Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines

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Multiple myeloma is a malignant plasma cell neoplasm that affects more than 20,000 people each year and is the second most common hematologic malignancy. It is part of a spectrum of monoclonal plasma cell disorders, many of which do not require active therapy. During the past decade, considerable progress has been made in our understanding of the disease process and factors that influence outcome, along with development of new drugs that are highly effective in controlling the disease and prolonging survival without compromising quality of life. Identification of well-defined and reproducible prognostic factors and introduction of new therapies with unique modes of action and impact on disease outcome have for the first time opened up the opportunity to develop risk-adapted strategies for managing this disease. Although these risk-adapted strategies have not been prospectively validated, enough evidence can be gathered from existing randomized trials, subgroup analyses, and retrospective studies to develop a working framework. This set of recommendations represents such an effort—the development of a set of consensus guidelines by a group of experts to manage patients with newly diagnosed disease based on an interpretation of the best available evidence.

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CCT = conventional chemotherapy; CR = complete response; dex = dexamethasone; EFS = event-free survival; FISH = fluorescence in situ hybridization; HDM = high-dose melphalan; IMiD = immunomodulatory drug; ISS = International Staging System; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MP = melphalan-prednisone; MPT = MP plus thalidomide; MPV = melphalan, prednisone, and bortezomib; mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy; nCR = near-CR; ORR = overall response rate; OS = overall survival; PCLI = plasma cell labeling index; PFS = progression-free survival; PR = partial response; SCT = stem cell transplant; SMM = smoldering MM; thal = thalidomide; TRM = treatment-related mortality; TTP = time to progression; VAD = vincristine, Adriamycin (doxorubicin), dex; VGPR = very good PR

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells and is the second most common hematologic neoplasm after lymphoma.[1] An estimated 20,000 new patients will be diagnosed as having MM in 2009 in the United States.[2] More than 10,000 patients die each year as a direct result of MM and its complications. Traditionally, MM has been thought of as incurable, but as treatments have improved in recent years, increasing numbers of patients are dying with, but not necessarily because of, their disease. Considerable progress has been made during the past decade in understanding the basic biology of this disease and in development of more effective therapies.[3] One of the most important advances in the field has been the appreciation of the genetic heterogeneity that underlies this disease and its impact on the outcome of patients with myeloma.[4,5] These newly identified genetic abnormalities, along with previously described prognostic factors, have opened up the possibility of prospective risk stratification of patients with MM and subsequent tailoring of therapy in an individualized manner.[6] The availability of new drugs that are highly effective in controlling the disease and a better understanding of the differential impact of these drugs in the different risk groups of myeloma have further enhanced the ability to move toward a risk-adapted treatment strategy. This concept was originally put forth in the form of Mayo Stratification of Myeloma

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TABLE 1. **Classification System for Levels of Evidence and Grades of Recommendations**

	Type of evidence
Level	
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least 1 well-designed experimental study. Randomized trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasiexperimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
	Grade of recommendation
Grade	
A	Evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	Evidence of type II, III, or IV, and findings are generally consistent
C	Evidence of type II, III, or IV, but findings are inconsistent
D	Minimal or no systematic empirical evidence

and Risk-Adapted Therapy (mSMART) consensus guidelines published in 2007.[7,8] Semiannually, the guidelines have been modified as new data become available; the most current guidelines are always available at www.mSMART.org. These guidelines represent an attempt to offer a simplified, primarily evidence-based algorithm for making treatment decisions for patients with newly diagnosed MM. Similar recommendations have been put forth by Mayo Clinic physicians to guide treatment of other cancers.[9-20] When specific evidence is lacking, our group of 21 Mayo Clinic myeloma experts reached a consensus based on current practice patterns. The preferential use of oral vs intravenous therapies, when evidence does not conclusively favor one over the other, is largely a function of our practice pattern, rather than any implied statement about differences in efficacy.

Long-term management of patients with newly diagnosed MM can be broadly divided into the following components. In the subsequent sections, we analyze the available evidence to support specific guidelines for each of these steps.

1. Diagnose and determine need for treatment.
2. Stratify risk.
3. Initiate therapy to control disease and treat or reverse complications.
4. Consolidate initial response.
5. Maintain response.

In addition, treatment of disease complications and institution of appropriate supportive care measures are the cornerstone of disease management and should be considered at every stage of the disease. In this set of guidelines, we limit our discussion of supportive care to those steps needed to decrease the risk of thrombotic complications associated with the new therapeutic regimens. A detailed set of guidelines regarding supportive care of patients with MM will be the focus of another manuscript. The criteria used to evaluate available evidence and the strength of the recommendations are detailed in Table 1.

DIAGNOSIS OF MYELOMA AND INDICATIONS FOR THERAPY

Multiple myeloma is almost always preceded by monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic phase characterized by a relatively small burden of clonal plasma cells and low levels of monoclonal protein.[21] Patients with MGUS have a small risk of progression (1% per year) to MM and require only observation.[22-24] In some individuals, an intervening phase of smoldering MM (SMM) can be identified, which is characterized by a higher burden of malignant plasma cells and higher levels of monoclonal proteins.[25] Although SMM has a much higher risk of progression to symptomatic myeloma (10% per year in the first 5 years), many of these patients can be observed for years before any active therapy is required.[26] Given the lack of any demonstrated benefit for initiating therapy for this early disease stage,[27,28] it is important to distinguish this presymptomatic phase from symptomatic myeloma that requires therapy. However, availability of more active drugs has once again raised the question of early intervention to prevent progression of SMM, and current trials are evaluating this issue.[29] The diagnosis of active *symptomatic* MM *requiring therapy* should be based on end-organ effects of the disease[30] (Table 2). Although the presence of an M protein is the hallmark of myeloma, 1% to 2% of patients will have nonsecretory myeloma with no M protein detectable on serum or urine electrophoresis or elevated κ or λ light chains on free light chain assay. Finally, other disorders associated with monoclonal proteins, such as amyloidosis, Waldenström macroglobulinemia, or POEMS (polyneuropathy, organomegaly, endocrine, monoclonal protein, and skin) syndrome, should be kept in the differential diagnosis when the diagnosis of myeloma is being considered.

Recommendation: Multiple myeloma should be diagnosed in accordance with the International Myeloma Working Group criteria, and therapy should be initiated only for symptomatic disease.[30] Symptomatic MM should be clearly distinguished from MGUS and SMM because these patients do not need therapy. Patients who otherwise satisfy the criteria for myeloma but are symptomatic due to amyloidosis or POEMS syndrome should be managed differently, taking into consideration the manifestations of the associated condition.

***Level of Evidence*:** II

***Grade of Recommendation*:** A

RISK STRATIFICATION OF NEWLY DIAGNOSED MM

Multiple myeloma has very heterogeneous outcomes. At one end of the spectrum are patients with more aggressive disease that becomes rapidly resistant to available therapies, and they die of the disease. At the other end of the spectrum are patients with relatively indolent disease who require intermittent therapy and have a lengthy survival. The ability to identify these groups of patients prospectively has always been important. However, because of the increasing number of available therapies with different mechanisms of action, this ability has become particularly relevant for development of risk-adapted therapeutic strategies.[31] This approach, mSMART, forms the cornerstone of our recommendations. Several disease- and host-related factors have been shown to influence the disease course in myeloma, but there is increasing appreciation that the primary driver is the genetic heterogeneity present in the disease.[32-36] Several genetic risk stratification systems using different genetic abnormalities have been proposed, but no universally accepted system exists.[32,37-43] Although classifications such as the International Staging System (ISS)[44] and the Durie-Salmon staging system,[45] have significant clinical utility, we defined high-risk myeloma primarily on the basis of the genetic characteristics and plasma cell proliferative rate. We took this approach because of the relative specificity of these findings and data showing their relevance in the setting of current treatment approaches such as stem cell transplant (SCT) and the immunomodulatory drugs (IMiDs) and bortezomib. Thus, the current high-risk classification is a practical approach based on the results of 3 tests: plasma cell fluorescence in situ hybridization (FISH), metaphase cytogenetics, and plasma cell labeling index (PCLI) (Figure 1). We do not recommend that this system replace the existing prognostic systems or variables being used; these nongenetic factors, including the ISS, are still valuable, especially in the standard-risk population.

Presence or absence of specific genetic abnormalities allows us to classify patients as having hyperdiploid or nonhyperdiploid myeloma.[5,33] Hyperdiploid myeloma is characterized by trisomies of various odd-numbered chromosomes, especially 3, 5, 7, 9, 11, 15, 19, or 21, and is observed in 50% to 60% of patients.[46-50] In contrast, the nonhyperdiploid group (40%-50% of patients) typically has translocations involving the immunoglobulin heavy chain locus on chromosome 14.[43] The translocations can involve different partner chromosomes, leading to activation of oncogenes; the sites (genes) typically involved are 11q13 (*CCND1*), 6p21 (*CCND3*), 16q23 (*MAF*), 20q12 (*MAFB*), and 4p16 (FGFR3 and MMSET).[51] In addition, monoallelic loss of chromosome 13 or deletion of its long arm (del 13q) can be seen in nearly 15% of patients when examined by conventional cytogenetics and in as many as 50% when FISH is used.[35,39-41,52,53] Additional abnormalities with clinical relevance include deletion of 17p13, leading to loss of the tumor suppressor gene p53.[54,55] The prognostic relevance of these genetic abnormalities has been examined in multiple studies in the context of different therapies.[32,37-43] In general, patients with hyperdiploidy and those with t(11;14) appear to have a relatively better outcome, whereas those with t(4;14), t(14;16), and del 17p have inferior outcomes. A more aggressive disease typically characterizes the clini-

TABLE 2. **International Myeloma Working Group Diagnostic Criteria for MGUS, SMM, and MM[a]**

MGUS
Serum monoclonal protein (<30 g/L)
Bone marrow <10% plasma cells
No evidence of other B-cell proliferative disorders
No related organ or tissue impairment[b]
SMM (asymptomatic)
Serum monoclonal protein (≥30 g/L) *and/or*
Bone marrow clonal plasma cells ≥10%
No related organ or tissue impairment[b]
MM (active or symptomatic)
Bone marrow clonal plasma cells ≥10%
Monoclonal protein present in serum and/or urine
Clonal bone marrow plasma cells or plasmacytoma
Related organ or tissue impairment[b]

[a] MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; SMM = smoldering MM.

[b] Absence of CRAB (***C***alcium elevation [>1 mg/dL above upper limit of normal], ***R***enal dysfunction [creatinine >2 g/dL], ***A***nemia [hemoglobin, 2 g/dL below lower limit of normal], ***B***one lesions [lytic lesions or osteoporosis with compression fracture] attributable to the plasma cell disorder).

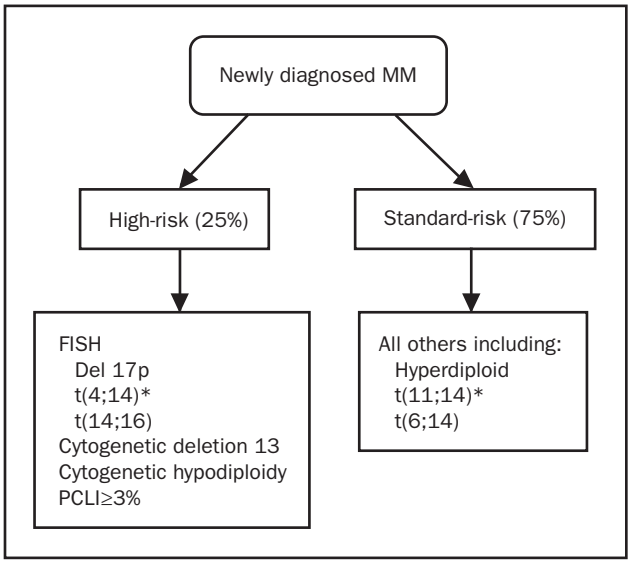

FIGURE 1. Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART). FISH = fluorescence in situ hybridization; MM = multiple myeloma; PCLI = plasma cell labeling index.
*Patients with t(4;14), β_2-microglobulin <4 mg/L, and hemoglobin ≥10 g/dL may have intermediate-risk disease.

cal course of patients with the latter abnormalities, resulting in shorter response duration to different therapies and short overall survival (OS). Although del 17p may be acquired during the disease course, 5% to 10% of patients have this finding at presentation, and it is associated with a relatively short survival.[46,55,56] With use of FISH, abnormalities of chromosome 13 can be seen in nearly half of the patients, but they appear to influence outcome only when seen on metaphase cytogenetics, likely acting as a surrogate marker for the plasma cell proliferative rate.[35,39-41,52,53]

Plasma cell labeling index uses slide-based fluorescence methods to measure the plasma cell proliferative rate. Plasma cells typically have a low rate of proliferation, with most patients having a PCLI of less than 1%. Multiple studies have shown the prognostic value of an elevated PCLI in various plasma cell diseases, especially in MM.[57,58] We chose a value of 3% for identifying patients with high-risk myeloma to improve the specificity of the test and allow us to identify patients with maximum risk. One of the disadvantages of incorporating this measure into the criteria has been the lack of universal availability or access to the PCLI test. Ongoing efforts by multiple groups to use flow-based assessment of plasma cell proliferation will eventually make this measurement easily available.

Recommendation: All patients should undergo risk stratification with FISH, metaphase cytogenetics, and, when feasible, assessment of the plasma cell proliferative rate. If a choice must be made between FISH and metaphase cytogenetics, FISH will provide more information from a risk stratification standpoint and should be given priority. Other laboratory parameters used for prognostication, such as β_2-microglobulin and albumin (for ISS) and lactate dehydrogenase, allow additional risk assessment, particularly in the standard-risk group.

***Level of Evidence*:** II

***Grade of Recommendation*:** A

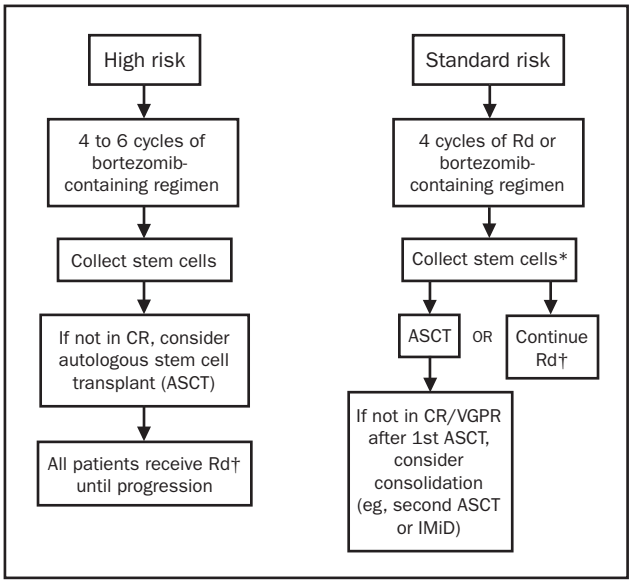

FIGURE 2. Treatment approach in patients eligible for autologous stem cell transplant. CR = complete response; iMiD = immunomodulatory drug; Rd = lenalidomide, dexamethasone; VGPR = very good partial response.

*If age >65 y or ≥4 cycles of Rd, consider chemotherapy plus granulocyte–colony-stimulating factor mobilization or plerixafor.

†Continuing Rd is an option for patients responding well to induction therapy with low toxicities; dexamethasone is usually discontinued after first year.

INITIAL THERAPY FOR NEWLY DIAGNOSED MM

Initial therapy for MM should ideally satisfy the following goals. It should (1) allow rapid disease control and reversal of disease-related complications such as hypercalcemia, renal dysfunction, and anemia; (2) be well tolerated with minimal and manageable toxicity; (3) decrease the risk of early death; and (4) allow successful collection of stem cells when SCT is considered as a therapeutic option.

High-dose melphalan (HDM) with SCT is considered an integral part of the therapeutic approach in patients with MM because of supporting data from randomized, controlled trials. Given the possibility of initial therapy affecting the ability to collect stem cells, especially after prolonged therapy with oral melphalan, the conventional approach has been to determine initial therapy on the basis of the possibility of HDM being a therapeutic option anytime during the disease course. Although age is the parameter most commonly used to determine transplant eligibility in clinical trials, the physiologic age, functional status, and presence of comorbidities are used for guidance.

Two classes of drugs introduced for treatment of MM in recent years have been very effective in controlling both relapses and newly diagnosed disease. These include the IMiDs thalidomide (thal) and lenalidomide and the proteasome inhibitor bortezomib. Thalidomide and its analogue lenalidomide are orally administered, whereas bortezomib is intravenously administered. These drugs have characteristic toxicity patterns; the most common and clinically relevant are as follows: neuropathy, thrombosis, constipation, and somnolence with thal; fatigue, thrombosis, leukopenia, and skin rash with lenalidomide; and fatigue and painful neuropathy with bortezomib.

For the purposes of the guidelines, we will group patients into those eligible for SCT and those considered ineligible, recognizing that "eligibility" for SCT can vary from center to center and physician to physician.

TRANSPLANT-ELIGIBLE PATIENTS

The recommended approach in transplant-eligible patients is summarized in Figure 2 and detailed as follows.

Initial Therapy

Initial therapy for MM in transplant-eligible patients has undergone a sea change in the past decade.[59] Before the advent of IMiDs and bortezomib, single-agent dexamethasone (dex) and VAD (vincristine, Adriamycin (doxorubicin), dex) were the most commonly used approaches.[60-62] Several clinical trials were conducted in the past decade, first comparing these newer drugs in combination with dex against single-agent dex or VAD (Table 3). More recent trials have compared combinations of IMiDs and bortezomib together vs using them individually. These clinical trials have consistently shown superior response rates and progression-free survival (PFS) for IMiDs and bortezomib compared with older therapies and for the combinations compared with any single therapy; however, they have also shown higher rates of toxicity without important differences in OS, particularly in clinical trials that incorporated HDM as a consolidation approach.[65,72,76] This could be a reflection of short follow-up, especially given the recent improvement in survival of patients with MM and access to more effective salvage approaches. However, these trials do confirm the ability of IMiDs and bortezomib to achieve the other goals of initial therapy, such as decreasing early mortality with manageable toxicity while preserving the ability to collect stem cells.

Thalidomide-Based Regimens. Given the promising results in phase 2 trials, the combination of thal and dex was evaluated in 2 large randomized trials.[63,64] The results were similar: significantly higher overall response rates (ORRs) with the combination compared to dex alone (63% vs 41%-46%), but at the cost of significantly higher toxicity. Grade 3 to 4 adverse events were higher with the combination and included deep venous thrombosis and pulmonary embolism, cerebral ischemia, myocardial infarction, and peripheral neuropathy. This improved response rate translated into better PFS for the thal combination, albeit with no impact on OS. Thal-dex was also compared to vincristine, doxorubicin (Adriamycin), and dex (VAD) as initial therapy before initiation of HDM and demonstrated superior response rates before HDM, differences that were no longer significant after HDM.[65] The adverse-effect profile of the drug, coupled with its lack of improvement in OS outcome and the introduction of lenalidomide, has led to decreasing use of this regimen in the setting of newly diagnosed myeloma. Subsequent trials examined the addition of alkylating agents or anthracyclines to thal and dex in an attempt to maximize the response rates by exploiting any potential synergy between these drugs. The combination of thal, dex, and doxorubicin was compared to VAD in one trial, again showing improved ORR and very good partial response (VGPR) rates before initiation of HDM.[66] The combination of cyclophosphamide, thal, and dex was also compared with cyclophosphamide plus VAD, again confirming improved response rates and depth of response with the addition of thal.[67]

TABLE 3. **Regimens Used for Initial Therapy for Myeloma in Recent Clinical Trials**[a]

Regimen	Trial type	ORR (%)	≥VGPR (%)	CR (+ nCR) (%)
Thal + dex	Phase 3[63]	63	44	8
Dex		46	16	3
Thal + dex	Phase 3[64]	63	NR	4
Dex		41	NR	0
Thal + dex[b]	Phase 3[65]	76	19	10
VAD		52	14	8
Thal + Adria + dex[b]	Phase 3[66]	72	33	4
VAD		54	15	2
CTX + thal + dex	Phase 3[67]	96	38	20
CVAD		83	26	12
Len + dex	Phase 3[68]	75	62	15
Dex		48	19	2
Len + dex	Phase 3[69]	81	51	17
Len + low-dose dex		70	40	14
Clarithromycin (Biaxin) + len + dex (BiRD)	Phase 2[70]	90	74	39
CTX + len + dex	Phase 2[71]	85	32	NA
Bortezomib + dex[b]	Phase 3[72]	82	39	15
VAD[c]		65	16	7
Bortezomib + Adria + dex[b]	Phase 2[73]	89	62	24[c]
CTX + bortezomib + dex	Phase 2[74]	77	NR	10
CTX + bortezomib + dex	Phase 2[75]	88	61	39
Bortezomib + thal + dex[b]	Phase 3[76]	94	62	32[c]
Thal + dex[b]		79	29	12[c]
Bortezomib + len + dex	Phase 2[77]	100	74	44[c]
CTX + bortezomib + len + dex	Phase 2[78]	100	68	36[c]

[a] CR = complete response; CTX = cyclophosphamide; CVAD = CTX, vincristine, Adriamycin (Adria), and dexamethasone (dex); len = lenalidomide; NA = not available; nCR = near-complete response; NR = not reported; ORR = overall response rate; VAD = vincristine, Adria, dex; VGPR = very good partial response.

[b] Trials were designed to evaluate induction therapies, and patients proceeded to stem cell transplant after a fixed number of cycles of induction therapy per protocol.

[c] Includes nCR + CR.

Bortezomib-Based Regimens. Bortezomib, the first-in-class proteasome inhibitor, has been studied as a single agent, in combination with dex, or as part of multidrug combinations in previously untreated myeloma. Jagannath et al[79] studied 32 consecutive patients with untreated symptomatic MM, giving bortezomib (1.3 mg/m^2) for six 3-week cycles and adding dex for patients with a less than partial response (PR) after 2 cycles or a less than complete response (CR) after 4 cycles. The ORR after 2 cycles of bortezomib alone was 40%, and the best response was 88%, including CR in 2 patients. The PETHEMA group treated 40 patients younger than 66 years who had newly diagnosed MM with standard-dose bortezomib (odd cycles) and pulsed-dose dex (even cycles) followed by HDM.[80] The ORR was 65%, including 12.5% CR and 10% VGPR.[81] The IFM 2005/01 trial randomized patients to receive 4 cycles of bortezomib

and dex or VAD as initial therapy for their myeloma followed by randomization in each arm to additional consolidation with 2 cycles of dex, cyclophosphamide, etoposide, and cisplatin or none before initiation of HDM.[72] In the most recent report, the ORR with the induction therapy was 82% with bortezomib compared to 65% with VAD.

Bortezomib has been combined with doxorubicin or alkylating agents to further improve responses. In a phase 2, single-institution trial of bortezomib, liposomal doxorubicin, and dex given every 3 weeks for 6 cycles, ORR was 89%.[73] The regimen was very well tolerated, with a low rate of neuropathy; similar results were seen in another trial using the same combination.[82] The combination of cyclophosphamide, bortezomib, and dex was associated with a high ORR and deep responses in 2 different studies.[74,75] Reeder et al[75] observed an ORR of 88%, with 61% VGPR and 39% CR or near-complete response (nCR), when administering this combination every 28 days, and no adverse impact on stem cell collection was noted. Barlogie et al[81] incorporated bortezomib into their Total Therapy 3 regimen, with induction before and consolidation chemotherapy after transplant that consisted of 2 cycles of VTD-PACE (bortezomib [Velcade], thal, dex, cisplatin, doxorubicin, cyclophosphamide, and etoposide); 3-year maintenance consisted of monthly cycles of bortezomib [Velcade], thal, and dex in the first year and thal-dex in the remaining years. At 24 months, 83% of patients had achieved nCR, which was sustained in 88% at 2 years; 2-year estimates of event-free survival (EFS) and OS were 84% and 86%, respectively.

Lenalidomide-Based Regimens. Because of the promising results from phase 3 randomized trials of relapsed MM, lenalidomide was studied in combination with dex for newly diagnosed MM. The initial phase 2 study demonstrated an overall objective response rate of 91%, including a 6% CR and 32% VGPR.[83] Long-term results of this study showed an excellent 3-year OS of 85% for patients who continued receiving primary therapy with lenalidomide and dex.[84] More importantly, continued therapy resulted in improvement in the response rates. This study was followed by 2 phase 3 randomized trials, one comparing lenalidomide and dex to dex, and another comparing 2 different doses of dex in combination with lenalidomide. In the first trial, addition of lenalidomide resulted in a 75% ORR (≥62% VGPR) compared to 48% (≥19% VGPR) for dex alone, translating to an improved PFS.[68] In the second trial, patients were randomized to low-dose (40 mg weekly) or standard-dose (days 1-4, 9-12, 17-20) dex.[69] This trial surprisingly showed a significant improvement in the OS with low-dose dex, despite a significantly lower response rate. As expected, use of a higher dose of dex was associated with greater toxicity, including higher rates of thromboembolic events. Like thal and bortezomib, lenalidomide was also studied in combination with a variety of other drugs. Niesvizky et al[70] studied the addition of clarithromycin (Biaxin) to lenalidomide and dex (BiRD) as initial therapy. Among the 72 patients enrolled, the ORR was 90%, including a 39% CR and 74% VGPR. In another phase 2 study, cyclophosphamide was added to lenalidomide and dex, yielding an ORR of 85%, including a 32% VGPR or better.[71]

Combinations of IMiDs and Bortezomib. The high response rates seen with the IMiDs and bortezomib led to their evaluation in combinations. In a phase 2 study, 38 patients with newly diagnosed MM received up to 3 courses of bortezomib (1.3 mg/m^2 on days 1, 4, 8, 11), dex (20 mg/m^2 on days 1-4, 9-12, 17-20), and thal (100-200 mg/d orally).[85] A rapid response was seen, with an ORR of 87%, including a 16% CR. In a phase 3 study of untreated myeloma, Cavo et al[76] randomized patients to thal and dex with (n=226) or without (n=234) bortezomib as initial therapy before HDM. The ORR and VGPR were significantly better in the bortezomib group (94% and 62%, respectively) compared to those in the thal and dex group (79% and 29%, respectively). The improved depth of response was preserved after HDM and translated into better PFS (90% vs 80% at 2 years) and similar OS (96% vs 91% at 2 years). These response rates were further improved by combining lenalidomide with bortezomib, as shown in a phase 2 trial by Richardson et al.[77] This combination resulted in a 100% response rate, including a 74% VGPR or better and a 44% CR. The EVOLUTION trial added cyclophosphamide to this combination, again resulting in a 100% response rate, including a 68% VGPR and a 36% CR.[78]

Impact of IMiDs and Bortezomib on Outcomes in Patients With High-Risk Myeloma. Estimates of outcome among patients in the different risk groups, as defined by genetic markers or other conventional prognostic factors, have been made in the context of alkylator-based therapies. With the introduction of IMiDs and bortezomib, investigations increasingly focused on their ability to overcome some of these adverse prognostic factors. Although no prospective randomized trials have examined the role of any specific agent in high-risk patients, subgroup analysis from randomized trials and single-institution experiences have provided valuable insight. In matched-pairs subset analyses of patients from bortezomib trials with and without del(13), who were matched for age and ISS stage, response and survival appeared comparable in bortezomib-treated patients with or without del(13) by metaphase cytogenetics.[86] However, patients with del(13) who received dex appeared to have decreased survival compared with those without del(13) by metaphase cytogenetics. In the phase 3 trial that compared melphalan with or without bortezomib

in elderly patients with newly diagnosed MM, the CR rate was similar among patients in the bortezomib arm whether (n=26) or not (n=142) they had high-risk cytogenetics (presence of t(4;14) or t(14;16) translocation or a 17p deletion).[87] Unlike their counterparts in the melphalan-only arm, these groups also had a similar time to progression (TTP) and OS. The presence of del(13) did not show an adverse effect in the bortezomib group. In the context of lenalidomide, a retrospective analysis of 100 patients with newly diagnosed disease treated initially with lenalidomide and dex showed that the median PFS was shorter (18.5 vs 36.5 months) in the high-risk group (as defined by presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), IgH translocations [t(4;14) or t(14;16)], or PCLI ≥3%).[88] However, the OS was comparable.

Recommendations:

***Standard-Risk Patients*.** Patients with newly diagnosed myeloma should receive initial therapy with a lenalidomide- or bortezomib-containing regimen. This recommendation is based on the improved response rates seen with regimens that contain these drugs, manageable adverse effects, and the low 1-year mortality rates vs those with previous approaches. Results with either lenalidomide or bortezomib in combination with dex are comparable in ORR and VGPR rate after 4 to 6 cycles of therapy. Other regimens, such as bortezomib, lenalidomide, and dex or cyclophosphamide, bortezomib, and dex, are also suitable for initial therapy and can lead to higher response rates. Advantages of lenalidomide and dex are the convenience of oral administration and monthly clinic visits, important considerations in a referral practice, and the ease of continued therapy for patients who decide to delay initiation of HDM. In situations in which these logistical concerns are not valid, and in those definitely planning to undergo HDM early, either regimen can be used. Bortezomib-based regimens are recommended in patients with renal failure at presentation. A low threshold should be maintained to add another novel agent (lenalidomide to bortezomib-dex or bortezomib to lenalidomide-dex) in the absence of response within a couple of cycles (a sequential approach in contrast to a combination approach up front). In the context of renal failure, we prefer use of bortezomib and dex with or without addition of thal or doxorubicin or cyclophosphamide baecause of the primarily nonrenal clearance of these drugs and the rapid responses seen with the 3-drug combinations.

***Level of Evidence*:** II-III

***Grade of Recommendation*:** B

***High-Risk Patients*.** We recommend that patients with high-risk myeloma receive initial therapy with a bortezomib-containing regimen, such as bortezomib-dex with cyclophosphamide, thal, doxorubicin, or lenalidomide. In contrast, in patients with standard-risk disease, as discussed earlier, either lenalidomide-based or bortezomib-based induction can be used. Our strong preference for bortezomib-based initial therapy for high-risk patients is based on the finding that bortezomib may overcome some of the adverse prognostic effects of high-risk disease, especially in patients with the t(4;14) translocation. In addition, patients with high-risk disease benefit the most from CR, and therefore therapy for these patients should be aimed at achieving CR, whereas in patients with standard-risk disease, CR or VGPR may be adequate. Finally, in patients with high-risk disease, we prefer the use of routine maintenance therapy (discussed subsequently).

***Level of Evidence*:** III

***Grade of Recommendation*:** B

Approaches to Consolidation Therapy

***Autologous SCT*.** The conventional approach to consolidation therapy in this group of patients has been the use of HDM and autologous SCT. The use of HDM in patients with MM has been based on the positive results from 2 large randomized trials of SCT compared to conventional chemotherapy (CCT), both of which showed an improvement in PFS and in OS.[89,90] In addition to efficacy, safety and the feasibility of an outpatient approach have been demonstrated with SCT.[91] However, not all randomized trials in this setting have shown an improvement in OS for SCT compared to CCT (Table 4).[92-96] The heterogeneity of the results seen in these trials is likely related to differences in patient selection and the use of HDM as salvage therapy for patients undergoing CCT. At least 3 of these trials can be considered as a comparison of early vs delayed SCT rather than SCT vs CCT, and the fourth trial included only patients who had responded to the induction therapy.[92-95] These trials clearly raise the question as to the benefit of HDM in all patient groups. Only 1 of the trials was specifically designed to address the question of early vs delayed SCT.[92] The MAG90 clinical trial evaluated the time without systemic therapy and toxicity as a measure of quality of life among patients undergoing early or delayed SCT and concluded that HDM early in the disease course was associated with better quality of life. As a result, the balance was tilted heavily in favor of early HDM until the advent of IMiDs and bortezomib.

Initial therapy with IMiDs and bortezomib, especially in combination, has led to response rates that rival those seen with SCT. Use of these new regimens has been associated with unprecedented rates of VGPR or better among patients with newly diagnosed MM. These results have brought forth the question about the current role of HDM in MM. Examination of recent clinical trials that have used the IMiDs and bortezomib in preparation for HDM confirm that

TABLE 4. **Clinical Trials Comparing Autologous Stem Cell Transplant to Conventional Therapies**[a]

Reference	Arm	No. of patients	ORR (%)	CR (%)	PFS[b]	OS[b]
Attal et al[89] (IFM 90)	SCT	100	81	22	28	57
	CCT	100	57	5	18	44
Child et al[90] (MRC VII)	SCT	200	86	44	31.6	54.1
	CCT	201	48	8	19.6	42.3
Fermand et al[92] (MAG90)	SCT	91	78	57	39	65
	CCT	94	58	20	13	64
Fermand et al[93] (MAG91)	SCT	94	59	6	25.3	47.8
	CCT	96	56	4	18.7	47.6
Barlogie et al[94] (S9321)	SCT	261	93	17	17% (7 y)	38% (7 y)
	CCT	255	90	15	14% (7 y)	38% (7 y)
Bladé et al[95] (PETHEMA)	SCT	81	82	30	42	66
	CCT	83	83	11	33	61
Palumbo et al[96] (MMSG)	SCT (Mel 100 × 2)	95	72	25	28	58
	CCT	99	66	6	16	42

[a] CCT = conventional chemotherapy; CR = complete response; Mel = melphalan; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SCT = autologous stem cell transplant.
[b] Duration is in months unless stated otherwise.

HDM provides an incremental improvement in response rates even in the presence of high response rates with the induction therapy itself (Figure 3). Stem cell transplant is a well-understood and effective therapy that results in durable responses in most patients. Before the introduction of IMiDs and bortezomib as initial therapies, the median PFS of patients receiving HDM early in the disease course was about 24 months in various studies. Preliminary evidence from the IFM 2005/01 trial suggests that the induction regimen with a higher response rate before transplant results in a longer TTP after transplant.[72] In that study, the 2-year PFS was 60% after VAD induction and 69% after bortezomib-dex therapy. Similar results were seen in the phase 3 comparison of bortezomib-thal-dex vs thal-dex.[76] Given

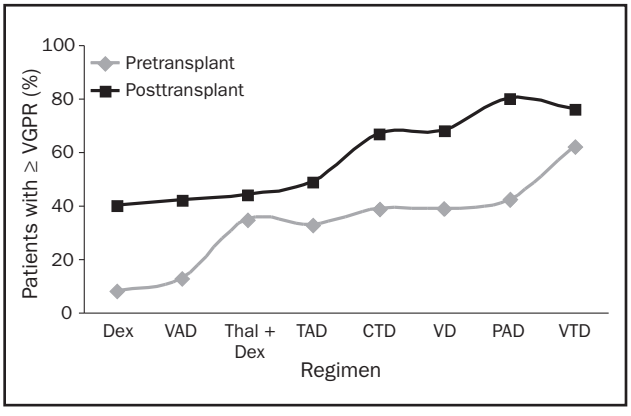

FIGURE 3. Incremental response to stem cell transplant after induction therapy. CTD = cyclophosphamide, thalidomide, dexamethasone; Dex = dexamethasone; PAD = bortezomib, Adriamycin, dexamethasone; TAD = thalidomide, Adriamycin, dexamethasone; Thal = thalidomide; VAD = vincristine, Adriamycin, dexamethasone (dex); VD = bortezomib, dexamethasone; VGPR = very good partial response; VTD = bortezomib, thalidomide, dexamethasone.

these results, we can expect that PFS will be significantly longer than that in the future as increasingly more effective induction regimens are used. In contrast, the response duration with IMiDs and bortezomib, especially after a limited duration of therapy, is not well characterized, whereas the median TTP for patients treated continuously with primary lenalidomide-dex is 31 months.[84] This lack of characterization, along with the lack of evidence that the new strategies have any curative potential, justifies the continued use of HDM for the treatment of myeloma. However, one cannot be dogmatic about the timing of early vs late HDM therapy because results from randomized trials suggest similar survivals.[92] Advantages of early HDM include the very long remission duration (particularly as more effective induction regimens are used), during which patients have an excellent quality of life and require no drug treatment. In addition, several studies have clearly shown that bolus HDM is more effective than intermittent oral melphalan. Because the median age at diagnosis of MM is 70 years, a number of patients initially eligible for early HDM will no longer be eligible if it is delayed for several years, and they will miss their opportunity to receive an effective therapy. Advantages of delayed HDM include the excellent results and tolerability of the continued use of newer induction regimens.[84,97] These advantages have led to increased use of delayed HDM in patients with MM in conjunction with continued initial therapy. Randomized controlled trials are lacking in terms of a comparison between early and delayed HDM since the introduction of IMiDs and bortezomib. In a landmark analysis of the E4A03 clinical trial that compared lenalidomide and 2 doses of dex, patients who continued to receive primary therapy had a 3-year OS of 79% compared with 92% for those who proceeded directly to HDM therapy.[97] Given the strong selection bias

in that nonrandomized study, this analysis cannot be used to suggest that early HDM is superior to delayed HDM; however, it seems unlikely to be inferior. Because of the excellent results with early HDM and pending the results of randomized trials addressing this question, our preference is to gently encourage patients to proceed directly to early HDM with SCT.

Impact of Initial Therapy and Timing of Stem Cell Collection. In the context of delayed HDM therapy, it is important to highlight the impact of initial therapy on the ability to collect stem cells. Although the effect of alkylating agents on the stem cell collection process was well appreciated, only recently have studies specifically analyzed this question with IMiDs and bortezomib.[98-100] Several reports have highlighted the decrease in the number of CD34 cells collected and the increased rate of failure to collect an adequate number of CD34 cells with initial use of lenalidomide.[100,101] These difficulties seem to be particularly relevant in patients older than 65 years who have received more than 4 cycles of therapy. This hurdle can be easily overcome by early collection of stem cells (after 4 cycles) or by use of stem cell mobilization with chemotherapy and granulocyte colony–stimulating factor or agents such as plerixafor.[102] Some reports suggest a trend toward decreased stem cell collection with thal or bortezomib as well, but the impact appears to be smaller.

IMiD- and Bortezomib-Based Consolidation. The high response rates seen with the IMiDs and bortezomib have increasingly led to their use as a means of consolidating the initial response. This has taken the form of either continued use of the initial therapy regimens or use of multidrug regimens that incorporate the most active agents available to obtain the maximum possible depth of response. The tolerability of the IMiDs and bortezomib, as well as the ability of patients to continue oral treatment regimens for a prolonged duration, has led to increasing use of continued initial therapy as a consolidation approach. Continued initial therapy has been accompanied by increasing depth of response, as shown in the initial phase 2 trial of lenalidomide and dex.[84] The rate of a VGPR or better improved from 32% after 4 cycles of therapy to 67% after 19 cycles of therapy. Another approach has been to use combinations of IMiDs and bortezomib, as with the use of bortezomib, thal, dex; bortezomib, lenalidomide, dex; or a combination of cyclophosphamide, lenalidomide, bortezomib, and dex.[76-78,85] These regimens have been associated with an ORR greater than 90% and VGPR rates of 60% to 70%.

Tandem Autologous SCT. A second SCT in a planned sequential fashion after the first SCT has been studied as additional consolidation therapy to further reduce tumor. Randomized trials comparing single to double (tandem) SCT have been completed (Table 5). In the French (IFM94) trial, at 7 years, EFS (20% vs 10%) and OS (42% vs 21%) doubled with the addition of the second autologous SCT, despite only modest improvement in the combined CR and VGPR rate with tandem SCT compared to single SCT (50% vs 42%).[103] In the Bologna 96 trial, the addition of a second autologous SCT prolonged EFS by 12 months and TTP by 17 months, with the OS at 6 years projected to be 44% for single transplant and 63% for double transplant, a significant improvement.[104] In both these trials, patients who failed to achieve a VGPR after the first SCT benefitted the most from the addition of the second SCT. In the HOVON 24 clinical trial, EFS was significantly better in patients treated with double SCT (22 vs 20 months), the difference becoming evident only after 4 years of follow-up.[105] However, OS was not different between arms (median, 55 vs 50 months). In the MAG95 clinical trial, patients were randomly assigned to undergo a single or tandem SCT and then further randomized to receive selected or unselected CD34-positive cells, leading to an improved OS for the tandem SCT group.[106]

Allogeneic SCT. Studies suggest that a graft-vs-myeloma effect can be induced by allogeneic SCT, potentially leading to long-term control of the disease. However, studies thus far have been hampered by high treatment-related mortality (TRM) rates, tempering the enthusiasm for this treatment modality. Most of the available data on the efficacy of allogeneic SCT have come from small single-center studies or from transplant registry reports. In a retrospective case-matched analysis from the European Blood and Marrow Transplant Registry that compared patients treated with allogeneic SCT to a similar group of patients undergoing autologous SCT, the OS was better for the autologous group.[107] This is likely due to the high TRM (nearly 40%) seen with myeloablative allogeneic SCT, given the trend toward better OS and EFS for those surviving the first year. Nonmyeloablative allogeneic SCT has been used to curb TRM by depending more on the antitumor effect of the graft than on the initial cytoreduction from conditioning. The IFM99-03/99-04 trials included patients with high-risk myeloma (β_2-microglobulin level >3 mg/L and chromosome 13 deletion at diagnosis).[108] In IFM99-03, 65 patients with an HLA-identical sibling donor were assigned to undergo reduced-intensity conditioning allogeneic SCT; in IFM99-04, 219 patients without an HLA-identical sibling donor were assigned to undergo a second autologous SCT. This study showed that reduced-intensity conditioning allogeneic SCT was associated with an inferior outcome compared with tandem autologous SCT. In an Italian trial, 108 patients younger than 65 years in whom MM was newly diagnosed underwent standard SCT, followed by low-dose total body irradiation conditioning and HLA-matched sibling allogeneic SCT or a second autologous SCT.[109] At

TABLE 5. **Randomized Clinical Trials Comparing Double to Single Autologous Stem Cell Transplant**

Study	Randomization	No. of patients	ORR (%)	CR (%)	EFS (mo)	OS (mo)
Attal et al[103]	Double (VAD induction, Mel 140 for SCT1, Mel 140 and TBI for SCT2)	200	88	50 (CR + VGPR)	30	58
	Single (VAD induction, SCT with Mel 140)	199	84	42 (CR + VGPR)	25	48
Cavo et al[104]	Double (VAD induction, SCT1 with Mel 200, SCT2 with Mel 120 with busulfan)	158	NA	47 (CR + nCR)	35	71
	Single (VAD induction, SCT with Mel 140)	163	NA	33 (CR + nCR)	23	65
Sonneveld et al[105]	Double: VAD induction, SCT1 (Mel 70 × 2), SCT2 with CTX + TBI	155	90	13	22	55
	Single: VAD followed by SCT (Mel 70 × 2)	148	86	28	20	50
Fermand et al[106]	Double: VAD induction, SCT1 with Mel 140, SCT2 with Mel 140, etoposide, TBI	99	NA	39 (CR + VGPR)	ND	ND
	Single: VAD induction, SCT 1 with carmustine, etoposide, Mel 140, CTX, TBI	94	NA	37 (CR + VGPR)	ND	ND

CR = complete response; CTX = cyclophosphamide; EFS = event-free survival; Mel = melphalan; NA = not available; nCR = near-complete response; ND = not determined; ORR = overall response rate; OS = overall survival; SCT = autologous stem cell transplant; TBI = total body irradiation; VAD = vincristine, Adriamycin (doxorubicin), dexamethasone; VGPR = very good partial response.

a median follow-up of 3 years, TRM was 11% for the allogeneic SCT group vs 4% for the double SCT group; CR rate was 46% vs 16%; OS was 84% vs 62% (P=.003); and PFS was 75% vs 41% (P=.00008). This trial had several shortcomings, and the results have not been widely accepted. A phase 3 trial of tandem HDM vs single HDM followed by HLA-matched sibling nonmyeloablative allogeneic SCT (BMT-CTN 0102) has been completed, and results are awaited. Currently, allogeneic approaches should be considered investigational, and future trials should work toward identifying patients most likely to benefit from this modality.

***Should CR Be the Goal of Therapy*?** The relationship between depth of response and long-term outcome has been a hotly debated area of myeloma therapy. In the context of alkylating agent–based regimens as well as with HDM, deeper responses typically translate to improvement in the TTP, although the impact on OS is inconsistent. Either a CR or a VGPR has been used as a measure of deep response in various studies, and in general, attainment of a VGPR or better appears to correlate with a better outcome. The importance of depth of response is further highlighted by studies in which minimal residual disease was detected by polymerase chain reaction or flow cytometry–based methods; these studies showed that attainment of minimal residual disease–negative status was associated with improved survival. Although a consensus exists on the benefit of obtaining a VGPR or CR, the need to obtain this degree of tumor reduction for all patients is unclear. In the absence of randomized trials incorporating response-driven treatment approaches, it is difficult to understand how much of the ability to obtain a VGPR or CR depends on disease biology vs treatment impact. However, available data suggest that patients who benefit the most are those with high-risk disease.[110,111] In contrast, patients with MM who have a more MGUS-type gene expression profile have a lower CR rate but appear to have equivalent survival.[112,113]

Recommendations:

***Standard-Risk Patients*.** We recommend that all patients who are transplant candidates undergo stem cell collection after 3 or 4 cycles of induction therapy. Patients may then either start taking HDM or continue taking lenalidomide and dex with the plan to initiate HDM at the time of relapse. This decision should be based on patient preference, tolerability of the current induction therapy, and response to induction therapy. Among patients receiving HDM, use of tandem SCT should be discussed with those who do not obtain a VGPR with the first HDM. This recommendation is based on the results of prospective trials that show a benefit for this group of patients. Duration of the initial therapeutic regimen among those who do not initiate HDM is not well determined, and therapy may be continued until progression or for a defined period of 12 to 18 months. Argument in favor of a defined period of therapy is the lack of continued improvement in response depth after 12 to 18 months among patients treated until progression. However, this decision should be made in consultation with the patient after explaining the pros and cons of the 2 approaches and taking into account the adverse effects of treatment.

***Level of Evidence*:** II

***Grade of Recommendation*:** B

***High-Risk Patients*.** We recommend initiation of HDM for patients who have not achieved a CR with induction therapy. In these patients, as in those with a CR, stem cells should be collected for future use. No randomized trials have prospectively addressed the need to obtain a CR

among this group of patients. However, several lines of evidence support the hypothesis that patients with high-risk disease have the maximum benefit from obtaining a CR from therapy.

***Level of Evidence*:** III

***Grade of Recommendation*:** B

Maintaining Response

Patients invariably experience relapse after HDM, and the concept of maintaining or prolonging response among these patients is not new. Various trials have attempted to maintain the response with HDM through maintenance approaches. A small randomized clinical trial of interferon alfa (3×10^6 units/m^2 administered subcutaneously 3 times weekly) after initial autologous SCT suggested a modest improvement in EFS.[114] The IFM99-02 trial randomized patients with standard-risk MM (β_2-microglobulin <3 mg/L, no chromosome 13 deletion) to receive no maintenance, pamidronate, or pamidronate plus thal after tandem SCT.[115] The response rates were significantly higher for the thal arm; this translated into improved EFS at 4 years of 52% compared with 36% with no maintenance and 37% with pamidronate alone. With a median follow-up of 32 months, the 4-year estimated survival after diagnosis was higher with thal (87%) than with no maintenance (77%), but additional follow-up showed no difference in survival. Several other studies were designed to address this question; a PFS improvement was seen in all studies, but an OS advantage was seen only in some.[116,117] In the Australian trial, patients were randomized to receive prednisolone indefinitely with or without 12 months of thal.[116] After a median follow-up of 3 years, the post-randomization 3-year PFS rates were 42% and 23% and the OS rates were 86% and 75% in the thal and control groups, respectively. In these trials, the benefit of maintenance appeared to be primarily among patients with less than a VGPR from HDM. In contrast, in the Total Therapy 2 trial, incorporation of thal appeared to benefit only patients with metaphase cytogenetic abnormalities.[110] Bortezomib has also been studied as post-HDM maintenance in smaller studies as well as a larger phase 3 study (HOVON-65). Interim analysis of the phase 3 study showed a higher response rate for the arm receiving bortezomib as induction therapy and as maintenance therapy.[118] An ongoing large study (Cancer and Leukemia Group B) is evaluating lenalidomide as maintenance therapy after single HDM.

Recommendations:

***Standard-Risk Patients*.** Among patients receiving HDM, we recommend use of thalidomide maintenance or consolidation therapy in those who fail to achieve a VGPR with the first course of HDM (for those who have not opted for a tandem SCT).

***Level of Evidence*:** II

***Grade of Recommendation*:** B

***High-Risk Patients*.** We recommend use of lenalidomide maintenance therapy until progression of disease in these patients. Randomized data suggest benefit of maintenance with thal in patients with high-risk disease. Because of the less favorable adverse-effect profile, we recommend lenalidomide over thal.

***Level of Evidence*:** II (thalidomide), V (lenalidomide)

***Grade of Recommendation*:** B (thalidomide), D (lenalidomide)

TRANSPLANT-INELIGIBLE PATIENTS

The recommended approach in transplant-ineligible patients is summarized in Figure 4 and detailed as follows.

Initial Therapy

Given the median age at presentation, this group of patients represents a sizeable proportion of patients with newly diagnosed MM. Rapid control of disease and disease-related complications is the immediate goal of therapy, as with younger patients; however, therapy should be based on comorbidities and performance status. For decades, until the introduction of thal, the melphalan-prednisone (MP) combination had been the mainstay of therapy for patients ineligible for HDM.[119] In a phase 3 clinical trial, Italian investigators randomized patients with MM who were older than 65 years or younger than 65 years but ineligible for HDM to MP (melphalan, 4 mg/m^2, days 1-7; and prednisone, 40 mg/m^2, days 1-7) or MP plus thal (MPT), 100 mg/d for 6 cycles.[120] Patients in the MPT arm continued taking maintenance thal after the 6 cycles until relapse. Six months after initiation of therapy, 76% of patients in the MPT arm had a response (CR or PR) compared with 47.6% in the MP arm, which translated to a doubling of EFS at 2 years (54% vs 27%). However, grade 3 and 4 adverse events nearly doubled with the addition of thal (48% for MPT vs 25% for MP), and 11 patients in the MPT group died of toxicity-related events compared with 6 patients in the MP group. Deep venous thrombosis was the most common grade 3 or 4 adverse event in the MPT group; it developed in 13 of the first 65 patients. After introduction of enoxaparin prophylaxis, thrombosis developed in only 2 of the remaining 64 patients, and that occurred after interruption of enoxaparin. A similar trial (IFM 99-06) performed in France randomly assigned patients aged 65 to 75 years to receive MP (12 cycles at 6-week intervals), MPT (maximum tolerated thal dose, up to 400 mg/d), or MEL100 (induction therapy with VAD × 2; cyclophosphamide-based mobilization; and 2 courses of HDM (100 mg/m^2) with stem cell support).[121] A VGPR or CR was seen in 9%, 64%, and 58% of patients in the MP, MPT, and MEL100 groups, respectively; at a median follow-up of 32.2 months, the corresponding

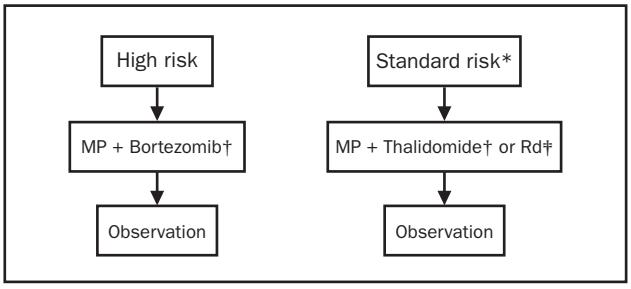

FIGURE 4. Treatment approach in patients ineligible for autologous stem cell transplant. MP = melphalan-prednisone; Rd = lenalidomide, dexamethasone.
*Bortezomib-containing regimens preferred for patients with renal failure or if rapid response is needed.
†In patients in whom administration of thalidomide or bortezomib is of concern, consider MP or Rd.
‡Continuing Rd is an option for patients responding well to induction therapy with low toxicities; dexamethasone is usually discontinued after the first year.

PFS rates were 17.2, 29.5, and 19 months. The median OS rates were 30.3 months, not reached at 56 months, and 38.6 months in the MP, MPT, and MEL100 groups, respectively. A second French trial specifically evaluated patients older than 75 years, the group most susceptible to treatment-related complications and more likely to have other comorbidities at diagnosis.[122] At a median follow-up of 4 years, median OS was significantly longer in the thal group (44.0 vs 29.1 months), as was PFS (24.1 vs 18.5 months). However, this was accompanied by a significant increase in neutropenia and in peripheral neuropathy. A total of 5 randomized trials have compared MPT to MP; all showed significantly increased toxicity and prolongation of PFS with the addition of thal, but only 2 showed a significant improvement in OS (Table 6).[120,122-125] Another phase 3 trial, by Ludwig et al,[126] compared thal-dex with MP in 289 elderly patients. Although thal-dex resulted in a higher rate of CR and VGPR (26% vs 13%) as well as overall responses (68% vs 50%), TTP and PFS were similar. However, toxicity was higher with thal-dex, particularly in patients older than 75 years with poor performance status, and OS was significantly shorter in the thal-dex group (41.5 vs 49.4 months). The increased toxicity seen with the addition of thal suggests that in frail, elderly patients, in whom administration of thal may be of concern, therapy can be safely initiated with MP and thal can be reserved for later use as necessary.

Mateos et al[127] compared the results of a phase 2 trial of melphalan, prednisone, and bortezomib (MPV) in patients 65 years of age or older with historical controls. After a median follow-up of 26 months, the median TTP with MPV was 27.2 months, compared with 20.0 months with MP. The median OS with MPV was not reached vs 26 months with MP; the survival rate at 38 months was 85% vs 38%, respectively. This was followed by a large phase 3 (VISTA) trial that randomized patients with newly diagnosed MM who were not candidates for autologous SCT to receive MPV or MP alone.[87] Patients in the MPV arm received intravenous bortezomib, 1.3 mg/m^2 twice per week (weeks 1, 2, 4, 5) for 4 cycles of 6 weeks (8 doses per cycle), followed by once per week (weeks 1, 2, 4, 5) for 5

TABLE 6. **Randomized Clinical Trials of Initial Therapy for Myeloma in Elderly Patients**[a]

Reference	Drug	ORR (%)	VGPR (%)	CR (%)	PFS (mo)	OS (mo)
Palumbo et al[120] (GIMEMA)	MPT	69	29	16	21.8	45
	MP	48	11	4	14.5	47.6
Facon et al[123] (IFM 99-06)	MPT	76	47	13	27.5	51.6
	MP	35	7	2	17.8	33.2
	Mel 100	65	43	18	19.4	38.3
Hulin et al[122] (IFM 01-01)	MPT	62	21	7	24.1	44
	MP	31	7	1	18.5	29.1
Waage et al[124]	MPT	57	22	12[b]	16	29
	MP	40	7	4[b]	14	36
Wijermans et al[125] (HOVON 24)	MPT	62	29	NA	13	37
	MP	47	9	NA	10	30
Ludwig et al[126]	TD	68	24	2	16.7	41.5
	MP	50	11	2	20.7	49.4
San Miguel[87]	MPV	74	41	33	20.7	NR
	MP	39	8	4	15	NR

[a] CR = complete response; Mel = melphalan; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; MPV = melphalan, prednisone, bortezomib; NA = not available; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TD = thalidomide, dexamethasone; VGPR = very good partial response.
[b] Includes near CR.

cycles of 6 weeks (4 doses per cycle), in combination with oral melphalan, 9 mg/m^2, and prednisone, 60 mg/m^2, once daily on days 1 to 4 of each cycle. Patients in the MP arm received MP once daily on days 1 through 4 for 9 cycles of 6 weeks. Both the median TTP and OS at 2 years were significantly better in the MPV group: TTP, 24 months with MPV vs 16.6 months with MP; OS at 2 years, 82.6% with MPV vs 69.5% with MP.[55] The major adverse effect in the MPV arm was peripheral neuropathy (any grade in 43%; grade 3 or 4 in 13%). A subsequent randomized trial studied the combination of MP with weekly bortezomib, comparing it to the same combination with thal. Although no survival differences have been seen to date, this study was associated with significantly lower neuropathy rates related to the weekly bortezomib regimen.[128] More recently, lenalidomide has been safely added to MP with promising results from phase 2 studies, paving the way for randomized comparison of MP plus lenalidomide vs MPT.[129]

Recommendation:

***Standard-Risk Patients*.** Our recommendation is to use MPT in this group of patients. We prefer to use 100 mg/d of thal with the MP regimen and limit treatment to 12 months. We acknowledge that the MPV combination is comparable in efficacy, but the logistics of our referral practice and concern about neuropathy coupled with the more extensive and mature data with the thal combination, including in patients older than 75 years, drive our preferential use of MPT. However, given the increased toxicity seen in all the randomized trials with addition of thal, in frail, elderly patients we recommend initiating therapy with MP, reserving IMiDs and bortezomib for later use as dictated by the clinical course. No data are available regarding the safety of lenalidomide-dex in the very elderly, and given the surprising toxicity of thal-dex in this age group, we reserve lenalidomide-dex for the unusual circumstance in which an MP-based regimen is inappropriate.

***Level of Evidence*:** I-II

***Grade of Recommendation*:** A

***High-Risk Patients*.** Our recommendation is to use MPV in this group of patients, following the regimen studied in the VISTA trial and limiting therapy to 54 weeks as in that trial. This recommendation is based on the analysis from the VISTA trial that showed comparable outcomes for patients with high-risk cytogenetic abnormalities compared with patients with standard-risk MM.

***Level of Evidence*:** I-II

***Grade of Recommendation*:** A

Maintenance Approaches

There is a paucity of data to support use of routine maintenance therapy for the older patient who has completed a year of MP therapy in combination with either thal or bortezomib. Even in the high-risk group, in which maintenance approaches may be of more benefit, the limited duration of therapy in the VISTA trial and the impact of high-risk markers appear to have been minimized with the addition of bortezomib.

Recommendation: We do not recommend maintenance therapy after MPT or MPV in this patient group, except in the context of a clinical trial.

***Level of Evidence*:** V

***Grade of Recommendation*:** D

PREVENTION OF THROMBOSIS

Patients with monoclonal gammopathies are at a higher risk of thromboembolic complications, and the risk is greatest for the patient with newly diagnosed myeloma in whom therapy is being initiated. The risk is further accentuated by the type of therapy and is particularly high among patients receiving thal or lenalidomide. As single agents, thal and lenalidomide do not appear to have any heightened risk; however, concomitant chemotherapy[120] with anthracyclines,[130,131] high-dose corticosteroids,[132] and erythropoietin[133] does appear to increase the risk of thrombosis. In addition to therapy, patient-related factors such as previous thromboembolism, central venous lines, surgical procedures, immobility, obesity, comorbidities, hyperviscosity, and presence of inherited thrombophilic states all increase the risk of events. The International Myeloma Working Group recently published a detailed set of recommendations for thromboprophylaxis in patients with newly diagnosed myeloma.[134]

Recommendation for Use of Thal or Lenalidomide as Single Agents or in Combination With Low-Dose Corticosteroid. Aspirin, 325 mg/d orally

***Level of Evidence*:** III

***Grade of Recommendation*:** B

***Guideline for Thal or Lenalidomide When Given in Combination With High-Dose Dex, Doxorubicin, Liposomal Doxorubicin, or Erythropoietin*.** Prophylactic low-molecular-weight heparin (equivalent of enoxaparin, 40 mg/d subcutaneously) or full-dose warfarin to a therapeutic international normalized ratio of 2 to 3.

***Level of Evidence*:** V

***Grade of Recommendation*:** D

REFERENCES

1. Kyle RA, Rajkumar SV. Multiple myeloma. *Blood*. 2008;111(6):2962-2972.

2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59(4):225-249.

3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.

4. Fonseca R. Many and multiple myeloma(s). *Leukemia*. 2003;17(10):1943-1944.

5. Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. *Cancer Res*. 2004;64(4):1546-1558.

6. Stewart AK, Bergsagel PL, Greipp PR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia*. 2007;21(3):529-534.

7. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc*. 2007;82(3):323-341.

8. Lonial S. Designing risk-adapted therapy for multiple myeloma: the Mayo perspective [editorial]. *Mayo Clin Proc*. 2007;82(3):279-281.

9. Markovic SN, Erickson LA, Rao RD, et al; Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. *Mayo Clin Proc*. 2007;82(3):364-380.

10. Markovic SN, Erickson LA, Rao RD, et al; Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century, part 2: staging, prognosis, and treatment. *Mayo Clin Proc*. 2007;82(4):490-513.

11. Alberts SR, Gores GJ, Kim GP, et al. Treatment options for hepatobiliary and pancreatic cancer. *Mayo Clin Proc*. 2007;82(5):628-637.

12. Aletti GD, Gallenberg MM, Cliby WA, Jatoi A, Hartmann LC. Current management strategies for ovarian cancer. *Mayo Clin Proc*. 2007; 82(6):751-770.

13. Pruthi S, Brandt KR, Degnim AC, et al. A multidisciplinary approach to the management of breast cancer, part 1: prevention and diagnosis. *Mayo Clin Proc*. 2007;82(8):999-1012.

14. Pruthi S, Boughey JC, Brandt KR, et al. A multidisciplinary approach to the management of breast cancer, part 2: therapeutic considerations. *Mayo Clin Proc*. 2007;82(9):1131-1140.

15. Buckner JC, Brown PD, O'Neill BP, Meyer FB, Wetmore CJ, Uhm JH. Central nervous system tumors. *Mayo Clin Proc*. 2007;82(10):1271-1286.

16. Long HJ III, Laack NN, Gostout BS. Prevention, diagnosis, and treatment of cervical cancer. *Mayo Clin Proc*. 2007;82(12):1566-1574.

17. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. *Mayo Clin Proc*. 2008;83(1):97-112.

18. Sher T, Dy GK, Adjei AA. Small cell lung cancer. *Mayo Clin Proc*. 2008;83(3):355-367.

19. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008;83(5):584-594.

20. Sekulic A, Haluska P Jr, Miller AJ, et al; Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin Proc*. 2008;83(7):825-846.

21. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood*. 2006;107(3):904-906.

22. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002;346(8):564-569.

23. Landgren O, Katzmann JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc*. 2007;82(12):1468-1473.

24. Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance: study of 52,802 persons in Nagasaki City, Japan. *Mayo Clin Proc*. 2007;82(12):1474-1479.

25. Kyle RA, Greipp PR. Smoldering multiple myeloma. *N Engl J Med*. 1980;302(24):1347-1349.

26. Kyle RA, Remstein ED, Therneau TM, et al; . Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007;356(25):2582-2590.

27. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rödjer S, Westin J; Myeloma Group of Western Sweden. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I—a randomized study. *Eur J Haematol*. 1993;50(2):95-102.

28. Riccardi A, Mora O, Tinelli C, et al; Cooperative Group of Study and Treatment of Multiple Myeloma. Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. *Br J Cancer*. 2000;82(7):1254-1260.

29. Lust JA, Lacy MQ, Zeldenrust SR, et al. Induction of a chronic disease state in patients with smoldering or indolent multiple myeloma by targeting interleukin 1β-induced interleukin 6 production and the myeloma proliferative component. *Mayo Clin Proc*. 2009;84(2):114-122.

30. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.

31. Fonseca R, Stewart AK. Targeted therapeutics for multiple myeloma: the arrival of a risk-stratified approach. *Mol Cancer Ther*. 2007;6(3):802-810.

32. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109(8):3489-3495.

33. Avet-Loiseau H. Role of genetics in prognostication in myeloma. *Best Pract Res Clin Haematol*. 2007;20(4):625-635.

34. Fonseca R, Oken MM, Harrington D, et al. Deletions of chromosome 13 in multiple myeloma identified by interphase FISH usually denote large deletions of the q arm or monosomy. *Leukemia*. 2001;15(6):981-986.

35. Fonseca R, Harrington D, Oken MM, et al. Biological and prognostic significance of interphase fluorescence in situ hybridization detection of chromosome 13 abnormalities (Δ13) in multiple myeloma: an Eastern Cooperative Oncology Group study. *Cancer Res*. 2002;62(3):715-720.

36. Fonseca R, Coignet LJ, Dewald GW. Cytogenetic abnormalities in multiple myeloma. *Hematol Oncol Clin North Am*. 1999;13(6):1169-1180, viii.

37. Chiecchio L, Protheroe RK, Ibrahim AH, et al. Deletion of chromosome 13 detected by conventional cytogenetics is a critical prognostic factor in myeloma. *Leukemia*. 2006;20(9):1610-1617.

38. Fassas AB, Spencer T, Sawyer J, et al. Both hypodiploidy and deletion of chromosome 13 independently confer poor prognosis in multiple myeloma. *Br J Haematol*. 2002;118(4):1041-1047.

39. Facon T, Avet-Loiseau H, Guillerm G, et al: Intergroupe Francophone du Myélome. Chromosome 13 abnormalities identified by FISH analysis and serum β_2-microglobulin produce a powerful myeloma staging system for patients receiving high-dose therapy. *Blood*. 2001;97(6):1566-1571.

40. Tricot G, Barlogie B, Jagannath S, et al. Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood*. 1995;86(11):4250-4256.

41. Königsberg R, Zojer N, Ackermann J, et al. Predictive role of interphase cytogenetics for survival of patients with multiple myeloma. *J Clin Oncol*. 2000;18(4):804-812.

42. Fonseca R, Blood E, Rue M, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood*. 2003;101(11):4569-4575.

43. Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C, Groupe Français de Cytogénétique Hématologique. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood*. 2001;98(7):2229-2238.

44. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23(15):3412-3420.

45. Durie BG, Salmon SE, Moon TE. Pretreatment tumor mass, cell kinetics, and prognosis in multiple myeloma. *Blood*. 1980;55(3):364-372.

46. Drach J, Schuster J, Nowotny H, et al. Multiple myeloma: high incidence of chromosomal aneuploidy as detected by interphase fluorescence in situ hybridization. *Cancer Res*. 1995;55(17):3854-3859.

47. Pérez-Simón JA, García-Sanz R, Tabernero MD, et al. Prognostic value of numerical chromosome aberrations in multiple myeloma: A FISH analysis of 15 different chromosomes. *Blood*. 1998;91(9):3366-3371.

48. García-Sanz R, Orfão A, González M, et al. Prognostic implications of DNA aneuploidy in 156 untreated multiple myeloma patients. Castelano-Leonés (Spain) Cooperative Group for the Study of Monoclonal Gammopathies. *Br J Haematol*. 1995;90(1):106-112.

49. Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. *Leukemia*. 2003;17(2):427-436.

50. Wuilleme S, Robillard N, Lodé L, et al; Intergroupe Francophone de Myélome. Ploidy, as detected by fluorescence in situ hybridization, defines different subgroups in multiple myeloma. *Leukemia*. 2005;19(2):275-278.

51. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. *J Clin Oncol*. 2005;23(26):6333-6338.

52. Desikan R, Barlogie B, Sawyer J, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. *Blood*. 2000;95(12):4008-4010.

53. Chng WJ, Santana-Dávila R, Van Wier SA, et al. Prognostic factors for hyperdiploid-myeloma: effects of chromosome 13 deletions and IgH translocations. *Leukemia*. 2006;20(5):807-813.

54. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood*. 1998;92(3):802-809.

55. Avet-Loiseau H, Li JY, Godon C, et al. p53 deletion is not a frequent event in multiple myeloma. *Br J Haematol*. 1999;106(3):717-719.

56. Chang H, Qi C, Yi QL, Reece D, Stewart AK. p53 gene deletion detected by fluorescence in situ hybridization is an adverse prognostic factor for patients with multiple myeloma following autologous stem cell transplantation. *Blood*. 2005;105(1):358-360.

57. Greipp PR, Lust JA, O'Fallon WM, Katzmann JA, Witzig TE, Kyle RA. Plasma cell labeling index and β_2-microglobulin predict survival indepen-

dent of thymidine kinase and C-reactive protein in multiple myeloma. *Blood*. 1993;81(12):3382-3387.

58. Witzig TE, Timm M, Larson D, Therneau T, Greipp PR. Measurement of apoptosis and proliferation of bone marrow plasma cells in patients with plasma cell proliferative disorders. *Br J Haematol*. 1999;104(1):131-137.

59. Rajkumar SV. Treatment of myeloma: cure vs control. *Mayo Clin Proc*. 2008;83(10):1142-1145.

60. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. *Blood*. 1992;80(4):887-890.

61. Kumar S, Lacy MQ, Dispenzieri A, et al. Single agent dexamethasone for pre-stem cell transplant induction therapy for multiple myeloma. *Bone Marrow Transplant*. 2004;34(6):485-490.

62. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med*. 1984;310(21):1353-1356.

63. Rajkumar SV, Rosiñol 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(13):2171-2177.

64. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR: Eastern Cooperative Oncology Group. 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(3):431-436.

65. Cavo M, Zamagni E, Tosi P, et al; Writing Committee of the Bologna 2002 Study. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood*. 2005;106(1):35-39.

66. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al; Dutch-Belgian HOVON and German GMMG. 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(1):124-127.

67. Morgan GJ, Davies FE, Owen RG, et al. Thalidomide combinations improve response rates: results from the MRC IX Study [abstract 1051a]. *Blood (ASH Annual Meeting Abstracts)*. 2007;110(11, pt 1):3593.

68. 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 [abstract 77]. *Blood (ASH Annual Meeting Abstracts)*. 2007;110(11):77.

69. Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2007;110:74.

70. 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(3):1101-1109.

71. Kumar S, Hayman S, Buadi F, et al. Phase II trial of lenalidomide (Revlimid™) with cyclophosphamide and dexamethasone (RCd) for newly diagnosed myeloma. [abstract 91]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:91.

72. Harousseau JL, Mathiot C, Attal M, et al. VELCADE/Dexamethasone (Vel/D) versus VAD as induction treatment prior to autologous stem cell transplantion (ASCT) in newly diagnosed multiple myeloma (MM): updated results of the IFM 2005/01 trial [abstract 450]. *Blood (ASH Annual Meeting Abstracts)*. 2007;110(11):450.

73. Jakubowiak AJ, Friedman J, Kendall T, Al-Zoubi A, Kaminski MS. A phase II study of combination of bortezomib, liposomal doxorubin, and dexamethasone (VDD) as first line therapy for multiple myeloma [abstract 17504]. *J Clin Oncol. (ASCO Meeting Abstracts)*. 2006;24(pt 1):18S.

74. Kropff M, Liebisch P, Knop S, et al; Deutsche Studiengruppe Multiples Myelom, DSMM. DSMM XI study: dose definition for intravenous cyclophosphamide in combination with bortezomib/dexamethasone for remission induction in patients with newly diagnosed myeloma. *Ann Hematol*. 2009;88(11):1125-1130.

75. 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;23(7):1337-1341.

76. Cavo M, Patriarca F, Tacchetti P, et al. Bortezomib (Velcade(R)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM) [abstract 73]. *Blood (*ASH *Annual Meeting Abstracts)*. 2007;110:30a.

77. 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. [abstract 92]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:92.

78. 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. [abstract 93]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:93.

79. 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(6):776-783.

80. Rosiñol 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(28):4452-4458.

81. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol*. 2007;138(2):176-185.

82. Popat R, Oakervee HE, Hallam S, et al. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. *Br J Haematol*. 2008;141(4):512-516.

83. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106(13):4050-4053.

84. Lacy MQ, Gertz MA, Dispenzieri A, et al. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc*. 2007;82(10):1179-1184.

85. Wang M, Giralt S, Delasalle K, Handy B, Alexanian R. Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. *Hematology.* 2007;12(3):235-239.

86. Jagannath S, Richardson PG, Sonneveld P, et al. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. *Leukemia*. 2007;21(1):151-157.

87. San Miguel JF, Schlag R, Khuageva NK, et al; VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906-917.

88. Kapoor P, Kumar S, Fonseca R, et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood.* 2009;114(3):518-521.

89. Attal M, Harousseau JL, Stoppa AM, et al; Intergroupe Français du Myélome. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335(2):91-97.

90. Child JA, Morgan GJ, Davies FE, et al; Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348(19):1875-1883.

91. Gertz MA, Ansell SM, Dingli D, et al. Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. *Mayo Clin Proc*. 2008;83(10):1131-1138.

92. Fermand 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(9):3131-3136.

93. Fermand 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(36):9227-9233.

94. 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(6):929-936.

95. Bladé J, Rosiñol L, Sureda A, et al; Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA). 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(12):3755-3759.

96. 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(10):3052-3057.

97. Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [abstract]. *Blood* (*ASH Annual Meeting Abstracts).* 2007;110:74.

98. Kumar S, Giralt S, Stadtmauer EA, et al; International Myeloma Working Group (IMWG). Mobilization in myeloma revisited: IMWG con-

sensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. *Blood*. 2009;114(9):1729-1735.

99. 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(6):1294-1299.

100. 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(9):2035-2042.

101. 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(6):718-723.

102. 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(7):795-798.

103. Attal M, Harousseau JL, Facon T, et al; InterGroupe Francophone du Myélome. Single versus double autologous stem-cell transplantation for multiple myeloma [published correction appears in *N Engl J Med*. 2004;350(25):2628]. *N Engl J Med*. 2003;349(26):2495-2502.

104. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol*. 2007;25(17):2434-2441.

105. Sonneveld P, van der Holt B, Vellenga E, et al. Intensive versus double intensive therapy in untreated multiple myeloma: final analysis of the HOVON 24 Trial [abstract 2545]. *Blood (ASH Annual Meeting Abstracts)*. 2005;106:2545.

106. Fermand JP, Alberti C, Marolleau JP. Single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD34-enriched ABSC: results of a two by two designed randomized trial in 230 young patients with multiple myeloma (MM) [abstract P10.2.2]. *Hematol J*. 2003;4(suppl 1):S59.

107. Björkstrand BB, Ljungman P, Svensson H, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood*. 1996;88(12):4711-4718.

108. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006;107(9):3474-3480.

109. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356(11):1110-1120.

110. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of total therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112(8):3115-3121.

111. Haessler J, Shaughnessy JD Jr, Zhan F, et al. Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clin Cancer Res*. 2007;13(23):7073-7079.

112. Pineda-Roman M, Bolejack V, Arzoumanian V, et al. Complete response in myeloma extends survival without, but not with history of prior monoclonal gammopathy of undetermined significance or smouldering disease. *Br J Haematol*. 2007;136(3):393-399.

113. Zhan F, Barlogie B, Arzoumanian V, et al. Gene-expression signature of benign monoclonal gammopathy evident in multiple myeloma is linked to good prognosis. *Blood*. 2007;109(4):1692-1700.

114. Cunningham D, Powles R, Malpas J, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. *Br J Haematol*. 1998;102(2):495-502.

115. Attal M, Harousseau JL, Leyvraz S, et al; Inter-Groupe Francophone du Myélome (IFM). Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108(10):3289-3294.

116. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27(11):1788-1793.

117. Morgan GJ, Jackson GH, Davies FE, et al. Maintenance thalidomide may improve progression free but not overall survival: results from the Myeloma IX Maintenance Randomisation [abstract 656]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:656.

118. 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). [abstract 635]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:653.

119. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *J Clin Oncol*. 1998;16(12):3832-3842.

120. Palumbo A, Bringhen S, Caravita T, et al; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet*. 2006;367(9513):825-831.

121. Facon T, Mary JY, Hulin C, et al. Randomized clinical trial comparing melphalan-prednisone (MP), MP-thalidomide (MP-THAL) and high-dose therapy using melphalan 100 MG/M² (MEL100) for newly diagnosed myeloma patients aged 65-75 years: interim analysis of the IFM 99-06 trial on 350 patients [abstract 206]. *Blood*. 2004;104:63a

122. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol*. 2009; 27(22):3664-3670.

123. Facon T, Mary JY, Hulin C, et al; InterGroupe Francophone du Myélome. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209-1218.

124. Waage A, Gimsing P, Juliusson G, Turesson I, Fayers P. Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomised phase 3 trial [abstract 78]. *Blood (ASH Annual Meeting Abstracts)*. 2007;110:78.

125. Wijermans P, Schaafsma M, van Norden Y, et al. Melphalan + prednisone versus melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: final analysis of the Dutch Cooperative Group HOVON 49 Study. [abstract 649]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:649.

126. Ludwig H, Hajek R, Tóthová E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood*. 2009;113(15):3435-3442.

127. Mateos MV, Hernández JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. *Haematologica*. 2008;93(4):560-565.

128. Palumbo A, Bringhen S, Rossi D, et al. A prospective, randomized, phase III study of bortezomib, melphalan, prednisone and thalidomide (VMPT) versus bortezomib, melphalan and prednisone (VMP) in elderly newly diagnosed myeloma patients. [abstract 652]. *Blood (ASH Annual Meeting Abstracts)*. 2008;112:652.

129. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide Treatment for newly diagnosed myeloma: a report from the GIMEMA-Italian Multiple Myeloma Network. *J Clin Oncol*. 2007;25(28):4459-4465.

130. Zangari M, Barlogie B, Anaissie E, et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br J Haematol*. 2004;126(5):715-721.

131. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc*. 2005;80(12):1568-1574.

132. Rajkumar SV, Blood E. Lenalidomide and venous thrombosis in multiple myeloma [letter]. *N Engl J Med*. 2006;354(19):2079-2080.

133. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma [letter]. *N Engl J Med*. 2006;354(19):2079-2080.

134. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22(2):414-423.