple Myeloma (MM) Patients for Autologous Hematopoietic Stem Cell (aHSC) Transplantation. *ASH Annual Meeting Abstracts*. 2007;110:445-.
41. Rajkumar SV, Rosinol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol*. 2008;26:2171-2177.
42. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica*. 2008;93:124-127.
43. Lacy M, Gertz M, Dispenzieri A, et al. Lenalidomide Plus Dexamethasone (Rev/Dex) in Newly Diagnosed Myeloma: Response to Therapy, Time to Progression, and Survival. *Blood*. 2006;108:798-.
44. Kumar S, Hayman SR, Buadi FK, et al. Phase II Trial of Lenalidomide, Cyclophosphamide, and Dexamethasone (CRd) for Newly Diagnosed Myeloma. *ASH Annual Meeting Abstracts*. 2007;110:190-.
45. Richardson PG, Lonial S, Jakubowiak A, et al. Safety and efficacy of lenalidomide (Len), bortezomib (Bz), and dexamethasone (Dex) in patients (pts) with newly diagnosed multiple myeloma (MM): A phase I/II study. *J Clin Oncol (Meeting Abstracts)*. 2008;26:8520-.

46. Niesvizky R, Jayabalan DS, Christos PJ, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood*. 2008;111:1101-1109.
47. Rosinol L, Oriol A, Mateos MV, et al. Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: efficacy and clinical implications of tumor response kinetics. *J Clin Oncol*. 2007;25:4452-4458.
48. Kumar S, Hayman S, Buadi F, et al. Phase II Trial of Lenalidomide (Revlimid<sup>TM</sup>) with Cyclophosphamide and Dexamethasone (RCd) for Newly Diagnosed Myeloma. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:91-.
49. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia*. 2009.
50. Kumar S, Flinn IW, Noga SJ, et al. Safety and Efficacy of Novel Combination Therapy with Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide in Newly Diagnosed Multiple Myeloma: Initial Results from the Phase I/II Multi-Center EVOLUTION Study. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:93-.
51. Richardson P, Lonial S, Jakubowiak A, et al. Lenalidomide, Bortezomib, and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Encouraging Efficacy in High Risk Groups with Updated Results of a Phase I/II Study. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:92-.
52. Cavo M, Tacchetti P, Patriarca F, et al. Superior Complete Response Rate and Progression-Free Survival after Autologous Transplantation with up-Front Velcade-Thalidomide- Dexamethasone Compared with Thalidomide-Dexamethasone in Newly Diagnosed Multiple Myeloma. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:158-.

53. Rosinol L, Cibeira MT, Martinez J, et al. Thalidomide/Dexamethasone (TD) Vs. Bortezomib(Velcade(R))/Thalidomide/Dexamethasone (VTD) Vs. VBMCP/VBAD/Velcade(R) As Induction Regimens Prior Autologous Stem Cell Transplantation (ASCT) in Younger Patients with Multiple Myeloma (MM): First Results of a Prospective Phase III PETHEMA/Gem Trial. Blood (ASH Annual Meeting Abstracts). 2008;112:654-.
54. Breitkreutz I, Lokhorst HM, Raab MS, et al. Thalidomide in newly diagnosed multiple myeloma: influence of thalidomide treatment on peripheral blood stem cell collection yield. Leukemia. 2007;21:1294-1299.
55. Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. Biol Blood Marrow Transplant. 2009;15:718-723.
56. Mazumder A, Kaufman J, Niesvizky R, Lonial S, Vesole D, Jagannath S. Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients. Leukemia. 2008;22:1280-1281; author reply 1281-1282.
57. Paripati H, Stewart AK, Cabou S, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia. 2008;22:1282-1284.
58. Jagannath S, Durie BG, Wolf J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol. 2005;129:776-783.
59. Goldschmidt H, Lokhorst HM, Bertsch U, et al. Successful Harvesting of Peripheral Hematopoietic Stem Cells after Induction Treatment with Bortezomib, Adriamycin, Dexamethasone (PAD) in Patients with Newly Diagnosed Multiple Myeloma (MM). Blood (ASH Annual Meeting Abstracts). 2008;112:3470-.

60. Bensinger W, Jagannath S, Vescio R, et al. A Phase II Study of Bortezomib (Velcade (R)), Cyclophosphamide (Cytosan(R)), Thalidomide (Thalomid(R)) and Dexamethasone as First-Line Therapy for Multiple Myeloma. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:94-.
61. Mark T, Stern J, Furst JR, et al. Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14:795-798.
62. Cook RJ, Vogl D, Mangan PA, et al. Lenalidomide and stem cell collection in patients with multiple myeloma. *J Clin Oncol (Meeting Abstracts)*. 2008;26:8547-.
63. Kumar S, Lacy M, Dispenzieri A, et al. Stem Cell Mobilization Following Initial Therapy with Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:3467-.
64. Koh KR, Janz M, Mapara MY, et al. Immunomodulatory derivative of thalidomide (IMiD CC-4047) induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis. *Blood*. 2005;105:3833-3840.
65. Anderson G, Gries M, Kurihara N, et al. Thalidomide derivative CC-4047 inhibits osteoclast formation by down-regulation of PU.1. *Blood*. 2006;107:3098-3105.

**Table 1. Studies of novel agents with data available for success of stem cell collection**

Reference	Treatment Regimen	N	Clinical Trial	Mobilization Regimen	CD34 yield (x 10 <sup>6</sup> /kg)	P	Days of Leukapheresis	Failed collection % (Definition)
Breitkrutz <sup>54</sup>	TAD	93	Phase III (GMMG-HD3)	CAD	9.8 (2-33.6)	0.02	1 (1-6)	4 (<2.5 x 10 <sup>6</sup> /kg)
	VAD	105			10.9 (3-36)		1 (1-7)	7
Breitkrutz <sup>54</sup>	TAD	100	Phase III (HOVON-50)	CAD	7.4 (2-33)	0.009	1 (1-4)	3 (<2.5 x 10 <sup>6</sup> /kg)
	VAD	100			9.4 (0-48.7)		1 (1-4)	5
<sup>1</sup> Rajkumar <sup>15</sup>	TD	99	Phase III (E1A00)	Various	NA	NA	NA	10 (NA)
	D	100					NA	10
Cavo <sup>18</sup>	TD	100	Matched pair analysis	CTX + G-CSF	7.85	0.4	2	17 (< 4 x 10 <sup>6</sup> /kg)
	VAD	100			10.5		2	12
Kumar <sup>33</sup>	Dex	78	Retrospective	G-CSF	9.6 (1-18)	< 0.01	3 (1-10)	1 (<2.5 x 10 <sup>6</sup> /kg)
	VAD	22			9.8 (2.1-16.2)		4 (2-10)	1
	TD	99			10.0 (3.5-30.1)		4 (1-10)	0
	LD	43			7.9 (0-15.6)		5 (1-12)	3
Mazumder <sup>56</sup>	LD	28	Retrospective	G-CSF	5.4 (0-17.5)	NA	NA	43 (< 2x10 <sup>6</sup> /kg)
Paripati <sup>57</sup>	Other	41	Retrospective	G-CSF	7.4	0.003		7.3 (< 2x10 <sup>6</sup> /kg)
	LD	20			5.1			45
<sup>2</sup> Rajkumar <sup>12</sup>	LD	223	Phase III (E4A03)	Various	NA	NA		3 (NA)
	Ld	220						3 (NA)
Kumar <sup>63</sup>	LD/Ld	92	Retrospective	G-CSF	7.9 (0-16)	NA		11 (<2.5 x 10 <sup>6</sup> /kg)
		11		CTX + G-CSF	8.6 (0-21)			
Mark <sup>61</sup>	BiRD	9	Retrospective	G-CSF	3.1 (0.2-8.6)	< 0.01		3 (< 4 x 10 <sup>6</sup> /kg)
		19		CTX + G-CSF	14.2 (4.9-236)			0
Cook <sup>62</sup>	LD	21	Retrospective	CTX + G-CSF (4 with G-CSF +/- AMD3100)	6.3 (2.4-19.7)		3 (1-8)	9 (<2.5 x 10 <sup>6</sup> /kg)
		137			7.3 (2.4-72.5)		2 (1-11)	1.5
Popat <sup>55</sup>	LD	64	Retrospective	G-CSF	NA			25 (< 2x10 <sup>6</sup> /kg in 4 days)
	Other	238						4
Jagannath <sup>21</sup>	BD	8			13-20 (7.2-16.1)		2 (2-3)	0
Harousseau <sup>17</sup>	BD	240	Phase III (IFM 2005-01)	G-CSF	6.8		2.0 (mean)	4 (< 2x10 <sup>6</sup> /kg)
	VAD	242			8.4		1.6 (mean)	2
Sonneveld <sup>20</sup>	BAD	150	HOVON-65	CTX + G-CSF	10.48 (4-37)		1 (1-5)	
	VAD	150			9.26 (4.1-37.6)		1 (1-4)	
Richardson <sup>51</sup>	VRD	23	Phase II	G-CSF	6.2			8.7

VAD: vincristine, doxorubicin and dexamethasone; TAD: Thal, doxorubicin and dexamethasone ; CAD: cyclophosphamide 1 g/m<sup>2</sup>/day, i.v., on day 1; doxorubicin 15 mg/m<sup>2</sup>/day, i.v., on days 1–4; dexamethasone 40 mg orally, days 1–4) and granulocyte colony-stimulating factor (G-CSF); CTX: cyclophosphamide; TD: Thalidomide, dexamethasone; LD: Lenalidomide, dexamethasone; Ld: Lenalidomide and weekly dexamethasone, BD: Bortezomib and Dexamethasone; NA: not available

<sup>1</sup> Information on whether a stem cell harvest was attempted was available only for 79% of patients among whom 37% attempted stem cell harvest. Collection details were not available.

<sup>2</sup> Details of stem cell collection regarding cell counts and definition of failure not available and likely to represent a mix of practices given the multicenter nature of trial.