

The Current Status and Future of Multiple Myeloma in the Clinic

Sundar Jagannath,¹ Robert A. Kyle,² Antonio Palumbo,³
David S. Siegel,⁴ Sonia Cunningham,⁵ James Berenson⁶

Abstract

It is now recognized that all cases of multiple myeloma (MM) are preceded by the premalignant condition of monoclonal gammopathy of undetermined significance (MGUS). Although patients with MGUS are generally asymptomatic and currently managed by “watch and wait,” the identification of high-risk patients whose disease will progress more rapidly to smoldering MM (SMM) and MM aids in timely intervention. The immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib are now routine components of MM therapy in both first-line and relapsed/refractory settings. These targeted agents are used in various combinations with chemotherapy for the treatment of both transplantation-ineligible and transplantation-eligible patients. More recently, a trend toward evaluation of 3- and 4-drug multiagent combinations before transplantation and prolongation of primary therapy has generated new treatment paradigms. Ultimately, the physician’s choice of therapy and treatment strategy requires consideration of regimen-associated toxicities and integration of the patient’s risk, comorbid status, and response and tolerability of previous treatment regimens. Particular attention needs to be paid to baseline and/or treatment-emergent peripheral neuropathy, thrombotic risk, changes in renal function, and bone health. Despite recent advances, all patients with MM eventually relapse, and efforts to identify novel synergistic combinations and new agents are ongoing. This review highlights challenges in the clinic and newer approaches under evaluation for the treatment and/or management of patients with MGUS, SMM, and MM.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, No. 1, 28-43, 2010; DOI: 10.3816/CLML.2010.n.003

Keywords: Comorbidity, Monoclonal gammopathy, Multiagent regimens, Smoldering myeloma, Solitary plasmacytoma

Introduction

Immediately before the 2009 annual meeting of the American Society of Clinical Oncology (ASCO), a group of multiple myeloma (MM) key opinion leaders (KOLs) gathered to discuss the

current status of myeloma therapy, define areas of controversy, and identify gaps in knowledge among community oncologists. This article highlights the key issues discussed by the participants* and does not attempt to provide an exhaustive review of the literature.

Monoclonal Gammopathy of Undetermined Significance/Smoldering Myeloma/Solitary Plasmacytoma: Where Are We Moving in 2009?

Monoclonal Gammopathy of Undetermined Significance

The premalignant condition of monoclonal gammopathy of undetermined significance (MGUS) is diagnosed in asymptomatic patients, and accordingly, most remain undiagnosed for considerable periods of time (Table 1).¹⁻³ At the Mayo Clinic, the median duration of MGUS before its recognition is 11 years, and some 28% of those patients diagnosed at age 70 have had MGUS for ≥ 20 years. Prevalence is higher in men versus women (approximately 30%) and increases with age (≥ 50 years, 3.2%; ≥ 85 years, 8.9%).^{1,3,4}

The implication of MGUS diagnosis is a life-long higher risk of progression to MM or other plasma cell disorders (Table 2).⁵ It

¹New York Medical College, Multiple Myeloma and Transplant Program, St. Vincent’s Comprehensive Cancer Center, New York

²College of Medicine, Mayo Clinic, Rochester, Minnesota

³Section of Hematology, Department of Oncology, University of Torino, Italy

⁴Hackensack University Medical Center, New Jersey

⁵Physicians’ Education Resource, Dallas, Texas

⁶Institute for Myeloma and Bone Cancer Research, West Hollywood, California

Submitted: Nov 6, 2009; Revised: Dec 3, 2009; Accepted: Dec 3, 2009

Address for correspondence: Sundar Jagannath, MD, New York Medical College, Multiple Myeloma and Transplant Program, St. Vincent’s Comprehensive Cancer Center, 325 West 15th St, New York, NY 10011

Fax: 212-604-6029; e-mail: sundar_jagannath@hotmail.com

Address for correspondence: James Berenson, MD, Institute for Myeloma and Bone Cancer Research, 9201 Sunset Blvd, Ste 300, West Hollywood, CA 90069

Fax: 310-623-1120; e-mail: jberenson@imbc.org

*Attendees included Drs. Melissa Alsina, Robert Audell, Guido Tricot, Raymond L. Comenzo, Suzanne Lentzsch, Ruben Niesvizky, A. Keith Stewart, David H. Vesole, Andre Jakubowiak, Jatin Shah, Todd Zimmerman, and Ravi Vij.



This summary may include the discussion of investigational and/or unlabeled uses of drugs and/or devices that may not be approved by the FDA.

Electronic forwarding or copying is a violation of US and International Copyright Laws.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by CIG Media Group, LP, ISSN #2152-2650, provided the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA. www.copyright.com 978-750-8400.

Table 1 Plasma Cell Disorders			
Disorder	M-Protein	Bone Marrow Plasma Cells	CRAB/End-Organ Damage
Monoclonal Gammopathy of Undetermined Significance	< 3 g/dL (and)	< 10%	None evident
Smoldering Multiple Myeloma	≥ 3 g/dL (and/or)	≥ 10%	None evident
Solitary Plasmacytoma	0 ^a	Solitary lytic bone lesion	None evident

^aLow level of M-protein may be present.

Abbreviation: CRAB = hypercalcemia, renal insufficiency, anemia, or bone lesions

Table 2 Association of Monoclonal Gammopathy of Undetermined Significance With Development of Plasma Cell Disorders: A Geographically Defined US Population-Based Study (N = 605)		
MGUS →	Risk Ratio (95% CI)	P Value
Multiple Myeloma	32.6 (18.1-58.7)	P < .001
Macroglobulinemia	96.2 (11.0-836.5)	P < .001
Plasma Cell Proliferative Disorder	28 (11.4-68.7)	P < .001

Abbreviation: MGUS = monoclonal gammopathy of undetermined significance

is most important to recognize that virtually all cases of MM are preceded by MGUS: cumulative probability for progression ranges from 10% to 17% at 10 years and 25% to 34% at 20 years.^{6,7} However, other competing factors for death such as heart attacks, stroke, and non-plasma cell malignancy also increase with age such that the risk for development of MM is modest. On a cautionary note, careful interpretation of elevated M-protein is required because transient elevations can be associated with normal humoral immunity, and polyclonal gammopathies could be observed following viral infection.

The conventional approach to the management of MGUS is to watch and wait. However, patients with MGUS can often present with other disease manifestations, including clinical peripheral neuropathy (PN), associated skin conditions, or amyloidosis.⁸ Correct diagnostic classification is crucial in these cases to ensure that patients qualify for appropriate therapy. Screening for osteosclerotic lesions is necessary to exclude POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin defects) syndrome, and examination of bone marrow and subcutaneous fat aspirates for amyloid will identify 90% of systemic AL amyloidosis (light-chain amyloidosis) cases, a condition that confers poor prognosis.⁹ Standard approaches to treating sensorimotor PN associated with these conditions have yielded limited success, although a number of new agents are currently under evaluation.¹⁰ For patients with MGUS and a diagnosis of chronic inflammatory demyelinating polyneuropathy, intervention might not be necessary in the absence of progressive neuropathy. Of note, progressive demyelination is a complication associated with immunoglobulin (Ig)M MGUS.¹⁰ Increased risk for a number of other morbidities, includ-

Table 3 Prognostic Factors Associated With High-Risk Monoclonal Gammopathy of Undetermined Significance				
Risk Factors ^a	Number of Patients	Relative Risk Ratio	Progression at 20 Years	
			Absolute Risk, %	Adjusted Risk, %
None	449	1	5	2
1	420	5.4	21	10
2	426	10.1	37	18
3	53	20.8	58	27

^aRisk factors: M-protein ≥ 1.5 g/dL; abnormal serum free light-chain ratio (< 0.26 or > 1.65); M-component (IgA and/or IgM).

ing osteopenia/osteoporosis, bone fractures, and thromboembolic complications, is associated with MGUS.¹ To preserve quality of life (QOL), further research is needed to determine whether the level or type of M-protein predicts for progression to these events.

There is a need to closely follow patients with high-risk MGUS so that diagnosis of MM or development of MGUS-related symptoms can be recognized in a timely manner. High-risk MGUS is associated with an abnormal serum free light-chain (sFLC) ratio, non-IgG type, and elevated serum M-protein ≥ 1.5 g/dL (Table 3).¹¹ In community clinics where accessibility to sFLC measurement might be limited, the levels of M-component and serum albumin can serve as independent predictors of progression of non-IgG MGUS.¹² Currently, the lack of curative treatment and the fact that most patients with MGUS do not experience progression to myeloma precludes early treatment with currently available agents.

A lower incidence of t(4;14) and deletion of chromosome (del[13]) cytogenetic abnormalities that confer high risk have been noted in MGUS compared to MM.^{13,14} However, definitive correlation between any particular chromosomal abnormality and the evolution of MM has yet to be discerned and likely involves additional and subsequent events. Moreover, because the majority of patients with MM have standard-risk cytogenetics, transition to high-risk chromosomal abnormalities alone cannot be the determining factor for progression. Most recently, global mapping of single-nucleotide polymorphisms has identified candidate genes implicated in this process,¹⁵ and monosomy 18 has been identified as a possible predictive factor.¹⁶

There is currently a lack of consensus regarding the role, timing, and benefit of performing testing other than the routine procedures carried out at diagnosis and follow-up.¹ In MGUS, some physicians delay bone marrow analysis and metastatic bone survey, only proceeding when M-protein levels reach 1.5-2 g/dL. In contrast, other physicians routinely perform these tests at diagnosis for all patients. However, because mature B-cell lymphoma can be associated with MGUS, it is prudent to determine the cellular source of the M-protein before ordering bone marrow analysis. The other extreme is not to further work up or follow patients with a small M-protein component in the absence of other risks factors or symptoms, signs, or laboratory findings suggestive of a more serious B-cell disorder. The application of these tests to MGUS remains questionable

Table 4 Smoldering Multiple Myeloma: Risk Groups

Prognostic Group	Clinical Characteristics		Time to Progression	
			Median, Months	Percent, 15 Years
Group 1 (n = 106)	Serum M-Protein	≥ 3 g/dL	27	87
	BMPCs	≥ 10%		
Group 2 (n = 143)	Serum M-Protein	< 3 g/dL	93	70
	BMPCs	≥ 10%		
Group 3 (n = 27)	Serum M-Protein	≥ 3 g/dL	228	39
	BMPCs	< 10%		
Total (N = 276)	—	—	58	73

Abbreviation: BMPC = bone marrow plasma cells

because, regardless of results, the current management approach would not change. On a related note, considerable variance in bone marrow biopsy data between institutional core laboratories and those in the community has been observed, making it difficult to accurately diagnose MGUS or asymptomatic MM in the clinic. Indeed, the bone marrow milieu is not homogeneous, and serial sampling would be expected to yield somewhat different results. One should always diagnose based on the sample that yields the highest proportion of plasma cells, and it might be preferable to perform a bone biopsy in addition to needle aspiration to more accurately determine the percentage of plasma cells. Other suggested tests included assessment of creatinine levels to circumvent development of renal complications and 24-hour urine protein analysis to check for light-chain-only MGUS; these patients will ultimately develop light-chain-only MM and are rarely recognized in the clinic.³

Diagnosis of MGUS can be associated with osteopenia or osteoporosis with increased risk for bone fractures, including vertebral compression fractures (VCFs)¹; these patients might need treatment for the underlying osteopenia or osteoporosis. Bisphosphonates have significantly improved bone mineral density among patients with MGUS with osteopenia or osteoporosis.^{17,18} Although these drugs have decreased skeletal complications for patients with breast cancer with bone metastases and patients with myeloma with lytic disease,^{17,19-22} similar data on the impact of these drugs on actual skeletal events is lacking in MGUS. Long-term preventative care cost issues need to be weighed against the costs of management of fractures and impact of these events on patient QOL. Similarly, although M-protein levels should be assessed among patients with osteopenia or osteoporosis without other obvious risk factors (eg, premenopausal women), it is unclear whether patients with MGUS should be routinely assessed for osteoporosis/osteopenia; this could be feasibly addressed by a prospective cooperative group trial.

Smoldering Multiple Myeloma

Patients with smoldering MM (SMM) have substantial risk for progression to MM (relative risk [RR], 522) and primary amyloidosis (RR, 50).²³ A study from the Mayo Clinic reported a median time to progression (TTP) to symptomatic disease requiring therapy of 5 years (Table 4).²³ For all patients, the greatest risk of progression occurs in the first 5 years after diagnosis. Although the

Table 5 Solitary Plasmacytoma of the Bone: Risk Groups

Number of Patients	sFLC Ratio Abnormal at Diagnosis	M-Protein, ≥ 0.5 g/dL ^a	5-Year Progression, %
31	No	Normal	13
26	No	Abnormal	26
	Yes	Normal	
18	Yes	Abnormal	62

^aAt 1-2 years following diagnosis.

Abbreviation: sFLC = serum free light-chain

risk in subsequent years diminishes, it is still significant, and most patients eventually develop symptomatic myeloma. Patients with SMM can be risk stratified based on serum M-protein levels and the percentage of bone marrow plasma cells (BMPCs). In the highest-risk groups with BMPCs of ≥ 10%, detection of an abnormal sFLC ratio increases the RR of progression to symptomatic MM 2-fold (serum M-protein ≥ 3 g/dL: RR, 2.06; < 3 g/dL: RR, 1.72).

An individualized approach to the management of SMM is preferred based on differential prognosis and TTP for discrete clinical subsets as well as patient compliance for follow-up. As a practical approach, the doubling time of the M component should be factored into the physician's decision-making process. However, there is currently no evidence that supports early intervention. In patients with high-risk features despite absence of CRAB (hypercalcemia, renal insufficiency, anemia, or bone lesions), it can be hypothesized that early treatment might delay development of late-stage poor-prognostic genetic abnormalities, such as the p53 mutation, that evolve over time.²⁴ A number of ongoing clinical trials are evaluating targeted agents in this setting, and emerging early phase III data with lenalidomide/dexamethasone are promising.²⁵ However, the economics and safety of long-term treatment in this patient population will need to be considered when making future decisions regarding timing of initial therapy in high-risk SMM.

Solitary Plasmacytoma

Although inconsistent with current classification, M protein can be detected in approximately 50% of patients with solitary plasmacytoma of the bone.²⁶ To avoid understaging, patients should undergo magnetic resonance imaging (MRI) to determine whether there are additional sites of skeletal involvement,²⁷ but whether these results truly change the outcome for patients has not been demonstrated in any large studies. Although there is insufficient information to formalize a role for positron emission tomography (PET)/computed tomography (CT), this modality has been reported to detect additional bone disease beyond that seen with MRI.²⁷ Furthermore, PET/CT facilitates the detection of unsuspected sites of extramedullary plasmacytoma. Unfortunately, a diagnostic trial evaluating MRI and whole-body fluorine-18 fluorodeoxyglucose PET as a supplement to imaging with skeletal survey to determine how many patients with solitary plasmacytomas were misdiagnosed was closed because of lack of enrollment.²⁸ Because patients with solitary plasmacytoma comprise a small subset and might go underdiagnosed, additional screening with these radiologic tests to look for MM could be worthwhile.

Table 6 Response and Survival Outcomes: Selected Phase III Data

Outcome Measure	VD vs. VAD ^a	RD vs. Rd ^b	MPT vs. MP ^c	VMP vs. MP ^d
ORR, %	82 vs. 65	79 vs. 68	68.9 vs. 47.6	71 vs. 35
≥ VGPR, %	39 vs. 16	42 vs. 24	29.3 vs. 11	CR: 33 vs. 4
Median PFS/TTP	2-year rate: 69% vs. 60% <i>P</i> = .0115	19.1 vs. 25.3 months (PFS) <i>P</i> = .026	21.8 vs. 14.5 months (PFS) <i>P</i> = .004	24 vs. 16.6 months (TTP) <i>P</i> < .000001
OS	2-year rate: 90% vs. 88%	3-year rate: 75%, both arms	45 vs. 47.6 months <i>P</i> = .79	3-year rate: 72% vs. 59% <i>P</i> = .0032

^aResponse to induction; 2-year median follow-up on PFS and OS data.

^bResponse in 4 cycles; median follow-up, 35.8 months.

^cMedian follow-up, 38.1 months.

^dInternational Uniform Response Criteria.

Abbreviations: CR = complete response; MP = melphalan/prednisone; MPT = melphalan/prednisone/thalidomide; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RD = lenalidomide/high-dose dexamethasone; Rd = lenalidomide/low-dose dexamethasone; TTP = time to progression; VAD = vincristine/doxorubicin/dexamethasone; VD = bortezomib/dexamethasone; VGPR = very good partial response; VMP = bortezomib/melphalan/prednisone

Methods to determine the overall risk and factors that predict development of MM among patients with solitary plasmacytoma of the bone have been published. In a cohort of 116 patients with solitary plasmacytoma, 37% progressed to MM, with a median TTP of 1.8 years.²⁹ Risk groups for progression could be delineated based on abnormal sFLC ratio at diagnosis and M-protein levels of ≥ 0.5 g/dL at 1-2 years (Table 5). Patients at highest risk for progression exhibited both abnormal features. Radiation therapy can achieve local control of both solitary bone plasmacytoma and solitary extramedullary plasmacytoma, although progression to myeloma is considerably more frequent in patients with bone disease.³⁰ For solitary bone plasmacytoma with a low proportion of plasma cells in the bone marrow, treatment with irradiation and subsequent observation is sufficient; however, patients with a higher level of plasmacytosis need to be monitored more closely.³

Treatment Options for Previously Untreated Myeloma

With the advent of novel targeted agents, improved survival outcomes have been realized by the majority of patients with MM.³¹ The immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib are now routine components of first-line therapy.^{24,32} For transplantation-ineligible patients, melphalan/prednisone plus thalidomide, or plus bortezomib, has prolonged overall survival (OS) and/or progression-free survival (PFS) in randomized trials. For younger patients, an array of targeted agent combinations have yielded high overall response rates and complete response (CR) rates as induction therapy before autologous stem cell transplantation (ASCT), although increased follow-up is required to determine OS benefit.

Three drug combinations (VTD [bortezomib/thalidomide/dexamethasone], VCD [bortezomib/cyclophosphamide/dexamethasone], VRD [bortezomib/lenalidomide/dexamethasone]) are superior to 2-drug combinations (TD [thalidomide/dexamethasone], VD [bortezomib/dexamethasone], RD [lenalidomide/dexamethasone]). For patients proceeding to ASCT, it is important to bear in mind that prolonged lenalidomide can negatively affect stem cell collection, and this might possibly hinder the success of ASCT if stem cells are not harvested early.^{33,34} However, plerixafor and cyclophosphamide chemomobilization can provide alternative

mobilization strategies for these patients. Emerging preclinical data show that lenalidomide (and pomalidomide) are, in fact, not toxic to stem cells but rather, they effect reversible changes in transcriptional status with differential impact on discrete clonal populations: myeloid clones are stimulated while granulocyte populations are suppressed.³³

Considerable crossover on clinical trials often complicates analysis of OS.³⁵ As a result, PFS has become a more feasible endpoint, though it might not be an accurate surrogate for a true survival benefit. Many studies use CR as a surrogate for OS, but its translation into prolonged OS can vary (Table 6).^{32,36-39} Underlying reasons for different outcomes are multifactorial and include a balance between toxicity and efficacy of different regimens in addition to patient risk.³⁵ Because novel therapies and combinations thereof continue to yield increasingly higher CR rates, other posttreatment prognostic factors require consideration, including durability of CR and attainment of minimal residual disease (MRD).³² Recent data have shown that patients with MRD-negative versus MRD-positive status at day 100 after ASCT have superior PFS and OS; remarkably, MRD-negative/immunofixation (IF)-positive MM was associated with prolonged PFS compared with MRD-positive/IF-negative MM.⁴⁰ Despite these new developments, it is unclear whether a primary goal of CR can be effectively translated to, or is indeed practical at, the bedside. Accordingly, the goals for first-line treatment in the clinic can be confounding.

Diverging management approaches were revealed when attending KOLs were probed for their primary treatment goals (CR, TTP, OS) in newly diagnosed MM, and differing opinions on criteria dictating change of therapy were uncovered (Table 7). Although prolonged OS was the ultimate goal for all patients, QOL and prevention of end-organ damage were particularly sought in elderly patients. There was disagreement on the use of CR as a surrogate for improved OS; CR might be prognostic only in high-risk MM.⁴¹ For transplantation-eligible MM, there was a lack of consensus regarding the optimal number of induction cycles and the necessity to change induction therapy based on suboptimal response. In support of limited cycles, high-dose melphalan/ASCT yields efficacy independent of response to induction and also benefits patients with progressive disease.⁴²⁻⁴⁴ However, because many targeted agents induce incremental increases in response over a number

Table 7 Areas of Discord in Newly Diagnosed Myeloma

1	Should patients proceeding to ASCT receive a standard 4 cycles of induction therapy or be treated to maximum response?
2	Should therapy be changed if $\leq$ PR or $\leq$ VGPR in younger patients?
3	Use of CR as a surrogate for OS
4	Separation of patients with higher-risk cytogenetics up front for clinical trials
5	Different goals of therapy according to age and transplantation eligibility
6	Benefits of maintenance therapy in different patient subsets

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; OS = overall survival; PR = partial response; VGPR = very good partial response

of cycles, it might be preferable to prolong treatment until best response. Several KOLs explored all avenues to attain CR before ASCT, including change of therapy.

Patients with suboptimal response to ASCT may receive consolidation/maintenance therapy or a second transplantation, although this latter approach is associated with increased treatment-related mortality (TRM).^{35,45} Furthermore, an OS advantage with tandem versus single transplantation has been variably reported despite superior CR rates and event-free survival.⁴⁶ This could be accounted for in large part by effective salvage with novel agents in the single-transplantation arms.⁴⁷ Attainment of $\geq$ very good partial response (VGPR) to induction/single ASCT in the IFM 2005-01 trial evaluating bortezomib/dexamethasone versus standard vincristine/doxorubicin/dexamethasone (VAD) has reduced the need for a second transplantation and has significantly prolonged PFS.⁴⁸ A 3-armed prospective trial will evaluate single transplantation versus single transplantation plus consolidation with novel agents versus tandem transplantation to determine the most beneficial approach.⁴⁷

For transplantation-ineligible MM, there is less eagerness to change therapy if $\geq$ PR has been reached, and preservation of QOL takes on greater significance. Importantly, treatment choices should be based on phase III data. Risk-adapted goals may also be applied in this setting, and stable disease (SD) could be a laudable goal for elderly patients without aggressive disease in the clinic. Chasing depth of response, including CR, for elderly patients can prove problematic.³⁵ In a phase III study by Ludwig et al, although response rates were higher among elderly patients receiving thalidomide/dexamethasone versus standard oral melphalan/prednisone, OS was inferior because of higher TRM in the thalidomide-treated group.⁴⁹ However, it should also be noted that in this study melphalan/prednisone yielded remarkable survival outcomes compared with other recent trials using melphalan/prednisone as a control arm⁵⁰; this likely reflects the availability of newer agents in the salvage setting. In another phase III trial evaluating melphalan/prednisone/thalidomide versus melphalan/prednisone, salvage of patients with $<$ PR led to inferior outcomes.⁵¹ Nonetheless, a subset analysis of the VISTA (Velcade as Initial Standard Therapy) study reported that superior depth of response is associated with prolonged TTP in transplantation-ineligible patients.³⁷

Approaches to reach best response vary. The aggressive total-therapy regimens that combine a multitude of conventional and targeted agents in a schedule of induction, transplantation, and maintenance

Table 8 Landmark Analysis of the Phase III E4A03 Trial: 3-Year Survival^a

Treatment Group	RD	Rd
	n = 104	n = 79
Primary Therapy, 4 Cycles		
Transplantation	92% (n = 50)	92% (n = 40)
No transplantation	55% (n = 54)	55% (n = 39)
Primary Therapy, $>$ 4 Cycles	79% (n = 108)	79% (n = 140)

^a3-year overall survival rate in intent-to-treat population, 75%.

Abbreviations: RD = lenalidomide/high-dose dexamethasone; Rd = lenalidomide/low-dose dexamethasone

have yielded provocative OS data.^{52,53} In support of this approach, it is generally observed that the first remission is usually the longest; thus, maximizing response to initial therapy could be predicted to be the most beneficial strategy. However, combination of the currently available novel agents has been shown to yield CR and VGPR rates comparable with those attained with total-therapy regimens.³⁵

For younger patients, the role of ASCT is being readdressed because prolonged responses have been reached in clinical trials by the application of synergistic combinations, 3- and 4-drug multi-agent regimens, prolonged induction, and/or first-line therapy plus maintenance.²⁴ A number of clinical trials are evaluating newer combinations of immunomodulatory agents and/or bortezomib with or without transplantation in order to help resolve whether ASCT should remain the default position.^{54,55} These studies build upon the landmark analysis of the E4A03 trial, which reported that patients choosing to continue primary therapy had similar OS to the intent-to-treat population scheduled for ASCT (Table 8).³⁸ However, it should be stressed that patients were not randomized to receive ASCT or prolonged primary therapy in the E4A03 trial; thus, until prospective trial data are available, ASCT should be viewed as a therapeutic modality associated with durable responses, a low mortality rate, and cost-effectiveness compared with targeted agents. Furthermore, current limited experience with 4-drug combinations shows that all patients eventually relapse; thus, ASCT remains another approach to consolidate responses.

Risk Stratification

Cytogenetic abnormalities associated with high-risk MM have been clearly defined, although these data have been derived in the most part from studies conducted before the widespread use of immunomodulators and bortezomib.²⁴ However, despite this era of multitargeted agent combinations, transplantation/consolidation, and maintenance approaches, patients with high-risk MM inevitably experience relapse, and optimal management of this patient subset remains unknown. Bortezomib-based regimens have yielded favorable $\geq$ VGPR rates for patients with MM and high-risk cytogenetics (Table 9),^{36,48} and similar TTP and OS for high-risk compared with standard-risk MM (Table 10).^{53,56} Although this evidence suggests use of bortezomib over lenalidomide- or thalidomide-based regimens among patients with high-risk cytogenetics, conclusions have primarily been drawn from small patient numbers. A recent report on MM treated with first-line lenalidomide/dexamethasone showed that patients with high-risk versus low-risk

Table 9 Impact of Bortezomib on Post-Induction $\geq$ Very Good Partial Response Rates in High-Risk Multiple Myeloma

High-Risk Cytogenetic Factor	$\geq$ VGPR Response Rate					
	VD	VAD	P Value	VTD	TD	P Value
Del(13q)	n = 103 47%	n = 101 15%	< .0001	n = 47 73%	n = 46 25%	< .001
t(4;14)	n = 40 40%	n = 29 17%	.04	n = 19 81%	n = 20 25.5%	< .001
Del(17p)				n = 7 73%	n = 8 6%	< .001

Abbreviations: TD = thalidomide/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; VD = bortezomib/dexamethasone; VGPR = very good partial response; VTD = bortezomib/thalidomide/dexamethasone

disease attained similar $\geq$ VGPR rates, but TTP was significantly inferior in those with high-risk MM.⁵⁷ Conflicting data have been reported with this doublet in relapsed/refractory MM: although a French study reports an inferior overall response rate, PFS, and OS in patients with del(13q) and t(4;14) compared with patients without these abnormalities, the Canadian MM-016 study found only patients with del(17p) to have significantly poorer outcomes.^{58,59} This highlights the need to study high-risk MM more systematically in prospective trials.⁶⁰

Low-risk MM is characterized by hyperdiploid features and t(11;14). One strategy to treat patients with low-risk MM involves the application of an immunomodulatory agent or bortezomib with steroids to avoid overtreatment, with reservation of more aggressive 3- or 4-drug combination regimens for salvage treatment. Any patients with high-risk MM would be expected to experience relapse early, and sequencing of targeted therapies could then be applied; however, early mortality might affect the ability to sequence. Another strategy involves up-front application of 3- and 4-drug combinations in order to treat disease when it is most sensitive to therapy and avoid undertreatment of patients with high-risk disease. Ultimately, it is not known which approach is most beneficial. However, among patients with more aggressive disease associated with plasma cells in the blood, significant renal impairment, or marked cytopenias felt to be due to myeloma, a rapid response is important to achieve, which is more likely to occur with more drugs combined together.

First-line Multiple Myeloma With Comorbid Disease

Renal Impairment. With regard to myeloma kidney, a bortezomib/thalidomide/dexamethasone-based regimen is the current therapy of choice in order to attain rapid tumor cytoreduction, which is important to prevent patients from developing irreversible kidney damage.⁶¹ The schedule and dose of lenalidomide needs further optimization for patients with renal impairment.⁶² Patients need to be grouped according to dialysis dependency, and the role of plasmapheresis needs to be further defined. Although phase III data support no role for plasmapheresis,⁶³ it could prove beneficial as adjunct therapy in biopsy-proven myeloma cast nephropathy.⁶⁴ A current study is evaluating high cutoff filters in newly diagnosed MM and acute kidney failure to define their efficacy in achieving rapid reduction of sFLC load.⁶⁵

Table 10 Impact of Bortezomib/Melphalan/Prednisone on Outcomes in High-Risk Multiple Myeloma

Outcome Measure	Standard-Risk (n = 142)	High-Risk (n = 26)
TTP	23.1 months	19.8 months
	HR, 1.297 (95% CI, 0.55-3.06; P = .55)	
OS	Not reached	Not reached
	HR, 1.104 (95% CI, 0.444-2.743; P = .8311)	

Abbreviations: HR = hazard ratio; OS = overall survival; TTP = time to progression

Cardiac Disease. Infrequently, patients receiving lenalidomide or thalidomide have been observed to develop unexplained ischemia or atrial fibrillation.^{38,66} Full anticoagulation prophylaxis should be instituted in at-risk patients according to guidelines.⁶⁷ Caution is required when using dexamethasone in these patients because of fluid retention and its possible role in flash pulmonary edema. Prolonged use of doxorubicin and its newer pegylated liposomal formulation could also be associated with the development of congestive heart failure.²⁴ As a result, all patients receiving these drugs should have a baseline assessment of ejection fraction (EF), and patients showing a reduced EF should not be given these drugs. Cyclophosphamide might also be associated with cardiac toxicity when administered at high doses.

Neuropathy. Patients with MM can present with baseline PN, and both thalidomide and bortezomib—and to a lesser extent, lenalidomide—are associated with treatment-emergent PN.²⁴ This side effect is rarely observed with lenalidomide.⁶⁸ Unlike thalidomide, symptoms are reversible in the majority of patients who experience PN after treatment with bortezomib.⁶⁹ Moreover, weekly administration of bortezomib rather than the standard twice-weekly schedule has reduced the occurrence/severity of PN in several ongoing trials in first-line treatment.^{70,71} The CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) trial also showed that a reduction in the dose from 1.3 mg/m² to 1 mg/m² was associated with a reduced risk of PN.⁷² Thalidomide-associated PN is most often irreversible.⁶⁸ It is both dose- and duration-dependent. Therefore, close monitoring of patients for emergence of neuropathy is required to ensure timely modification of dose and/or treatment discontinuation before neuropathy worsens.⁷³ Early studies report that the novel proteasome inhibitor carfilzomib might be associated with less neurotoxicity,⁷⁴ but larger studies will have to be completed to assess both its efficacy and overall safety. Finally, modification of prophylactic strategies might also be required in these patients, such as avoidance of voriconazole, an antifungal agent that could be associated with neuropathy.

Other Comorbidities. Obesity is important to consider in relation to the incidence of deep vein thrombosis (DVT).⁷⁵ Indeed, recommendations from an international panel on optimal thromboprophylaxis include obesity as a risk factor contributing to change of prophylactic agent.⁶⁷ For MM with cytopenia, lenalidomide, bortezomib, or thalidomide remain possible options.

Maintenance

Maintenance therapy can be used to prolong the duration and improve the quality of response.²⁴ Definitions for prolonged primary therapy and maintenance therapy are unclear, and it can be difficult to determine when maintenance actually begins. For example, should it be defined when induction therapy continues beyond a standard number of cycles or upon dose reduction and/or discontinuation of certain components of a multiagent regimen?

A randomized phase III study has shown that prednisone 50 mg administered every other day is effective as maintenance therapy among patients whose disease is responding to a VAD-like regimen as initial therapy.⁷⁶ For transplantation-ineligible MM, 1 year of induction therapy with bortezomib/melphalan/prednisone appears to be appropriate, although a rapid response to bortezomib should allow progressive dose reduction over the course of therapy. In this study group's experience, lenalidomide/dexamethasone is generally given indefinitely until disease progression based on single-institution studies⁷⁷ as well as on the E4A03 trial.³⁸ Whether there is a need to continuously expose the myeloma clone to lenalidomide in order to maintain suppression, even in the presence of CR, is unknown. The IFM 07-01 trial will answer the question of whether patients should get a fixed or indefinite number of cycles of lenalidomide.⁷⁸ Nevertheless, regardless of the clinician's choice, the patient ultimately dictates how long and at what doses first-line therapy is administered based on whether the therapy remains effective, is tolerable, and is affordable. On a cautionary note, there is potential for the development of long-term toxicities with prolonged novel-agent therapy, although use of novel combinations that allow for reduced dosing based on synergy could prove to be more feasible in the future.

The benefit of maintenance after high-dose therapy/ASCT in patients reaching CR, VGPR, or an MGUS-like disease state was discussed at the roundtable.^{35,79} Although outcomes in trials evaluating thalidomide maintenance have shown improvement in OS, its precise use after transplantation is still under investigation. Most recently, a significant OS advantage with 1 year of thalidomide/prednisolone consolidation has been seen in patients attaining < VGPR to transplantation, with a trend toward improved OS in those achieving ≥ VGPR.⁸⁰ This attests to the notion that consolidation/maintenance might be most beneficial for patients achieving less than an optimal response and that synergistic therapies might be more beneficial than monotherapy treatment.⁸¹ However, this latter trial was not a crossover design, and many patients randomized to only the steroid never received thalidomide, so it is impossible to know whether these patients' outcomes would have been similar to those in the group who received the immunomodulator if they were given thalidomide at the time of progression. Phase II data show that consolidation with lenalidomide/prednisone and maintenance lenalidomide after reduced-intensity ASCT provides considerable benefit among patients with VGPR.⁸² However, in the absence of more data, it is unclear whether maintenance therapy should be for a finite length of time. It is also unclear whether maintenance should be restricted to patients not having ≥ VGPR and patients at high risk for early relapse.

Relapsed/Refractory Disease: Where Are We in 2009?

The 3 key agents used in first-line MM, namely bortezomib, lenalidomide, and thalidomide, are also therapies of choice in relapsed/refractory MM (Table 11).^{73,83-85} Treatment choice is dependent on response and tolerability of previous therapy, comorbid status, and preferred mode of administration, among other factors. The timing of intervention in relapsed/refractory MM can vary, and precise values of serum/urinary M-protein or sFLC that dictate initiation of therapy in this setting have not been clearly defined. It is advisable to observe patients whose disease relapses solely on criteria of immunofixation positivity with a low (0.5 g/dL) M-protein spike or patients slowly emerging from plateau phase unless other signs, symptoms, or laboratory findings suggest intervention. Intervention is indicated for patients with more rapid progressive M-protein increments or obvious symptoms or signs of relapse, such as worsening renal function or cytopenias. Whether the doubling time of the M-protein might serve as a predictor of progression is unknown. Disease history needs to be considered in order to ensure prompt treatment for patients with previously aggressive MM. Moreover, although patients with high-risk MM might comprise only a small subset of the MM population, cytogenetic abnormalities evolve over time, and risk increases with disease duration and at each relapse. Patients who experience relapse after an extended remission might do so in a focal manner, and radiographic imaging will help determine the potential existence of a solitary site amenable to therapy.²⁷ For patients in biochemical relapse, a metastatic bone survey is sufficient. However, if specific sites of bone involvement are suspected, other imaging modalities are indicated. Neurologic relapse can be subtle, and the clinician needs to be sensitive to lower-extremity weakness or paresthesias, which could be due to spinal cord compression, and use MRI when appropriate.

Currently, the majority of patients experiencing first relapse have been exposed only to doublet regimens, and accordingly, alternative salvage strategies are feasible. However, optimal sequencing of targeted agents in relapsed/refractory MM is not adequately defined and tends to be at the discretion of the treating clinician. Of note, in some studies, previous thalidomide treatment has been reported to negatively affect salvage with other therapies.^{24,86} Although previous treatments can limit therapeutic options, they can also be informative, with salvage therapies chosen often by combining drugs from classes that previously yielded a durable response. Retreatment of patients who have shown long remission from their initial therapeutic regimen remains a reasonable option.⁸⁷ Current data demonstrate that retreatment with bortezomib is effective and tolerable, and in high-risk disease, novel combinations may be used to capitalize on synergy.^{88,89} Similarly, retreatment with thalidomide is often also effective but limited by neuropathic effects from long-term exposure to this drug.²⁴

For patients experiencing aggressive relapse, quantity of life might have to take precedent over QOL, and aggressive multiagent regimens should be considered. An interesting observation with multiagent combinations is that some patients can become resensitized to drugs given in previous regimens despite initial poor response or relapse. For example, patients experiencing relapse sequentially with melphalan/bortezomib and then with thalido-

Table 11 Phase III Trials in Relapsed/Refractory Multiple Myeloma

Outcome Measure	MM-009/MM-010		APEX		DOXIL-MMY-3001	
	RD (n = 353)	D (n = 351)	V (n = 333)	D (n = 336)	V/PLD (n = 324)	V (n = 322)
ORR	60.6%	21.9%	43%	18%	44%	41%
CR	15%	2%	9%	< 1%	4%	2%
Median TTP	13.4 months	4.6 months	6.2 months	3.5 months	9.3 months	6.5 months
	$P < .001$		$P < .001$		$P < .000004$	
Median OS	38 months	31.6 months	29.8 months	23.7 months	76% (15-month)	65% (15-month)
	$P = .045$		$P = .027$		$P = .03$	

Abbreviations: APEX = Assessment of Proteasome Inhibition for Extending Remissions; D = dexamethasone; OS = overall survival; PLD = pegylated doxorubicin; RD = lenalidomide/dexamethasone; TTP = time to progression; V = bortezomib

mide/steroid might respond subsequently to all 4 agents in combination. Likewise, patients experiencing relapse with lenalidomide/dexamethasone and then bortezomib/dexamethasone/doxorubicin have been noted to attain subsequent durable responses when all agents are combined together. Thus, decisions to omit drugs based on previous exposure might not be warranted. However, this resensitization phenomenon needs to be studied in prospective clinical trials before the formulation of any recommendations. It is also important to bear in mind that older regimens such as DCEP (dexamethasone/cyclophosphamide/etoposide/cisplatin), or even single-agent cyclophosphamide or melphalan, can yield durable responses in patients experiencing relapse with targeted therapies. Oral cyclophosphamide, although used widely by physicians specializing in MM, is used less frequently in the community and has not been well studied in the relapsed setting.

Goals of Therapy

Depth of response has been correlated with improved outcome in relapsed MM.⁹⁰ However, application of depth of response as a treatment goal can depend on a patient's age and whether he or she is in first relapse or in subsequent relapses. In an older patient ineligible for transplantation and in first relapse, attainment of SD without treatment intensification might be satisfactory as long as it is tied in with other factors such as adequate hemoglobin and lack of deterioration in renal function or occurrence of new bone-related problems. Conversely, in a younger patient experiencing relapse after ASCT, a more aggressive approach might be warranted, including a change of regimen to induce deeper response. Ultimately, satisfaction with SD is dependent upon the patient's symptoms, side effects from treatment, previous history of aggressive disease, presence of high-risk features, and comorbid status. For patients pursuing a second ASCT after suboptimal response to their first ASCT, application of a limited number of cycles (2 cycles) of interim therapy can determine if the patient is responsive and if a particular drug can be used as maintenance.

In relapsed/refractory MM, it is difficult to apply OS as a goal of therapy because effective salvage complicates analysis. However, time to next treatment (TTNT) can provide a valuable measure of how well the patient is doing compared with his or her last treatment.⁹⁰ Increased use of TTNT as an endpoint in clinical trials could enable the physician to gauge how different regimens

might perform at the bedside. However, TTNT is a poorly defined variable that is rather subjective and dependent on the clinicians'/investigators' threshold for implementation of next therapy, among other factors. Furthermore, it can be very difficult to determine TTNT for patients receiving continuous primary therapy or maintenance therapy. Additionally, it is unclear whether prolonging the first TTNT would negatively affect subsequent TTNTs, ultimately yielding little benefit.

With each subsequent relapse, treatment options become more limited, and patients might be more willing to continue current treatment despite treatment-related toxicities. At some point, after ≥ 3 relapses, both clinician and patient need to consider QOL as the primary treatment goal while remaining receptive to newer and potentially efficacious agents that could provide continued hope in the clinical trial setting.

Relapsed/Refractory Multiple Myeloma With Comorbidity

Peripheral Neuropathy. In patients with relapsed MM with ongoing significant neuropathic symptoms from previous exposure to thalidomide, it might be preferable to avoid the use of this agent and instead try a lenalidomide-based regimen. Clinical trials have demonstrated bortezomib-induced PN to be reversible upon dose reduction/interruption in the majority of patients, and these data translate well into the clinic.⁶³ However, despite improvement, low-grade PN can persist. Most importantly, PN is not cumulative with bortezomib, and previous PN with bortezomib might not predict subsequent emergence with retreatment, although this could be partly due to physician awareness and a more aggressive and timely dose reduction. Trials evaluating the safety and efficacy of bortezomib retreatment have reported a low incidence of grade ≥ 3 PN and/or decreased discontinuation because of PN.^{88,89,91} The guidelines for bortezomib dose reduction need to be followed carefully in order to maintain patients on therapy.⁶⁹ Current phase III trials evaluating first-line weekly versus standard biweekly bortezomib in MM report reduced neurotoxicity without apparent loss of efficacy.^{70,92}

Renal Impairment. Bortezomib is safe and effective in patients experiencing relapse with creatinine clearance ≤ 50 mL/min.⁶³ However, although there are pharmacokinetic data suggesting that reduced-dose lenalidomide is feasible in patients with MM

with renal impairment, these data were derived from a study population devoid of malignant disease, with no previous exposure to MM therapies associated with treatment-emergent PN.⁶² Furthermore, application of this algorithm might be difficult in practice. Nevertheless, implementation of lenalidomide therapy for patients with relapsed MM with renal impairment is feasible. Optimal thromboprophylaxis during lenalidomide/dexamethasone therapy in patients requiring dialysis is not established: MM-009 and MM-010 excluded patients with creatinine ≥ 2.5 mg/dL from enrollment.⁸³

Other Toxicity Considerations. Caution is required when using concurrent radiation therapy with anthracyclines and perhaps bortezomib because they are both known radiosensitizers.⁹³ In recent years, cytopenias have become much more prominent and are difficult to manage in the heavily pretreated patient. Thalidomide and steroids are generally nonmyelosuppressive. Steroids should be used with caution in patients with MM with coexistent diabetes mellitus, with dose adjustment based on toxicity, and omission of anthracyclines is prudent in patients with congestive heart failure. Thromboprophylaxis with warfarin or low-molecular-weight heparin (LMWH) is indicated with high-dose dexamethasone when combined with immunomodulatory molecules thalidomide or lenalidomide, particularly if there is a previous history of thromboembolism.⁶⁷

Maintenance. There are diverging opinions on the relative benefit afforded by maintenance in the relapsed/refractory setting. One view is that all patients with relapsed/refractory MM should receive maintenance or the disease will return rapidly. However, there are few data, if any, to support this approach. Generally, immunomodulatory molecules are given until progression.

Considerations for Clinical Trials. There is a need to educate patients regarding ongoing clinical trials in order to prepare them for potential enrollment as their disease progresses. Indeed, although reimbursement for $\leq$ third-line therapies is generally expected to continue, in the future clinical trials might be the only option available for heavily pretreated patients. Unfortunately, trials often disqualify patients with cytopenias or other comorbidities; thus, a considerable number remain ineligible. In recent years, there has been a shift toward accepting minimal response (MR), SD, duration of response, and PFS as clinically relevant endpoints in trials for relapsed/refractory MM. Although some novel drugs might not yield the deepest responses, prolonged response duration and minimal toxicity could allow patients to remain on study with positive impact on disease control. Treatment of patients with refractory MM can be challenging, and lowering the response bar to incorporate MR could identify additional agents that can be evaluated later for synergy in multiagent regimens. Moreover, the phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial demonstrated that patients attaining MR have prolonged TTP and OS compared with nonresponding patients.⁹⁰ There is a need to design risk-adapted trials for relapsed MM and to further investigate optimal sequencing of targeted agents. For asymptomatic patients whose disease is in biochemical relapse, suitable trials

would include those evaluating agents associated with minimal toxicity, such as humanized monoclonal antibodies (MoAbs). Finally, clinical trials often require considerable time commitments from the patient in relation to associated clinic visits, follow-up, pharmacokinetic studies, and so forth. In moving forward with drug development and clinical trial design, these issues need to be considered up front in order to decrease rates of discontinuation.

Managing Complications of Myeloma and Treatment Toxicities

Bone Complications: Nonsurgical Intervention

There has been a remarkable decline in the annual frequency of skeletal events in patients with MM over the past decade. With the integration of bisphosphonates and novel targeted agents into the routine treatment of patients with MM, the skeletal event rate has improved from about 2 events per year before the use of bisphosphonates in the mid-1990s to a current rate of about once every 10 years.^{20,94} A number of guidelines for use of bisphosphonates in MM all recommend continued monthly treatment with pamidronate or zoledronic acid for 2 years.^{21,22} Prolongation of therapy beyond this period is not recommended, although it is possible that some patients with continued active bone disease could benefit from this approach.²² Every-3-month dosing after 2 years of bisphosphonates or after optimal response to MM therapy is exploratory only, but a number of ongoing studies are evaluating alternative bisphosphonate dosing schedules.^{95,96} In order to maximize bone strength, it is important to monitor vitamin D levels during bisphosphonate therapy and supplement as appropriate. Although a number of studies have recently reported beneficial effects of proteasome inhibitors and immunomodulatory agents on bone health, these data have been based on analysis of bone resorption markers/bone density and not skeletal-related events (SREs); accordingly, their impact on SREs and clinical benefit is currently unknown.^{97,98} Several novel MoAbs are being evaluated for positive effects on bone health in MM. Denosumab (anti-receptor activator of nuclear factor- κ B ligand) has yielded rapid and prolonged reduction in bone resorption markers,⁹⁸ and an anti-DKK1 MoAb is currently being evaluated with SRE rate as the primary outcome measure.⁹⁹

Although pamidronate and zoledronic acid reduce bone complications with similar efficacy, zoledronic acid has a more convenient 15-minute infusion schedule.¹⁰⁰ Although there have been several reports suggesting that zoledronic acid could induce a higher incidence of osteonecrosis of the jaw (ONJ) compared with pamidronate, evidence is weak in the absence of prospective studies.^{22,101} Furthermore, emerging data indicate that antiangiogenic drugs might also be risk factors for development of ONJ¹⁰²; thus, use of immunomodulatory drugs or other novel agents in recent years could be a contributing factor to the increased reporting of ONJ in patients with MM receiving bisphosphonates. Regardless, patients beginning intravenous (I.V.) bisphosphonates should have an oral examination, and the increased risk associated with use of dentures and a history of dental extractions should be noted.²² Unless otherwise dictated by disease progression, it is currently recommended that bisphosphonates be halted if ONJ develops while patients are receiving therapy.²² Upon withdrawal, ONJ does heal over a

protracted period of time. Bisphosphonate drug holidays have been recommended for patients planning to have either dental extractions or implants, despite lack of evidence showing benefit from this approach.¹⁰³ It might be wise to delay bisphosphonate therapy in previously naive patients requiring dental surgery. In general, the occurrence of ONJ has diminished recently with increased awareness of these possible ways to reduce the risk.²²

The nephrotoxic effects of bisphosphonates are well described, and monitoring and dosing guidelines have been instituted.²¹ Clinicians should collect 24-hour urine samples to monitor Bence-Jones protein if present. In the absence of this protein, ASCO guidelines advise measurement of serum creatinine before each bisphosphonate infusion.²¹ Cost issues, convenience, renal impairment, and differing opinions on the efficacy of pamidronate versus zoledronic acid and the risk for ONJ make the choice of bisphosphonate an individual one. At this time, the only randomized study involving both drugs showed no significant difference in the primary endpoint, although some secondary endpoints favored zoledronic acid.¹⁰⁰

Bone Complications: Surgical Intervention

The majority of patients with MM present with some level of comorbid bone disease, and VCFs are common.⁹⁸ Although fractionated radiation has been used effectively for the management of localized bone pain, long-term use can affect the bone marrow and complicate bone healing; accordingly, radiation therapy needs to be limited.¹⁰⁴ Minimally invasive procedures, including vertebroplasty and balloon kyphoplasty to stabilize fractures and improve disability, are currently available treatments. Emerging data from the randomized Fracture Reduction Evaluation (FREE) trial demonstrate that early intervention with balloon kyphoplasty is superior to nonsurgical care in patients with MM and other cancers with VCFs (Table 12).¹⁰⁵ Nevertheless, these procedures can increase risk for adjacent VCFs.¹⁰⁶

Although there are no randomized trials directly comparing balloon kyphoplasty to vertebroplasty in MM, both methods appear to provide comparable and sustained pain management.⁹⁴ However, 2 recent studies showed that vertebroplasty provided no benefit over sham surgery for non-oncology patients with VCFs.^{107,108} Both vertebroplasty and kyphoplasty can be performed on an outpatient basis, allowing little impact on scheduling of myeloma therapy. Kyphoplasty is also effective on older fractures, yielding clinical responses and pain improvement despite bisphosphonate therapy. This highlights unresolved mechanisms of action that could be partly explained by local heating in the area during poly(methyl methacrylate) cement application with possible nerve ablation. Nonetheless, complications can occur. Vertebroplasty is associated with a higher rate of cement extravasation compared with kyphoplasty, and this can result in pulmonary embolism or neurologic symptoms.¹⁰⁶ This needs to be weighed against balloon kyphoplasty being a slightly longer and more costly procedure. These procedures may be performed on patients with VCF with limited retropulsion of the vertebral body, dependent upon the experience of the attending surgeon. Finally, the utility of braces in these patients is unclear because the majority report extreme discomfort with these supports, new fractures are rare while patients are receiv-

Table 12 The Fracture Reduction Evaluation (FREE) Trial

Mean SF-36 PCS, Points ^a	Kyphoplasty (n = 149)	Nonsurgical Care (n = 151)
Baseline	26	25.5
1 Month	33.4	27.4
Change	7.2 (95% CI, 5.7-8.8)	2.0 (95% CI, 0.4-3.6)
Difference	5.2 points; 95% CI, 2.9-7.4 points; <i>P</i> < .0001	

^aScale, 0-100.

Abbreviation: PCS = physical component summary score

ing active MM therapy, and braces often lead to increased osteopenia. It might be more prudent to refer the patient to a physical therapist with initiation of weight-bearing exercises.

Renal Problems

The application of sFLC to the management of MM with renal impairment is not well established.¹⁰⁹ However, a renal reference range for the sFLC ratio has recently been published for patients with renal impairment, with modification of the upper limit of normal from 1.65 to 3.1.¹¹⁰ Patients with Bence-Jones proteinuria should be monitored by 24-hour urine collections. Among patients with extensive light-chain-only MM, 24-hour urine tests with determination of paraprotein levels will aid in the detection of an early response. For patients responding to MM therapy with improved glomerular filtration rate, a decreased sFLC ratio might not be accompanied with a change in urinary protein. Furthermore, because of the inherent user-to-user variability in 24-hour urine tests/urinary protein electrophoresis and their interpretation, it is important to refrain from hasty treatment decisions based on the results of a single test. Other considerations in MM with renal impairment are appropriate hydration and dose adjustment of drugs that are cleared primarily through the kidney. Nephrotoxic agents/procedures should be avoided, including I.V. contrast media, nonsteroidal agents, and antibiotics.

Neuropathy

Dose reduction of bortezomib and thalidomide in treatment-emergent PN has already been discussed.^{69,70,73} Prophylactic alpha-lipoic acid (ALA) improves diabetic neuropathy symptoms,¹¹¹ and it could also be useful in treating PN associated with MM; however, ALA has the potential to antagonize bortezomib *in vitro*, but the underlying mechanisms of action are unknown.¹¹² Antioxidants, vitamin C, and green tea polyphenols have also been reported to inhibit bortezomib response.¹¹³⁻¹¹⁵ A number of common chemotherapeutic agents are associated with central nervous system (CNS) toxicity,¹¹⁶ and diminished cognitive function and personality disorders have been observed with immunomodulatory agents.¹¹⁷ Reversibility of thalidomide-emergent CNS toxicity has been seen in the clinic among patients discontinuing therapy within 2 years of thalidomide initiation, but the cumulative effects of longer-term treatment have not been well studied. Central nervous system stimulants might provide benefit, including amphetamines and duloxetine, and low doses of modafinil could be useful for fatigue and somnolence. Prospective trials with modafinil and

armodafinil in MM are in the planning stages. On an anecdotal note, a “natural remedy” currently used by athletes for cramping is pickle juice,¹¹⁸ and this might be beneficial in MM.

Thromboembolism

There is an increased incidence of venous thrombotic events (VTE) when immunomodulators are combined with steroids or anthracyclines, and recommendations for optimal thromboprophylaxis have been published.⁶⁷ Less well-recognized is the potential for arterial thromboembolic events with immunomodulatory agents.¹¹⁹ If a patient develops a clot while receiving an immunomodulator despite prophylaxis, therapy needs to be stopped until the clot has resolved. For patients with comorbid obesity and high risk for VTE, LMWH or warfarin is advised.

Cytopenias

Anemia is commonly observed among patients with MM as a disease manifestation at presentation. It is also seen in patients with renal impairment, and use of erythropoiesis-stimulating agents (ESAs) as replacement therapy is currently recommended for these patients as well as those with chemotherapy-induced anemia.¹²⁰ However, the use of ESAs should be approached cautiously in patients receiving immunomodulatory agents combined with dexamethasone because both of these treatment strategies are associated with increased thromboembolic complications. Generally, ESAs should be used only to boost hemoglobin levels to 10 g/dL. In patients receiving ESAs, parenteral iron should also be given as indicated in order to effectively stimulate erythropoiesis.¹²⁰ Caution needs to be practiced with regard to use of growth factors for patients with MM and cytopenias because disease-related cytopenias might be transient if the patient's disease responds to MM therapy. Most importantly, myeloma regimens should not be discontinued because of moderate cytopenias. Neutropenia can be counteracted with filgrastim or pegfilgrastim. However, thrombocytopenia is still a great challenge, especially in the setting of relapsed/refractory MM.

Infection

Both humoral and cell-mediated immunity are compromised in MM, and therapy can further exacerbate the risk of infection, particularly during initial treatment cycles.¹²¹ Attention is required because bacterial infections are a common cause of death in patients with MM. However, in most cases, infections occur during times of neutropenia or as part of the patient's terminal event with progressive myeloma. Bortezomib and arsenic trioxide have both been associated with reactivation of herpes zoster, and prophylactic acyclovir should be administered concurrently and continued for 4 weeks after discontinuation of therapy.¹²² Importantly, the live herpes zoster vaccine needs to be avoided until studies confirm both its efficacy and safety for patients with myeloma. The benefits of vaccination against such agents as influenza and pneumococci are unclear because the majority of these patients are immunosuppressed and will not be able to mount a sufficient immune response.¹²⁰ However, it is advisable to give both influenza and pneumococcal vaccines to patients with MM. Unpublished observations from the Eastern Cooperative Oncology Group U1099

trial report no benefit of prophylactic antibiotics during the initial 3 months of chemotherapy.¹²³

Which New Agents Might Add to the Treatment Armamentarium?

There is an expanding number of novel agents belonging to discrete drug classes in clinical trials for MM. Inhibitors are being developed that target the cell cycle, cell surface molecules, signaling pathways, the unfolded protein response, and epigenetic pathways.¹²⁴ Preclinical research has provided the rationale for evaluation of synergistic activity between novel agents and established partner drugs, and some combinations induce resensitization to previous therapies to which the disease has become refractory (Table 13).

Newer immunomodulatory agents and proteasome inhibitors have yielded improved safety profiles compared with their prototypes, and promising activity in relapsed/refractory MM has been noted.¹²⁵⁻¹²⁷ Single-agent carfilzomib has induced responses in heavily pretreated patients, including those with bortezomib-naïve and bortezomib-refractory MM.^{125,126} Peripheral neuropathy is less common and milder with carfilzomib, whereas safety in patients with severe renal impairment has yet to be demonstrated. The combination of carfilzomib with lenalidomide/low-dose dexamethasone has yielded promising activity including VGPRs (ORR, 50%), and a phase III trial with this triplet is in the planning stage.^{126,128} The third-generation immunomodulatory agent pomalidomide plus weekly dexamethasone has also shown efficacy, including in lenalidomide-refractory MM.¹²⁷ However, there is potential for cross-resistance between older and newer drugs; thus, dose optimization needs to be carefully addressed.²⁴

The histone deacetylase (HDAC) inhibitor (HDACI) vorinostat is approved in the United States for cutaneous T-cell lymphoma, but evaluation as a single agent in relapsed/refractory MM resulted in early termination of a phase I study.¹²⁹ The safety and efficacy of vorinostat in MM is currently being explored in combination with lenalidomide and dexamethasone¹³⁰ and with bortezomib with or without dexamethasone.¹³¹ In this latter study, objective responses have been noted in bortezomib-refractory patients. A phase III evaluating vorinostat plus bortezomib is currently enrolling patients with relapsed/refractory MM.¹³² Phase I analysis of single-agent panobinostat showed insufficient efficacy to move forward,¹³³ but combinations with lenalidomide/dexamethasone¹³⁴ or bortezomib¹³⁵ have yielded objective responses. When low-dose panobinostat is combined with melphalan, responses have been observed, but this combination is also associated with cytopenias.⁹⁴ On a cautionary note, prolonged QTc interval has been reported in a number of patients receiving HDACIs.⁸²

The heat shock protein 90 inhibitor tanespimycin has shown encouraging data in a phase I trial, and preclinical research has revealed a potentially neuroprotective effect and synergy with bortezomib.¹³⁶ Bortezomib plus tanespimycin has yielded a durable response in a phase I/II trial, with no grade 3/4 PN; this combination is currently under phase III study.¹³⁷ The Akt inhibitor perifosine is also in early trials with bortezomib and has yielded high response rates in combination with lenalidomide/dexamethasone.^{138,139} Among humanized MoAbs in early trials, clotuzumab

Table 13 Selected Novel Agents in Early Clinical Trials for Multiple Myeloma

Agents in Early Trials	Responses	Selected Toxicities
Novel Proteasome Inhibitors		
Carfilzomib: PR-171-003, Relapsed/Refractory Multiple Myeloma		Grade 3/4: anemia, 37%; thrombocytopenia, 26%; neutropenia, 4%; PN, 2%; renal, 15%
All patients (N = 46) ^a	PR, 7; MR, 3	
Bortezomib refractory (n = 26)	PR, 2; MR, 3	
Carfilzomib: PR-172-004, Relapsed Multiple Myeloma		Grade ≥ 3: anemia, 16%; thrombocytopenia, 10%; neutropenia, 10%; PN, 3% (grade 3)
Bortezomib naive (n = 14)	ORR, 57%; CR, 7%; VGPR, 14%	
Bortezomib exposed (n = 17)	≥ PR, 18%	
Novel Immunomodulators		
Pomalidomide/Low-Dose Dexamethasone		Grade 3/4: neutropenia, 32%; pneumonia, 8% thrombosis, 1.6%
All patients (N = 60)	ORR, 63%; CR, 5%; VGPR, 28%	
Lenalidomide refractory (n = 20)	ORR, 40%; VGPR, 5%	
Histone Deacetylase Inhibitors		
Panobinostat/Bortezomib With or Without Dexamethasone (n = 38)	≥ PR, 58%; CR, 10%; VGPR, 5%	Grade 3/4: thrombocytopenia, n = 30; neutropenia, n < 25; asthenia, n < 10
Panobinostat/Lenalidomide/Dexamethasone (n = 27) ^b	PR, 4; sCR/CR, 2; VGPR, 5; MR, 1	Grade 3/4: neutropenia, n = 5; thrombocytopenia, n = 5
Vorinostat/Bortezomib With or Without Dexamethasone (n = 23)	PR, 7; VGPR, 2	Grade > 3: myelosuppression, n = 13; fatigue, n = 11; diarrhea, n = 5
Bortezomib Refractory (n = 9)	PR, 3	
Vorinostat/Lenalidomide/Dexamethasone (n = 31) ^c	PR, 11; CR, 2; MR, 5	Grade 3/4: neutropenia, n = 8; thrombocytopenia, n = 5; DVT, n = 2 (grade 3 only)
Signaling Inhibitors		
Tanespimycin/Bortezomib (n = 72) ^d	≥ MR, 27%	Grade 3/4: thrombocytopenia, 25%; neutropenia, 3%; AST elevation, 4%
Bortezomib refractory (n = 23)	≥ MR, 13%	
Perifosine/Bortezomib With or Without Dexamethasone (n = 84) ^e	≥ PR, 22%; ≥ CR, 4%; MR, 19%	Grade 3/4: thrombocytopenia, 23%; pneumonia, 12%; neutropenia, 15%; PN, n = 2 (no grade 4)
Perifosine/Lenalidomide With or Without Dexamethasone (n = 30)	≥ PR, 50%; nCR, 7%; VGPR, 10%	Grade 3/4: neutropenia, 20%; hypophosphatemia, 17%; thrombocytopenia, 13%

^an = 39 evaluable for response.^bn = 23 evaluable for safety; n = 20 evaluable for response.^cA total of 28 patients evaluable for response.^dn = 67 evaluable.^eA total of 73 patients were evaluable for response.

Abbreviations: AST = aspartate aminotransferase; CR = complete response; DVT = deep-vein thrombosis; GI = gastrointestinal; MR = minimal response; nCR = near-complete response; PN = peripheral neuropathy; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

targeting the CS1 antigen has yielded SD as monotherapy¹⁴⁰ and is currently being evaluated with lenalidomide/dexamethasone and with bortezomib.¹⁴¹⁻¹⁴³ Other promising MoAbs include CNTO 328, which targets interleukin-6, and the anti-CD138 MoAb nBT062 drug conjugate.¹⁴⁴ There is also renewed interest in the alkylator bendamustine, which is approved for chronic lymphocytic leukemia and non-Hodgkin lymphoma in the United States and approved for MM in Germany.¹⁴⁵ Bendamustine is associated with decreased myelosuppression compared with melphalan, and it is currently under evaluation in MM as a conditioning regimen before ASCT and in combination with bortezomib in relapsed/refractory MM.^{146,147}

Despite this impressive development, a number of current trials evaluating novel-agent combinations are poorly designed and might not be addressing the correct questions.¹²⁴ In many cases, enrollment of undefined patient populations has made it very dif-

ficult to determine the benefit of the investigational agent over the partner drug and predict the future success of the combination in phase III trials. One approach to improving trial designs would be to enroll only patients whose disease is currently progressing on the intended partner drug, in order to more easily determine novel-agent efficacy, synergy, and/or partner drug resensitization. For novel agents that lack single-agent activity, the rationale and optimal approach for further development might not be immediately apparent. Moreover, key decision points that drive the development of new drugs from preclinical to clinical evaluation and from early- to late-phase trials are not clearly defined.¹⁴⁸ Finally, although the development of “me too” drugs can offer differing pharmacology with improved scheduling, toxicity, and/or efficacy, careful dose optimization for each new drug in the preclinical setting is required in order to avoid unnecessary and costly adjustments in clinical trials.

Despite all the clinical options available today, current therapies are not curative. Patients face repeated relapses with ever-increasing challenges to achieve control of their disease and avoid side effects that are often cumulative. Moreover, higher-risk disease develops over time in nearly all patients as the MM becomes more resistant, and accordingly, there is a need to identify regimens that differentially affect high-risk MM. One approach is to limit eligibility of some trials to patients with high-risk MM and, in so doing, facilitate a primary endpoint of OS. Caveats to this approach include the possibility of inadvertently classifying a regimen as poor when excellent responses might have been attained in good-risk patients. Furthermore, there is no provision for the differential impact of underlying pathobiology/cytogenetics on drug efficacy.

Conclusion

The *Clinical Lymphoma & Myeloma Panel: Focus on Myeloma* provided a platform for KOLs to express their opinions and discuss controversies in the field of MM. It was generally agreed that for patients with MGUS, the approach of “watch and wait” would remain the mainstay, though patients presenting with MGUS-related manifestations might require a different management approach. In first-line treatment of patients with MM, more data are needed concerning the relative long-term benefits of novel doublet regimens versus those incorporating multiple targeted agents before optimal therapies and management approaches can be selected. Current data still support the inclusion of transplantation for eligible patients as part of the treatment paradigm. For patients with relapsed/refractory MM, novel chemistries and targeted-agent combinations that provide for synergy are continually being evaluated, and a number of these strategies have yielded promising data. In the clinic, the ratio of good-risk to poor-risk patients returning for additional treatment has not changed with targeted-agent therapy; thus, continued new drug development for all MM risk categories is required. Finally, there is a need to more carefully design clinical trials in MM in order to propel development of those new drugs with the most potential.

Disclosures

Sundar Jagannath has served as a paid consultant or been on the Advisory Board of Celgene Corporation; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; and Pfizer Inc. Robert A. Kyle has served as a paid consultant or been on the Advisory Board of Celgene Corporation; Johnson & Johnson Services, Inc.; Kosan Biosciences, Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; and Novartis Pharmaceuticals Corporation. Antonio Palumbo has received honoraria from Celgene Corporation and Janssen-Cilag EMEA. David S. Siegel is a member of the Speaker's Bureau of and has served as a paid consultant or been on the Advisory Board of Celgene Corporation and Millennium Pharmaceuticals, Inc. Sonia Cunningham has no relevant relationships to disclose. James Berenson has received research funding from Celgene Corporation; Cephalon, Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and Ziopharm Oncology, Inc. and is a member of the Speakers Bureau of and has served as paid consultant or been on the Advisory Board of Amgen; Celgene Corporation; Cephalon, Inc.;

CuraGen Corporation; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Ortho Biotech Products, L.P.; and Seattle Genetics, Inc.

References

- Madan S, Greipp PR. The incidental monoclonal protein: Current approach to management of monoclonal gammopathy of undetermined significance (MGUS). *Blood Rev* 2009; 23:257-65.
- Kyle RA, Therneau TM, Melton LJ, III, et al. Monoclonal gammopathy of undetermined significance: estimated incidence and duration prior to recognition. *Blood* 2007; 110:79a (abstract 246).
- Kyle R. MGUS/asymptomatic myeloma/solitary plasmacytoma: where are we moving in 2009. Paper presented at: *Clinical Lymphoma & Myeloma* panel: focus on myeloma; May 28, 2009; Orlando, FL.
- Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance. *Br J Haematol* 2006; 134:573-89.
- Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. *Mayo Clin Proc* 2009; 84:685-93.
- Blade J, Rosinol L, Cibeira MT. Are all myelomas preceded by MGUS? *Blood* 2009; 113:5370.
- 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; 346:564-9.
- Decaux O, Laurat E, Perlat A, et al. Systemic manifestations of monoclonal gammopathy. *Eur J Intern Med* 2009; 20:457-61.
- Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. *Br J Haematol* 2008; 140:365-77.
- Ramchandren S, Lewis RA. Monoclonal gammopathy and neuropathy. *Curr Opin Neurol* 2009; 22:480-5.
- Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005; 106:812-7.
- Kyle RA, Rajkumar SV, Therneau TM, et al. Prognostic factors and predictors of outcome of immunoglobulin M monoclonal gammopathy of undetermined significance. *Clin Lymphoma* 2005; 5:257-60.
- Fonseca R, Bailey RJ, Ahmann GJ, et al. Genomic abnormalities in monoclonal gammopathy of undetermined significance. *Blood* 2002; 100:1417-24.
- Brousseau M, Leleu X, Gerard J, et al. Hyperdiploidy is a common finding in monoclonal gammopathy of undetermined significance and monosomy 13 is restricted to these hyperdiploid patients. *Clin Cancer Res* 2007; 13:6026-31.
- Walker BA, Leone PE, Jenner MW, et al. Integration of global SNP-based mapping and expression arrays reveals key regions, mechanisms, and genes important in the pathogenesis of multiple myeloma. *Blood* 2006; 108:1733-43.
- Llovetas E, Sole F, Florensa L, et al. Contribution of cytogenetics and in situ hybridization to the study of monoclonal gammopathies of undetermined significance. *Cancer Genet Cytogenet* 2002; 132:25-9.
- Berenson JR, Yellin O. Monoclonal gammopathy of undetermined significance: why identification of these patients and assessment of their skeletons is important. *Clin Lymphoma Myeloma* 2009; 9:311-5.
- Berenson JR, Yellin O, Boccia RV, et al. Zoledronic acid markedly improves bone mineral density for patients with monoclonal gammopathy of undetermined significance and bone loss. *Clin Cancer Res* 2008; 14:6289-95.
- Winter MC, Coleman RE. Bisphosphonates in breast cancer: teaching an old dog new tricks. *Curr Opin Oncol* 2009; 21:499-506.
- Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 1998; 16:593-602.
- Kyle RA, Yee GC, Somerfield MR, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; 25:2464-72.
- Terpos E, Sezer O, Croucher PJ, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. *Ann Oncol* 2009; 20:1303-17.
- Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007; 356:2582-90.
- Raab MS, Podar K, Breitkreutz I, et al. Multiple myeloma. *Lancet* 2009; 374:324-39.
- Mateos M, Lopez-Corral L, Hernandez MT, et al. Multicenter, randomized, open-label, phase III trial of lenalidomide-dexamethasone (len/dex) vs therapeutic abstinence in smoldering multiple myeloma at high risk of progression to symptomatic MM: results of the first interim analysis. *Blood* 2009; 114:243 (abstract 614).
- Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003; 121:749-57.
- Dimopoulos M, Terpos E, Comenzo RL, et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. *Leukemia* 2009; 23:1545-56.

28. ClinicalTrials.gov [Web site]. Magnetic resonance imaging and fludeoxyglucose F18 positron emission tomography in diagnosing patients with solitary plasmacytoma. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT109889>. Accessed: June 10, 2009.
29. Dingli D, Kyle RA, Rajkumar SV, et al. Immunoglobulin free light chains and solitary plasmacytoma of bone. *Blood* 2006; 108:1979-83.
30. Weber DM. Solitary bone and extramedullary plasmacytoma. *Hematology Am Soc Hematol Educ Program* 2005;373-6.
31. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; 111:2516-20.
32. Harousseau JL. Induction therapy in multiple myeloma. *Hematology Am Soc Hematol Educ Program* 2008; 306-12.
33. Kumar S, Giral S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide, lenalidomide or bortezomib-containing regimens. *Blood* 2009; 114:1729-35.
34. Giral S, Stadtmauer EA, Harousseau JL, et al. International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia* 2009; 23:1904-12.
35. Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood* 2009; 114:3139-46.
36. Cavo M, Tacchetti P, Patriarca F, et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. *Blood* 2008; 112:65 (abstract 158).
37. Harousseau J-L, Palumbo A, Richardson P, et al. Superior outcomes associated with complete response: analysis of the phase III VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. *Blood* 2008; 112:959 (abstract 2778).
38. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2009. Epub ahead of print.
39. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood* 2008; 112:3107-14.
40. Paiva B, Vidrales MB, Cervero J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood* 2008; 112:4017-23.
41. 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; 13:7073-9.
42. Alegre A, Diaz-Mediavilla J, San-Miguel J, et al. Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish Registry. Spanish Registry for Transplant in MM (Grupo Espanol de Trasplante Hematopoyetico-GETH) and PETHEMA. *Bone Marrow Transplant* 1998; 21:133-40.
43. Singhal S, Powles R, Sirohi B, et al. Response to induction chemotherapy is not essential to obtain survival benefit from high-dose melphalan and autotransplantation in myeloma. *Bone Marrow Transplant* 2002; 30:673-9.
44. Kumar S, Lacy MQ, Dispenzieri A, et al. High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. *Bone Marrow Transplant* 2004; 34:161-7.
45. Kumar A, Kharfan-Dabaja MA, Glasmacher A, et al. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2009; 101:100-6.
46. Blade J, Rosinol L. Advances in therapy of multiple myeloma. *Curr Opin Oncol* 2008; 20:697-704.
47. Giral S, Vesole DH, Somlo G, et al. Re: Tandem vs single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2009; 101:964; author reply 66-7.
48. Harousseau J, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): updated data from IFM 2005/01 trial. Paper presented at: the 2008 meeting of the American Society of Hematology; December 7, 2008; San Francisco, CA.
49. Ludwig H, Hajek R, Tothova E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood* 2009; 113:3435-42.
50. Facon T, Mary JY, Hulin C, et al. 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; 370:1209-18.
51. Waage A, Gimsing P, Juliusson G, et al. Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomised phase 3 trial. *Blood* 2007; 110:32a (abstract 78).
52. Barlogie B, Anaisie EJ, Shaughnessy JD Jr, et al. Ninety percent sustained complete response (cr) rate projected 4 years after onset of CR in gene expression profiling (GEP)-defined low-risk multiple myeloma (MM) treated with total therapy 3 (TT3): basis for GEP-risk-adapted TT4 and TT5. *Blood* 2008; 112:66 (abstract 162).
53. Shaughnessy JD, Zhou Y, Haessler J, et al. TP53 deletion is not an adverse feature in multiple myeloma treated with total therapy 3. *Br J Haematol* 2009; 147:347-51.
54. ClinicalTrials.gov [Web site]. A randomized clinical trial of lenalidomide (CC-5013) and dexamethasone with and without autologous peripheral blood stem cell transplant in patients with newly diagnosed multiple myeloma. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00777881>. Accessed: October 1, 2009.
55. ClinicalTrials.gov [Web site]. A phase II clinical trial for untreated patients with multiple myeloma eligible for stem cell transplant: lenalidomide (Revlimid) plus low-dose dexamethasone (Ld x 4 cycles) then stem cell collection followed by randomization to continued Ld or stem cell transplantation (SCT) plus maintenance Ld for SCT patients not achieving at least very good partial response (VGPR) or having high-risk disease. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00807599>. Accessed: October 1, 2009.
56. San Miguel JF, Schlag R, Khuageva NK, et al. Updated follow-up and results of subsequent therapy in the phase III VISTA trial: bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma. *Blood* 2008; 112:242 (abstract 650).
57. 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; 114:518-21.
58. Avet-Loiseau H, Soulier J, Fermand J-P, et al. Impact of chromosomal abnormalities del(13), t(4;14), and del(17p) and prior treatment on outcomes in patients with relapsed or refractory multiple myeloma treated with lenalidomide. *Blood* 2008; 112:1262 (abstract 3685).
59. Reece D, Song KW, Fu T, et al. Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. *Blood* 2009; 114:522-5.
60. Lonial S. Risky business in myeloma. *Blood* 2009; 114:496-7.
61. Jagannath S. Treatment of myeloma patients with comorbid conditions: considerations for the clinician. *Clin Lymphoma Myeloma* 2008; 8(suppl 4):S149-S56.
62. Chen N, Lau H, Kong L, et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; 47:1466-75.
63. San-Miguel JF, Richardson PG, Sonneveld P, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. *Leukemia* 2008; 22:842-9.
64. Pillon L, Sweeting RS, Arora A, et al. Approach to acute renal failure in biopsy proven myeloma cast nephropathy: is there still a role for plasmapheresis? *Kidney Int* 2008; 74:956-61.
65. Hutchison CA, Cook M, Heyne N, et al. European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): a randomised control trial. *Trials* 2008; 9:55.
66. Lenalidomide: new drug. Myeloma: many questions remain unanswered. *Prescribe Int* 2008; 17:230-2.
67. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008; 22:414-23.
68. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol* 2009; 6:596-603.
69. Richardson PG, Sonneveld P, Schuster MW, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. *Br J Haematol* 2009; 144:895-903.
70. Palumbo A, Bringhen S, Rossi D, et al. A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients. *J Clin Oncol* 2009; 27(15 suppl):437s (abstract 8515).
71. Richardson P, Lonial S, Jakubowiak A, et al. Lenalidomide, bortezomib and dexamethasone has notable activity in the frontline treatment of myeloma, including patients with high risk disease. Paper presented at: the XIIth International Myeloma Workshop; February 26-March 1, 2009; Washington, DC.
72. Jagannath S, Barlogie B, Berenson JR, et al. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. *Br J Haematol* 2008; 143:537-40.
73. Laubach JP, Mahindra A, Mitsiades CS, et al. The use of novel agents in the treatment of relapsed and refractory multiple myeloma. *Leukemia* 2009. Epub ahead of print.
74. O'Connor OA, Stewart AK, Vallone M, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. *Clin Cancer Res* 2009; 15:7085-91.
75. Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007; 44:62-9.
76. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood* 2002; 99:3163-8.
77. 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; 82:1179-84.
78. ClinicalTrials.gov [Web site]. Study to determine efficacy and safety of lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide in patients with previously untreated multiple myeloma (FIRST). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00689936>. Accessed: December 2, 2009.
79. Zhan F, Barlogie B, Arzoumanian V, et al. Gene-expression signature of benign monoclonal gammopathy evident in multiple myeloma is linked to good prog-

- nosis. *Blood* 2007; 109:1692-700.
80. 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; 27:1788-93.
81. Laubach JP, Richardson PG, Anderson KC. Hematology: thalidomide maintenance in multiple myeloma. *Nat Rev Clin Oncol* 2009; 6:565-6.
82. Palumbo A, Falco P, Gay F, et al. Bortezomib-doxorubicin-dexamethasone as induction prior to reduced intensity autologous transplantation followed by lenalidomide as consolidation/maintenance in elderly untreated myeloma patients. *Blood* 2008; 112:65 (abstract 159).
83. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009; 23:2147-52.
84. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007; 110:3557-60.
85. Orłowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol* 2007; 25:3892-901.
86. Vogl DT, Stadtmayer EA, Richardson PG, et al. Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed/refractory multiple myeloma. *Br J Haematol* 2009; 147:531-4.
87. Multiple myeloma. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology—v.2.2010. National Comprehensive Cancer Network [Web site]. Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed: November 4, 2009.
88. Sood R, Carlsson H, Kerr R, et al. Retreatment with bortezomib alone or in combination for patients with multiple myeloma following an initial response to bortezomib. *Am J Hematol* 2009; 84:657-60.
89. Conner TM, Doan QD, Walters IB, et al. An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma. *Clin Lymphoma Myeloma* 2008; 8:140-5.
90. Niesvizky R, Richardson PG, Rajkumar SV, et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. *Br J Haematol* 2008; 143:46-53.
91. Petrucci MT, Blau IW, Corradini P, et al. Efficacy and safety of re-treatment with bortezomib (Velcade(C)) in patients with multiple myeloma: results from a prospective international phase II trial. *Blood* 2008; 112:1264 (abstract 3690).
92. Mateos M-V, Oriol A, Martinez J, et al. Bortezomib (Velcade)-melphalan-prednisone (VMP) versus Velcade-thalidomide-prednisone (VTP) in elderly untreated multiple myeloma patients: which is the best partner for Velcade: an alkylating or an immunomodulator agent? *Blood* 2008; 112:243 (abstract 651).
93. Pervan M, Pajonk F, Sun JR, et al. Molecular pathways that modify tumor radiation response. *Am J Clin Oncol* 2001; 24:481-5.
94. Berenson J. Managing complications of myeloma and treatment toxicities. Paper presented at: *Clinical Lymphoma & Myeloma* panel: focus on myeloma. May 28, 2009; Orlando, FL.
95. ClinicalTrials.gov [Web site]. Zoledronic acid treatment (every 4 or 12 weeks) to prevent skeletal complications in advanced multiple myeloma patients (Z-MARK). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00622505>. Accessed: October 12, 2009.
96. ClinicalTrials.gov [Web site]. Study of zoledronic acid administered monthly versus every 3 months in multiple myeloma and breast cancer patients who were treated with zoledronic acid the prior year. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00424983>. Accessed: December 1, 2009.
97. Sezer O. Myeloma bone disease: recent advances in biology, diagnosis, and treatment. *Oncologist* 2009; 14:276-83.
98. Roodman GD. Skeletal imaging and management of bone disease. *Hematology Am Soc Hematol Educ Program* 2008; 313-9.
99. ClinicalTrials.gov [Web site]. A study to assess BQ880 in combination with zoledronic acid in relapsed or refractory myeloma patients. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00741377>. Accessed: October 12, 2009.
100. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; 98:1735-44.
101. Vahsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol* 2009; 27:5356-62.
102. Christodoulou C, Pervana A, Klouvas G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. *Oncology* 2009; 76:209-11.
103. Dickinson M, Prince HM, Kirsá S, et al. Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: an overview with recommendations for prevention and treatment. *Intern Med J* 2009; 39:304-16.
104. Palumbo A, Sezer O, Kyle R, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. *Leukemia* 2009; 23:1716-30.
105. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009; 373:1016-24.
106. Lee MJ, Dumonski M, Cahill P, et al. Percutaneous treatment of vertebral compression fractures: a meta-analysis of complications. *Spine (Phila Pa 1976)* 2009; 34:1228-32.
107. Kallmes DE, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; 361:569-79.
108. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-68.
109. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia* 2009; 23:215-24.
110. Abadie JM, van Hoven KH, Wells JM. Are renal reference intervals required when screening for plasma cell disorders with serum free light chains and serum protein electrophoresis? *Am J Clin Pathol* 2009; 131:166-71.
111. Ziegler D. Treatment of diabetic neuropathy and neuropathic pain: how far have we come? *Diabetes Care* 2008; 31(suppl 2):S255-61.
112. Steinberg J, Shen J, Sanchez E, et al. Alpha lipoic acid (ALA) inhibits the anti-myeloma effects of bortezomib. Paper presented at: the 2009 annual meeting of the American Society of Hematology; December 5-8, 2009; New Orleans, LA. Abstract 3832.
113. Llobet D, Eritja N, Encinas M, et al. Antioxidants block proteasome inhibitor function in endometrial carcinoma cells. *Anticancer Drugs* 2008; 19:115-24.
114. Perrone G, Hideshima T, Ikeda H, et al. Ascorbic acid inhibits antitumor activity of bortezomib in vivo. *Leukemia* 2009; 23:1679-86.
115. Golden EB, Lam PY, Kardosh A, et al. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood* 2009; 113:5927-37.
116. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol* 2009; 63:761-7.
117. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; 111:3968-77.
118. Morgan P. Running on pickle juice: marathoners find a sour solution to muscle cramps. Available at: http://www.mlive.com/bhealth/index.ssf/2009/10/running_on_pickle_juice_marath.html. Accessed: October 14, 2009.
119. Martin MG, Vij R. Arterial thrombosis with immunomodulatory derivatives in the treatment of multiple myeloma: a single-center case series and review of the literature. *Clin Lymphoma Myeloma* 2009; 9:320-3.
120. Ludwig H, Zojer N. Supportive care in multiple myeloma. *Best Practice & Research Clinical Haematology* 2007; 20:817-35.
121. Nucci M, Anaissie E. Infections in patients with multiple myeloma. *Semin Hematol* 2009; 46:277-88.
122. Vickrey E, Allen S, Mehta J, et al. Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer* 2009; 115:229-32.
123. ClinicalTrials.gov [Web site]. Antibiotic therapy in preventing early infection in patients with multiple myeloma who are receiving chemotherapy. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00002850>. Accessed: October 14, 2009.
124. Ocio EM, Mateos MV, Maiso P, et al. New drugs in multiple myeloma: mechanisms of action and phase I/II clinical findings. *Lancet Oncol* 2008; 9:1157-65.
125. Jagannath S, Vij R, Stewart AK, et al. Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). *J Clin Oncol* 2009; 27(15 suppl):435s (abstract 8504).
126. Vij R, Wang M, Orłowski RZ, et al. PX-171-004, a multicenter phase II study of carfilzomib (CFZ) in patients with relapsed myeloma: An efficacy update. *J Clin Oncol* 2009; 27(15 suppl):443s (abstract 8537).
127. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol* 2009; 27:5008-14.
128. Niesvizky R, Bensinger W, Vallone M, et al. PX-171-006: Phase Ib multicenter dose escalation study of carfilzomib (CFZ) plus lenalidomide (LEN) and low-dose dexamethasone (loDex) in relapsed and refractory multiple myeloma (MM): preliminary results. *J Clin Oncol* 2009; 27(15 suppl):44s (abstract 8541).
129. Richardson P, Mitsiades C, Colson K, et al. Phase I trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. *Leuk Lymphoma* 2008; 49:502-7.
130. Siegel D, Weber D, Mitsiades C, et al. Vorinostat in combination with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma: a phase I study. *J Clin Oncol* 2009; 27(15 suppl):455s (abstract 8586).
131. Badros A, Burger AM, Philip S, et al. Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. *Clin Cancer Res* 2009; 15:5250-7.
132. ClinicalTrials.gov [Web site]. Study of vorinostat (MK0683) an HDAC inhibitor, or placebo in combination with bortezomib in patients with multiple myeloma. Available at: www.clinicaltrials.gov/ct2/show/NCT00773747. Accessed: April 27, 2009.
133. San Miguel J, Sezer O, Siegel D, et al. A phase Ib, multicenter, open-label, dose escalation study of oral panobinostat (LBH589) and i.v. bortezomib in patients with relapsed multiple myeloma. *Blood* 2009; 114: (abstract 3852).

134. Spencer A, Taylor K, Lonial S, et al. Panobinostat plus lenalidomide and dexamethasone phase I trial in multiple myeloma (MM). *J Clin Oncol* 2009; 27(15 suppl):444s (abstract 8542).
135. Sezer O, Siegel D, San Miguel J, et al. Panobinostat and Bortezomib Phase I Trial in Multiple Myeloma. *Clin Lymphoma Myeloma* 2009; 9(suppl 1):S54 (abstract 337).
136. Mitsiades CS, Mitsiades NS, McMullan CJ, et al. Antimyeloma activity of heat shock protein-90 inhibition. *Blood* 2006; 107:1092-100.
137. Richardson P, Chanan-Khan A, Lonial S, et al. Tanespimycin plus bortezomib in patients with relapsed and refractory multiple myeloma: final results of a phase I/II study. *J Clin Oncol* 2009; 27(15 suppl):434s (abstract 8503).
138. Jakubowiak A, Hideshima T, Sportelli P, et al. Phase I Trial of perfosine, lenalidomide, and dexamethasone in relapsed or refractory myeloma. *Clin Lymphoma Myeloma* 2009; 9(suppl 1):S56 (abstract 347).
139. Richardson P, Wolf JL, Jakubowiak A, et al. Perfosine in combination with bortezomib and dexamethasone extends progression-free survival and overall survival in relapsed/refractory multiple myeloma patients previously treated with bortezomib: updated phase I/II trial results. *Blood* 2009; 114: (abstract 1869).
140. Zonder JA, Singhal S, Bensinger W, et al. Phase I study of elotuzumab (HuLuc63) in phase I study of elotuzumab (HuLuc63) in relapsed/refractory multiple myeloma. *Blood* 2008; 112:956 (abstract 2773).
141. van Rhee F, Szmania SM, Dillon M, et al. Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. *Mol Cancer Ther* 2009; 8:2616-24.
142. Lonial S, Singhal A, Jagannath S, et al. Phase 1b study of elotuzumab (HuLuc63) in combination with lenalidomide in relapsed multiple myeloma. *Clin Lymphoma Myeloma* 2009; 9(suppl 1):S20 (abstract 129).
143. Jakubowiak A, Bensinger W, Zimmerman TM, et al. Phase I study of elotuzumab in combination with bortezomib in relapsed multiple myeloma. *Clin Lymphoma Myeloma* 2009; 9(suppl 1):S45 (abstract 264).
144. Ikeda H, Hideshima T, Fulciniti M, et al. The monoclonal antibody nBT062 conjugated to cytotoxic Maytansinoids has selective cytotoxicity against CD138-positive multiple myeloma cells in vitro and in vivo. *Clin Cancer Res* 2009; 15:4028-37.
145. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol* 2009; 27:1492-501.
146. ClinicalTrials.gov [Web site]. Conditioning regimen of bendamustine and melphalan followed by transplant in patients with multiple myeloma. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00916058>. Accessed: October 14, 2009.
147. ClinicalTrials.gov [Web site]. Study of bendamustine combined with bortezomib for patients with relapsed/refractory multiple myeloma. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00920855>. Accessed: October 14, 2009.
148. Sargent DJ, Taylor JM. Current issues in oncology drug development, with a focus on Phase II trials. *J Biopharm Stat* 2009; 19:556-62.