Leukemia (2009), 1–9

www.nature.com/leu

ORIGINAL ARTICLE

International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100)

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Multiple myeloma is the most common indication for high-dose chemotherapy with autologous stem cell support (ASCT) in North America today. Stem cell procurement for ASCT has most commonly been performed with stem cell mobilization using colony-stimulating factors with or without prior chemotherapy. The target CD34+ cell dose to be collected as well as the number of apheresis performed varies throughout the country, but a minimum of 2 million CD34+ cells/kg has been traditionally used for the support of one cycle of high-dose therapy. With the advent of plerixafor (AMD3100) (a novel stem cell mobilization agent), it is pertinent to review the current status of stem cell mobilization for myeloma as well as the role of autologous stem cell transplantation in this disease. On June 1, 2008, a panel of experts was convened by the International Myeloma Foundation to address issues regarding stem cell mobilization and autologous transplantation in myeloma in the context of new therapies. The panel was asked to discuss a variety of issues regarding stem cell collection and transplantation in myeloma especially with the arrival of plerixafor. Herein, is a summary of their deliberations and conclusions.
Leukemia advance online publication, 25 June 2009; doi:10.1038/leu.2009.127
Keywords: myeloma; plerixafor; stem cell collection; high-dose therapy; IMWG; guidelines

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Received 15 January 2009; revised 10 March 2009; accepted 11 March 2009

Introductory overview

Current status of stem cell mobilization in multiple myeloma

Multiple myeloma is the most common indication for high-dose chemotherapy with autologous stem cell support (ASCT) in North America today.[1] High-dose therapy with ASCT remains the treatment associated with the highest complete remission rate and when compared with conventional chemotherapy is associated with improvements in survival. The role of high-dose therapy in the context of novel anti-myeloma therapies such as thalidomide, bortezomib, lenalidomide and combinations is being re-explored, but it is likely that high-dose therapy will remain an important component of frontline and relapsed myeloma therapy for the next 5–10 years. Table 1 demonstrates

the myeloma transplant activity as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplant (EBMT). Of particular interest is the continued increase in the number of autotransplants performed for myeloma, even after the approval of bortezomib and lenalidomide.

Stem cell procurement for ASCT has traditionally been guided by one of the two strategies:

(a) Marrow harvesting: involving direct penetration and aspiration of the marrow from the bones (usually the iliac crests) through multiple marrow aspirations to collect a total of 500–1000 ml of a blood and marrow mixture.
(b) Stem cell mobilization using colony-stimulating factors with or without prior chemotherapy.

Table 2 provides a summary of the current pros and cons of each collection method and the current proportion of patients as reported to the CIBMTR that undergo each procedure.

Table 1 Transplant activity (a) in North America and Europe as reported to the centers for international blood and marrow transplant research (CIBMTR); (b) in Europe as reported to the European group for blood and marrow transplant (EBMT)

	Year of transplant				
(a)	*2000*	*2001*	*2002*	*2003*	*2004*
Type of transplant					
Allogeneic	77	88	65	50	29
Autologous	1311	1529	1657	1822	2021
No planned 2nd tx	668	1205	1338	1535	1506
Planned 2nd auto	134	149	132	154	330
Planned 2nd allo	12	26	35	21	73
(b)	*2002*	*2003*	*2004*	*2005*	*2006*
Type of transplant					
Allogeneic	297	247	164	513	489
Autologous	4376	4971	5324	5787	5938

Stem cell mobilization for myeloma patients is primarily (but not exclusively) performed using filgrastim granulocyte-colony stimulating factor (GCSF) alone or after cyclophosphamide chemotherapy. The target CD34+ cell dose to be collected as well as the number of apheresis performed varies throughout the country, but a minimum of 2 million CD34+ cells/kg has been traditionally used for the support of one cycle of high-dose therapy.

With the advent of plerixafor (AMD3100), a novel stem cell mobilization agent, as well as novel induction regimens, it is pertinent to review the current status of stem cell mobilization for myeloma as well as the role of autologous stem cell transplantation in this disease. On 1 June, 2008, a panel of experts was convened by the International Myeloma Foundation to address issues regarding stem cell mobilization and autologous transplantation in myeloma. The panel was asked to discuss a variety of issues regarding stem cell collection and transplantation in myeloma in the context of plerixafor. This article is focused on the current role of ASCT, pros and cons of current mobilization approaches, factors influencing the success of collection and ideal cell doses in the context of plerixafor. The impact of novel agents on the stem cell collection process, possible mechanisms involved and approaches to improve stem cell collection in these patients are not part of this paper but will be addressed in a separate set of recommendations from our group.

Issues in stem cell collection

Is there an optimum CD34+ cell dose to be infused?

In the setting of allogeneic bone marrow transplantation, the beneficial effects of higher stem cell doses as determined by the numbers of nucleated cells or CD34+ cells has been confirmed in multiple retrospective analysis for both T-cell depleted and non-T-cell depleted transplants.[2–4] The improvement in outcomes is due to decreases in non-relapse mortality from improved hematologic reconstitution and lower rates of infection. However, in the setting of allogeneic peripheral blood stem

Table 2 Pros and Cons of commonly used mobilization strategies in patients with myeloma

Strategy	*Frequency used*	*Pros*	*Cons*	*Comments*
Single agent filgrastim	Most common	Ease of use Cost Effective >80% of time Minimal toxicity Predictable	Only moderate CD34 yield No anti-myeloma effect	Current gold standard
Cyclophosphamide plus filgrastim	Most common chemomobilization used	Predictability Overcomes lenalidomide stem cell effect Well tolerated Predictable	Cytopenias and infectious complications Adds costs Minimal anti-myeloma effect Resource utilization	Doses over 4 g/m^2 associated with more toxicity without clear clinical benefit
Combination chemotherapy plus filgrastim	In some selected centers or for patients with high tumor burden	Disease control *In vivo* purging	Toxicity Cytopenias and infectious complications Cost and delays in eventual transplantation	DTPACE and modified CVAD commonly used. No comparative trials
Combination growth factors	Filgrastim and GMCSF explored now rarely used	Theoretical improvement in graft composition	Costs GMCSF not available in Europe	No proven benefit

Table 3 Representative studies of various mobilization strategies[13–24]

References	*N mobilization strategy*	*CD34 collected × e6 per Kg*	*Median number of apheresis*
13	22 GCSF	5.8	NS
	22 Cy+GCSF	33.4	NS
14	18 Cy+GmCSF	6.8	5
	22 GCSF	4.9	3
15	25 GCSF (8 mcg/kg/d)	2.8	1
	25 GCSF (16 mcg/kg/d)	7.9	1
16	37 Cy+GMCSF	12	NS
	34 Cy+GCSF	16	NS
17	28 Cy	21.6	1
	49 Cy+Etoposide	22.5	1
18	126 Cy+GCSF	9	2
	74 GCSF	9	4
19	31 VAD+GCSF	7.7	1
	51 Cy (120 mg/kg)+GCSF	5.9	1
20	15 Cy+peg GCSF (6 mg)	10	1
	15 Cy+peg GCSF (12 mg)	7.4	1
	15 Cy+GCSF	8.6	1
21	313 VDTPACE	29	
22	61 Cy (1–2 g/m^2) +GCSF	5.1	1
	26 Cy (3–4 g/m^2)+GCSF	7.7	1
23	13 V+Cy	21	1
24	23 DCEP+pegGCSF	5.7	1

Abbreviations: Cy, cyclophosphamide; GCSF, filgrastim; GMCSF, sargromastin; N, number; NS, not stated; peg GCSF, pegylated filgrastim; VAD, vincristine, adriamycin, dexamethasone; VDTPACE, bortezomib, dexamethasone, thalidomide, platinum, adriamycin, cyclophosphamide, cyclophosphamide, etoposide.

cell transplantation, increases in the CD34+ cell dose infused has not translated into improvement in outcomes in most retrospective analysis. On the contrary, high CD34+ cell doses have been associated with increase in risks of chronic GVHD and increases in mortality, with the possible exception of high risk patients receiving reduced intensity regimens.[5–8]

In the setting of autologous peripheral blood stem cell transplantation, CD34+ cell doses of >3 million/kg have been associated with better outcomes, primarily due to faster hematologic recovery and lower incidence of infectious and bleeding complications.[9–11] Bensinger *et al* demonstrated that infusing doses of <2 million CD34 per kg was associated with slower hematologic recovery and worse outcomes, whereas patients receiving >5 million CD34 per kg seemed to have a faster robust platelet recovery. These data have been used to support the current patterns of practice with a minimal dose of 2 million CD34 per kg and an 'optimal' dose of 4–6 million CD34+ cells/kg or greater.[9]

Studies addressing the impact of the CD34+ cell dose have been primarily retrospective and have included heterogeneous groups of patients receiving a variety of conditioning regimens. Weaver *et al*[11] in 1995 analysed data on 692 patients. A CD34+ cell dose of >5 million CD34+ cells/kg appeared to be optimal, and only doses of >12.5 million CD34+ cells were associated with a faster platelet engraftment. Benedetti *et al* and Ketterer *et al* have reported that very large numbers of CD34+ cells/kg (>15 million CD34+ cells/kg) after high-dose melphalan administration can eliminate severe thrombocytopenia and platelet transfusion requirements.[12,13] In most studies, CD34 dose was not associated with different outcomes with the exception of a retrospective study performed by Oran *et al*[14] demonstrating that increasing CD34 doses were associated with improved outcomes in patients with amyloidosis who underwent ASCT. Thus, although retrospective analysis suggests a strong dose–response relationship between CD34+ cell dose and rate of neutrophil and platelet recovery after myeloablative therapy, the impact of the benefit has been small. However, all these studies have been retrospective and included heterogeneous populations of patients receiving a variety of conditioning regimens.

Conclusion. The issue of optimal CD34 dosing in the setting of ASCT for myeloma requires a prospective clinical trial designed to address this issue. The results of such a study could alter the current recommendations for both the threshold and 'optimal CD34 dosing' schedules.

Is there an optimal dose of CD34+ cells to be collected?

The current minimal threshold CD34 cell dose to be infused is agreed to be ⩾2 million CD34 cells/kg for a single transplant. However, the current optimal dose for ideal platelet recovery is considered to be 4–6 million CD34 cells/kg.[10] Persistent thrombocytopenia post-allogeneic SCT has been associated with severe acute GVHD and poor survival.[15] In the setting of autologous transplant, poor platelet recovery post-autologous transplant or secondary platelet failure has been observed in 8% of autograft recipients and was seen in the context of CMV infection or in patients receiving bone marrow as a stem cell source. Secondary failures of platelet recovery were associated with a higher risk of death.[16]

Conclusion/assessment. The committee suggested that a minimum target of 4 million CD34+ cells/kg be collected and that if feasible an average of 8–10 million CD34+ cells/kg be collected. These targets would allow most patients with myeloma to undergo at least two autografts with an optimal CD34 dose during the course of their disease.

Is there a standard collection strategy for patients with multiple myeloma?

Table 3 summarizes the most recent studies looking at a variety of strategies for stem cell collection in myeloma. Most of these studies have been retrospective and involved small number of patients.[17–28] Notwithstanding these drawbacks, the following conclusions are reasonable based on the evidence available:

Conclusion/assessment

(a) Both GCSF alone (non-pegylated) or chemotherapy followed by GCSF are reasonable strategies for stem cell collection. The data regarding stem cell collection after single agent pegylated GCSF is much more limited than for non-pegylated GCSF, but supports the use of this agent for stem cell collection.
(b) Most trials suggest that more CD34+ cells can be collected after chemomobilization than after GCSF only mobilization. However, the failure rate (in terms of 'minimal collection criteria' noted above) with chemomobilization is similar to the failure rate with GCSF alone. In addition, chemomobilization has not demonstrated superior outcomes.[18]
(c) Higher doses of cyclophosphamide are associated with more toxicity, and doses over 4 g/m^2 probably offer no benefit.
(d) Novel mobilization strategies need to be further explored looking at improving yields, efficiency, and cost issues.
(e) Impact of novel mobilization strategies on graft constitution and the relevance of graft constitution to transplant outcomes also require further research.
(f) Collections should be attempted between the second and fourth induction cycle regardless of response to therapy. In patients who have primary refractory myeloma without response to combinations including novel agents, mobilization with chemotherapy and GCSF is the practice.

What factors predict successful stem cell collection?

Very few studies have systematically assessed all known risk factors that can impact stem cell collection. Most retrospective studies addressing mobilization have identified patient age, method of mobilization, time to stem cell mobilization, number of prior regimens, and prior melphalan and/or radiation exposure as predictors of mobilization failing to achieve a minimal dose.[29–35]

More recently, exposure to lenalidomide has been associated with failure to mobilize adequate numbers of stem cells using growth factors alone. This inability to collect may be overcome by chemomobilization.[31–34] This may have an impact on the choice of induction therapy. It should be noted, however, that preliminary data indicate successful harvest with the addition of plerixafor in 85% of 50 patients previously treated with lenalidomide who failed to collect $\geqslant$2 million CD34+ cells with G-CSF alone (preliminary findings: CUP *post hoc* analysis).

Likewise, the negative effects of limited melphalan exposure should also be revisited due to the impressive results of melphalan in combination with bortezomib, thalidomide, or lenalidomide.[35,36] Table 4 summarizes the known risk factors and potential strategies to enhance stem cell collection when present.

What will be the impact of plerixafor on stem cell collection strategies in myeloma?

Plerixafor is a bicyclam molecule that inhibits the SDF-1 alpha/CXCR4 binding that occurs between CD34+ stem cells and the marrow stroma. The inhibition of this interaction results in the release of CD34+ stem cells into the blood stream facilitating their collection through apheresis methods.[37] Plerixafor in combination with GCSF resulted in increased CD34+ cell mobilization and was shown to be effective in mobilizing adequate stem cells in patients who had failed traditional mobilization techniques (Hard to Mobilize). Plerixafor also decreased the number of apheresis procedures needed to reach the target CD34+ cell dose in most patients.[38] Plerixafor in combination with GCSF has also been shown to be more effective as an initial mobilizing regimen than GCSF alone in patients with multiple myeloma.[39] The combination of plerixafor plus GCSF resulted in 72% of patients achieving a collection goal of 6 million or more CD34+ per kg in 2 or fewer apheresis procedures versus only 34% for patients receiving GCSF and placebo. Patients achieved $\geqslant$6 million CD34+ cells/kg in a median of 3 fewer days with plerixafor versus G-CSF alone, and collected 3 × as many cells on day 1 than with G-CSF alone (median 6.86 million versus 2.29 million).[40] See Table 5 for the potential benefits of plerixafor.

Table 4 Risk factors for poor stem cell mobilization and potential strategies to overcome them

Risk factor		
Age	Patients over 60 years of age have inferior stem cell mobilization	Consider plerixafor mobilization
Melphalan exposure	Melphalan exposure has traditionally been associated with poor stem cell collection	Observation needs to be confirmed in the context of novel therapies. Current practice of avoiding melphalan should continue until studies performed In patients with history of melphalan exposure consider upfront chemomobilization or plerixafor
Extensive prior therapy or prolonged disease duration	Collection failures are associated with disease duration and extent of prior therapy	Consider harvesting early in the course of the disease even in patients opting out of early high-dose therapy consolidation Consider upfront plerixafor or chemomobilization Assess marrow for secondary dysplastic changes before to collection (that is, morphology and cytogenetics)
Extensive radiotherapy to marrow bearing tissue	Collection failures increase	Consider collection before radiotherapy Consider upfront plerixafor or chemomobilization Assess marrow for secondary dysplastic changes before collection (that is, morphology and cytogenetics)

Table 5 Potential benefits of plerixafor

Improved collection predictability
- The addition of plerixafor resulted in a median 4.8-fold increase in circulating CD34+ cells in the peripheral blood, allowing patients and doctors to predictably schedule apheresis sessions
- Myeloma patients who received plerixafor achieved 3 × as many cells on day 1 than with G-CSF alone (median 6.86 million versus 2.29 million)

Reduction of SCT costs by
- Using less resources (that is, less apheresis procedures)
- In the phase III study, plerixafor patients achieved ⩾6 million CD34+ cells/kg in a median of 3 fewer days with plerixafor versus G-CSF alone

Potential of collecting more cells which
- Allows for more frequent use of high-dose therapy with stem cell support as salvage treatment
- Allows for exploration of improving stem cell transplant outcomes by exploring megadoses of CD34+ cells (that is, >10 million CD34 per kg)

Allows for collecting patients previously exposed to high-dose therapy

The use of plerixafor was both safe and predictable (in terms of cell yields) as a mobilization agent.

Conclusion/assessment. The committee recognized that more studies needed to be done with this agent to better define its role in the treatment of myeloma. These studies need to incorporate pharmacoeconomics and resource utilization endpoints.

What will be the role of high-dose therapy and autologous stem cell transplant for myeloma in the era of novel therapies?

The current paradigm for therapy in multiple myeloma involves determining whether a patient is considered a potential candidate for high-dose therapy consolidation or not. Patients who are considered candidates for high-dose therapy receive induction therapies without melphalan (to prevent stem cell damage). After an average of 2–4 cycles, stem cells are collected and most patients proceed to high-dose melphalan therapy followed by autologous stem cell infusion.

This paradigm is supported by the results of multiple randomized trials demonstrating a higher complete remission rate and longer event-free survival in high-dose therapy recipients.[41] With the advent of novel induction therapies containing either bortezomib, lenalidomide or combinations that result in complete remission rates of up to 30% and VGPR rates of over 50%, the role of both single and tandem high-dose therapy consolidation for transplant eligible patients needs to be re-explored in the context of well designed clinical trials. An important aspect of new trials will be the role of planned up front transplant versus transplant at the time of subsequent relapse. In addition, the value of a major response, such as VGPR, using novel induction strategies and the subsequent need to perform transplantation or not deserve further study. Both the timing and number of transplants recommended continue to be controversial.

Conclusion/assessment. The general consensus from the advisory board was that high-dose melphalan was still recommended for eligible patients, and that stem cell collection early in the course of therapy should be attempted in all transplant eligible patients. The advisory board recommended more studies looking at optimizing collection strategies after exposure to novel therapies (particularly lenalidomide-based combinations) with plerixafor and G-CSF or plerixafor plus chemotherapy.

There is considerable interest in the role of novel transplant approaches combined with the new induction strategies. Longer term follow-up is required to assess the ultimate impact of the various approaches to therapy.

In the United States, certain financial considerations also need to be taken into account particularly that some third party payers (that is, Medicare and some private insurance carriers) do not pay for 'harvest and hold' nor is tandem autografting routinely covered.

Under what circumstances is double autologous transplant considered, for example, as part of a protocol?

Although various randomized trials and retrospective analysis have shown that tandem autologous transplant have a superior event-free survival than single transplants, the benefit may not apply in the era of novel therapies.[42–44] Likewise, the benefit of tandem transplants may be limited to patients failing to achieve at least a 90% reduction of tumor burden after the initial induction and first high-dose therapy consolidation.[42,43] Second, the use of post-transplant maintenance with thalidomide may abrogate the benefits of a second autograft as demonstrated by Abdelkafi *et al*.[45] The use of second autologous transplants as salvage therapy for some patients has been shown to result in long disease-free intervals in patients with long remission after their first autograft.[46]

The committee recognized that the role of tandem transplantation will need to be reevaluated in the era of IMID's and proteosome inhibitors. This can only be done in the context of well done prospective trials. Recent meta-analysis, as well as *post hoc* analysis of previously performed randomized trials have been criticized due to lack of statistical power or methodologic flaws.[47,48]

Conclusion/assessment. The consensus of the advisory board was that double autologous transplant has a place in clinical trials, primarily in younger patients. In practice, a second transplant may be replaced by novel agents, or be considered, for example, if there was no response to therapy with novel agents and a first transplant. High response rates with combination therapies including bortezomib, lenalidomide, thalidomide, and alkylators were noted.

The age limit for transplant was also discussed in the context of a delayed transplant translating into older patients receiving high-dose therapy as salvage therapy. The differences between North America and Europe were noted, and the fact that age *per se* is not an adequate criterion for determining therapy was noted. Further study of plerixafor and GCSF mobilization is particularly warranted in older myeloma patients deemed eligible for high-dose therapy.

Is mini allogeneic transplant still a research therapy?

The committee agreed that this strategy may be useful for some young patients with compatible siblings depending on the patient's response to therapy and other prognostic factors. The current literature provides conflicting data. The results of the prospective IFM trials in high risk patients demonstrated no benefit for an auto/mini allo strategy in regards to overall and event-free survival.[49] These results contrast with retrospective analysis demonstrating a potential benefit of allografting for

some subsets of patients with specific cytogenetics abnormalities and cannot be compared with the results obtained by the Italian group that demonstrated a survival and event-free survival benefit for recipients of the auto/mini allo approach as the Italian study included all patients in their analysis.[50] The Spanish Group performed a study looking at the role of a second autograft versus a reduced intensity allograft in patients failing to achieve a very good partial response after initial induction therapy and high dose consolidation and reported a higher CR rate for the recipients of the reduced intensity allograft, but no improvement in survival.[51] Allografting has been reported to change the prognostic implications of some of the poor risk cytogenetic profiles.[52]

Conclusion/assessment. All these studies involved relatively small number of patients, the large North American Trial performed through the Blood and Marrow Transplant Clinical Trials Network will provide invaluable information regarding this issue, but the results will not be available for 2 years. In the meantime, allografting should continue to be explored in the context of clinical trials in carefully selected patients as frontline therapy or as salvage therapy.

What are the main goals of autologous transplant?

As for other forms of therapy, the goals of autologous transplant are to achieve the maximum depth and duration of response leading to the best overall survival.

The target depth of response surrogate varies from trial to trial. Although CR is a target, the new uniform response criteria identify VGPR plus CR as a better collective category for cross-trial comparisons. In addition, stringent CR (sCR) may prove to be a more decisive and predictive endpoint.[53]

It is recognized that PR and/or VGPR populations can include patients with post-therapy MGUS states with a good prognosis. Thus, detailed prognostic factor and risk assessment are required to fully evaluate short- and long-term outcomes.

Executive summary

Multiple myeloma is the most common indication for ASCT in the world today. Its role in the context of novel therapies, however, is currently being re-explored. Although high-dose therapy will remain an important component of anti-myeloma therapy, whether it will be considered as consolidation for all eligible patients or used more as salvage therapy remains to be defined. Notwithstanding, optimizing stem cell collection either early or later in the course of the disease will be an integral component of myeloma treatment planning. The advent of Plerixafor (a novel stem cell mobilization agent) as well as novel induction regimens will likely change the current standards for stem cell transplant and mobilization. How these standards will change depend on the result of current and future prospective trials. Likewise, current standards regarding optimal CD34 dose for autografting in myeloma may need to be re-explored particularly if prospective trials determine that higher doses of CD34+ cells impact patient outcomes (such as quality of life, post-transplant symptom burden, and hematopoietic recovery).

Conflict of interest

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 Kyle: No disclosures; 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 Celege; 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.

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